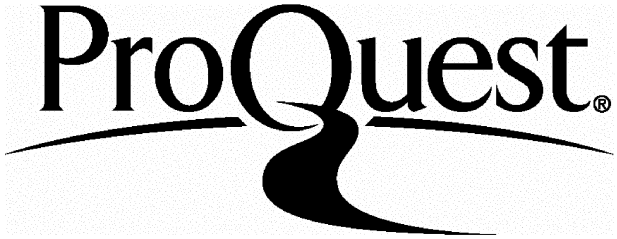
A STUDY OF THE CLINICAL OUTCOME OF COMPLEX CORONARY BALLOON ANGIOPLASTY

Kim Heung Tan
MBBS, MRCP

Thesis Submitted to the University of London
for the Degree of Doctor of Medicine, 1995



ABSTRACT

Percutaneous transluminal coronary angioplasty has gained wide acceptance as a non-surgical form of revascularisation. However, its application in certain complex patient or lesion subsets has been the subject of considerable debate. This thesis examines some of these controversial issues.

Coronary angioplasty of chronic total occlusions was shown to be associated with a low success rate, but also a low risk of complication. Successful recanalisation was adversely influenced by easily identifiable clinical and angiographic parameters, and reduced the use of subsequent bypass surgery.

Although angioplasty of ostial stenoses was found to be associated with a higher complication rate than angioplasty of non-ostial lesions, there was no difference in the success rate. Distinctive procedural features included higher inflation pressures and inflation frequency for aorta ostial lesions.

A third angioplasty for a second restenosis was shown to be safe and effective. Furthermore, the likelihood of a third restenosis could be predicted from the time interval between previous procedures. The restenosis pattern after 'tandem lesion' angioplasty, suggested that local factors were more important than systemic factors in influencing restenosis.

Coronary angioplasty was found to be safe and effective in patients with previous bypass surgery. In patients aged ≥70 years of age, complete revascularisation was unnecessary to achieve symptomatic relief, but incomplete revascularisation meant poorer long-term survival.

Evaluating angioplasty outcome using a lesion-specific morphological approach, was shown to allow better patient stratification than the ABC lesion classification scheme proposed by the American College of Cardiology/American Heart Association Task Force.

When chest pain recurred after successful angioplasty, the mechanisms found to be responsible included restenosis, incomplete revascularisation, progression of coronary atherosclerosis, and non-cardiac pain. The time from successful angioplasty to onset of recurrent chest pain was the strongest predictor of angiographic outcome. The incidence of new lesion development was also shown to be higher in the vessels that had instrumented angioplasty.

CONTENTS

ACKNOWLEDGEMENTS

The work presented in this thesis was carried out during my appointment at Guy's Hospital, London.

I am indebted to, and gratefully acknowledge the support and advice of Dr Edgar Sowton who directed my research into this field. His guidance and encouragement throughout my studies are much appreciated.

I am grateful to all the cardiologists who have performed coronary angioplasty at Guy's Hospital, and who have contributed to the data in this thesis. In particular I would like to thank Dr Neil Sulke for his help and advice during the preparation of this thesis, and Dr Cliff Bucknall for his constant encouragement.

I wish to thank Miss Sheila Karani for her help with data collection and management, and Mr Nick Taub for his advice in complex statistical analysis.

I thank Lisa for spending many of her precious hours in helping me to load data into the computer, and her extreme patience and tolerance while I was writing this thesis.

WORK PERFORMED PERSONALLY

All studies described in this thesis were conceived, organised and undertaken by myself.

All the quantitative angiographic measurements and qualitative assessments were performed by myself with a second independent observer.

The most recent follow-up data of all the patients included in this thesis were collected by myself.

The organisation and analysis of data was performed by myself with the assistance and advice of Mr Nick Taub in complex statistical analysis.

During the study period, I personally performed percutaneous transluminal coronary angioplasty in more than 300 patients as a first operator.

CONTRIBUTION TO THE MEDICAL LITERATURE

Publications in Support of the Thesis

(1) Chapter 3

Kim H Tan, Neil Sulke, Nick Taub, Elizabeth Watts, Sheila Karani, Edgar Sowton. Determinants of success of coronary angioplasty in patients with a chronic total occlusion: a multiple logistic regression model to improve selection of patients. Br Heart J 1993;70:126-131.

Kim H Tan. Predicting coronary angioplasty success when patients have chronic total occlusion. Cardiology Board Review (in press).

(2) Chapter 6

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(3) Chapter 9

Kim H Tan, Neil Sulke, Nick Taub, Edgar Sowton. Clinical and lesion morphologic determinants of coronary angioplasty success and complications: current experience. J Am Coll Cardiol (in press, scheduled to appear in the March 15, 1995, issue).

(4) Chapter 4

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Percutaneous transluminal coronary angioplasty of aorta ostial, non-aorta ostial, and branch ostial stenoses: Acute and long-term outcome.

Eur Heart J (in press, scheduled to appear in the March, 1995 issue).

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(6) Chapter 5

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Br Heart J (in press).

(7) Chapter 7

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Percutaneous transluminal coronary angioplasty in patients seventy years of age or older: acute and long-term results.

Br Heart J (submitted).

(8) Chapter 8

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The doors of truth are guarded by paradox and confusion

Unknown

To My Parents

1. *INTRODUCTION, HISTORICAL AND LITERATURE REVIEW*

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1.1 DEVELOPMENT OF PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

(a) HISTORY OF CARDIAC CATHETERISATION

The ancient Greeks were probably the first to undertake scientific experimentation into the workings of the heart and vessels, by putting air or water into the vascular system in an attempt to understand the function of the valves. Centuries passed before William Harvey stirred the medical community with his description of the blood circulation in 1628. It was not until decades later when Reverend Stephen Hales performed the first experimental catheterisation of a mammalian vascular system in the early 18th century. He put brass pipes into the carotid artery of a conscious mare to measure arterial pressure and calculate blood velocity. Although Claude Bernard is frequently cited as the first person to perform mammalian cardiac catheterisation, by introducing thermo-electric probes into the cardiac chambers of a live standing horse, to record the temperature of the blood in 1844, similar experiments were performed by John Davy as early as 1814 but only after the animal had been struck to make it insensible (Doby, 1976). In 1861, in an attempt to resolve the controversy regarding the origin and timing of the cardiac apex beat, Chaveau and Marey were the first to systematically employ catheterisation for the investigation of intracardiac pressures. A series of experiments were conducted with a double lumen catheter and a recording device developed by Pierre Charles Buisson, which resulted in the first systematic description and interpretation of intracardiac pressure recordings in 1863. Shortly after the end of the 19th century, the mathematical and theoretical basis of faithful reproduction in form, fine detail, magnitude, and timing of intravascular and intracardiac events were laid down by Otto Franck (Cournand, 1975). Although these studies led to major advances in the

understanding of mammalian cardiovascular physiology, the ability to study living organisms without intrusion was only made possible when Wilhelm Roentgen discovered X-rays in 1895 (Glasser, 1958).

In 1912, Bleichroder, Unger, and Loeb reported several successful passages of a catheter into arm and leg veins of patients, with subsequent advancement into the axilla and inferior vena cava (Bleichroder, 1912). However, no X-ray checks were used, nor were the cardiological aspects taken into consideration. The first cardiac catheterisation in a living human heart was performed by Werner Forssmann in 1929 in Eberswald, Germany (Forssmann, 1929). He was searching for a method of injecting drugs directly into the right atrium to treat certain serious medical conditions. Against the advice of his chief, he exposed the basilar vein of his own left arm, introduced a ureteral catheter into his venous system, and advanced it under fluoroscopic control and a mirror, up to his right atrium. The catheter remained in-situ until a chest X-ray to confirm the catheter tip position was taken without any untoward effect. In 1931, he reported direct intracardiac injection of radiopaque contrast medium via the cardiac catheter into the right atrium of dogs and himself (Forssmann, 1931).

In the decade that followed, not only were the physiological applications of Forssmann's experiments unrecognised, his experiments were received with scornful criticism by his medical colleagues. As a result, in the 1930s, apart from the rapid development of pulmonary angiography by Moniz, Perez, and Ameuille, and the use of cardiac catheterisation by Klein to obtain mixed venous blood samples in order to determine the cardiac output, the use of catheterisation for study of the circulation in normal and disease states was fragmentary and of little importance in furthering physiological or pathophysiological knowledge (Cournand,

1975). It was not until the early 1940s when Cournand, Richards, et al, working in Bellevue Hospital in New York, rediscovered cardiac catheterisation and used it to make physiological observations (Cournand and Ranges, 1941; Cournand et al, 1945; Richards, 1945). They embarked on a series of experiments to test the hypothesis that the heart, lungs, and circulation form a single system for the exchange of respiratory gases between the atmosphere and the tissues of the organism. New techniques for studying various aspects of ventilatory and alveolar-respiratory function were developed and the development of the double lumen catheters made it possible to secure simultaneous blood samples and pressure recordings in the right atrium and ventricle, or in the right ventricle and pulmonary artery. The study of cardiac output and pulmonary circulation in health and disease states was therefore made possible, and the first experiments with the heart catheter as a physiological monitor was accomplished.

Cardiac catheterisation was first used for diagnostic purposes by Brannon, Weens, and Warren in 1945, working in Eugene Stead's laboratory in Emory University School of Medicine, where the technique was used to diagnose atrial septal defect (Brannon et al, 1945). Further use of cardiac catheterisation for the diagnosis of congenital and acquired (rheumatic) heart disease flourished in the ensuing decades.

With considerable experience gained in catheterisation of the right heart, attention was turned to the left heart. In 1949, Henry Zimmerman described the first retrograde left heart catheterisation via the left ulnar artery (Zimmerman et al, 1950), and in 1953, the percutaneous arterial cannulation technique was developed by Seldinger, hence obviating the need for direct arterial exposure (Seldinger, 1953). The next milestone occurred in 1958 when the first selective coronary angiography via the right brachial artery was described by Mason Sones from

Cleveland Clinic (Sones et al, 1959; Sones and Shirey, 1962). This event changed the medical profession's entire approach to the diagnosis and treatment of coronary artery disease. In 1967, Melvin Judkins introduced a percutaneous transfemoral technique using Ducor catheters shaped over preformed stainless steel bending wires, and heating in boiling water to maintain the new, optimal configuration (Judkins, 1967). These advances in cardiac investigations paved the way for successful surgical treatment of congenital and acquired heart disease in the post-World War II years, and subsequently to coronary bypass surgery in the late 1960s by Favaloro (1968) and Green (1968).

(b) HISTORY OF PERCUTANEOUS TRANSLUMINAL ARTERIAL DILATATION

In 1964, an imaginative application of catheters for a therapeutic purpose was introduced by Charles Dotter and Melvin Judkins in Portland, Oregon (Dotter and Judkins, 1964). The technique was coined "transluminal angioplasty" and utilised a coaxial system of radio-opaque Teflon dilating catheters of up to 0.2 inch outer diameter to improve blood flow in patients with peripheral arteriosclerosis. Although several European exponents, in particular Zeitler (1971), used the "Dotter technique", the procedure did not gain widespread acceptance, and angioplasty was abandoned for 15 years in the United States. This was in part due to the local complications attributable to the large and rigid dilating catheters, and the risk of peripheral embolisation.

It was Dotter and Judkins (1964) who proposed that an ideal dilating device would be capable of externally controlled concentric expansion over part of its length. A number of investigators attempted to modify the catheter system by developing a

balloon, the most notable being an elastic caged Latex balloon developed by Werner Porstmann in 1973 (Porstmann, 1973). The Latex balloon was inflated within a cage formed by 4 longitudinal slits near the tip of an angiographic catheter. This overcame the problem of the compressible Latex balloon not being able to dilate rigid atherosclerotic lesions. Unfortunately, although it applied more force, it produced a lot of debris and a rough endothelial surface.

In 1974, Grüntzig, trained by Zeitler and influenced by Portsmann's balloon, described a non-elastic balloon catheter for the dilation of vascular stenosis in peripheral vascular occlusion (Grüntzig and Hopff, 1974). At the distal end of this catheter was fixed a distensible balloon over sideholes in the shaft of a flexible single lumen catheter. The balloon was made of a low compliant material called polyvinyl chloride, which exerted a circumferential pressure (rather than axial force in the Dotter technique) on the arteriosclerotic plaque, when inflated to a fixed diameter at balloon pressures up to 6 atmospheres. The catheter was advanced over a guidewire until the balloon was positioned across an arterial stenosis, when the guidewire was removed and the catheter tip obstructed with an occluding device. Repeated inflations and deflations could be made through the catheter side holes. Grüntzig used this system to treat iliac and femoral stenoses and reported encouraging success. The safety was also demonstrated because of the small shaft and flexibility of the balloon catheter. Further improvement in design resulted in a double lumen balloon catheter in which the larger lumen accommodated a guidewire and allowed pressure to be measured and contrast agents to be injected, and the other lumen communicated with the inflatable balloon (Grüntzig, 1976a).

In March 1977, Zeitler organised the first conference, held in Nuremberg, to review the European and American experience with peripheral transluminal angioplasty.

Although only 10 centres in the world were performing peripheral angioplasty at that time, the technique was rapidly established as an effective method of treating selected patients with peripheral vascular disease.

(c) HISTORY OF PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

The concept of treating coronary stenoses with angioplasty, as well as intra-coronary stents, was in fact suggested by Charles Dotter (1964), although he never performed these techniques. Success in treating femoro-popliteal and iliac atherosclerotic stenoses with transluminal angioplasty, and reports of high patency rates in these vessels after long-term follow-up, prompted consideration of the use of transluminal angioplasty in the coronary circulation.

In 1976, Grüntzig miniaturised his peripheral balloon catheter to perform coronary angioplasty. A soft distal guidewire allowed atraumatic passage of the balloon catheter to reduce arterial wall damage, and the central lumen communicated with the arterial lumen via sideholes to allow distal coronary perfusion and pressure measurement. The initial studies in coronary arteries were performed in dogs, where nonatherosclerotic coronary stenoses were produced by placing surgically applied silk ligatures around the coronary artery (Grüntzig 1976b; Grüntzig et al, 1976). Early experience with the canine model suggested that active distal perfusion of blood through the balloon catheter was necessary to prevent ventricular tachycardia or fibrillation during balloon inflation. Another concern was the possibility of embolisation of atherosclerotic material. The technique was extended to human cadaveric hearts (Gruentzig et al, 1976). In May 1977, the first coronary angioplasty in a living human was performed intra-operatively in a patient

undergoing coronary bypass surgery in San Francisco by Grüntzig, in collaboration with Myler and Hanna (Gruentzig et al, 1977). Collection of the effluent in millipore filters showed no evidence of debris and subsequent angiographic restudy showed improvement in diameter of the stenoses.

The scene was set for the first percutaneous transluminal coronary angioplasty, performed by Grüntzig on September 16, 1977, in Zurich, Switzerland (Hurst, 1986). The patient was a 37 year old insurance salesman with a proximal left anterior descending artery stenosis. Active distal coronary blood perfusion proved unnecessary, and the procedure was carried out with no electrocardiographic or rhythm changes, apart from transient right bundle branch block. Results of coronary balloon dilatation in the first 5 patients was published in February of 1978 in the Lancet (Grüntzig, 1978), and the technique was introduced in the United States by Myler and Stertzer in March of 1978 (Gruentzig et al, 1978; Stertzer et al, 1979). In July of 1979, Grüntzig reported the results of coronary angioplasty on 50 patients in the New England Journal of Medicine (Gruentzig et al, 1979). Few technical developments in recent times have led to comparable progress in knowledge and clinical practice; few such developments have benefited from so much enthusiastic response of clinical investigators. A registry for percutaneous transluminal coronary angioplasty was organised at the National, Heart, and Lung Institute in 1979, which by 1981 included information from over 110 centres with over 3,000 cases worldwide (Levy et al, 1979; Mullin et al, 1984). The registry protocol advocated recruitment of patients with anginal symptoms that were refractory to medical therapy and all patients were required to be candidates for coronary bypass surgery (Detre et al, 1984). Currently more than 300,000 coronary angioplasty procedures are performed annually in the United States, which exceeds the number of coronary artery bypass operations (Faxon, 1993).

Thus, following Grüntzig's initial experiments, percutaneous transluminal coronary angioplasty has developed into an effective and standard treatment for selected patients with coronary artery disease. It is interesting that on the tenth anniversary of the procedure, the first patient who underwent coronary angioplasty consented to repeat coronary angiography which demonstrated the vessel to be widely patent without obvious stenosis.

1.2 EQUIPMENT, TECHNOLOGY, AND TECHNIQUE

(a) HOSPITAL FACILITIES

The catheterisation laboratory functions as an X-ray room, as well as fulfilling some of the functions of an operating theatre and a physiological measurement laboratory. Full operating theatre sterility is unnecessary but sterile discipline is needed. Resuscitation equipment must be available at all times and include external defibrillation, emergency drugs, and full anaesthetic equipment with gases and suction.

X-Ray Apparatus

A high resolution image intensifier and cineangiographic X-ray unit is mandatory to visualise the guidewires which can be as fine as 0.01 inches (0.25 mm) in diameter and to delineate coronary morphology using multiple radiographic projections (Boucher et al, 1988; Holmes and Vlietstra, 1989). A high quality video tape with a freeze frame facility, or a digital recording system, allows instant recall of the images recorded during the procedure and provides a 'road map' for operators to work with. Effective monitoring of proper and consistent film processing, appropriate education and precaution to reduce exposure of patients and staff to ionising radiation (Dash and Leaman, 1984; Jeans et al, 1985; Finci et al, 1987a; Pipilis et al, 1990), and monitoring of radiation to exposed personnel, are all mandatory features of a modern cardiac intervention laboratory.

Physiological Monitoring

For the purpose of performing coronary angioplasty, the physiological measurements necessary entail the provision of strain-gauge pressure transducers

with a hydraulic calibration/flush system for pressure monitoring, a multiple (12 lead) display electrocardiographic channel to monitor S-T segment shift and rhythm changes, and a system for monitoring blood coagulation status (eg activated clotting time).

Surgical Back-up

The need for on-site surgical cover remains controversial and widely debated (Shaw 1990a, Parker 1990). Both the American College of Cardiology/American Heart Association Task Force (Ryan et al, 1988) and the Joint International Society and Federation of Cardiology/World Health Organisation Task Force (Bourassa et al, 1988) have issued guidelines recommending the presence of on-site surgery. However, in carefully selected patients, many centres have reported low complications without on-site surgical standby, provided it is available at a nearby centre (Richardson et al, 1990; Reifart et al, 1992a; Klinke and Hui, 1992; Iniguez et al, 1992).

(b) ANGIOPLASTY EQUIPMENT AND TECHNOLOGY

A coronary angioplasty system consists of 3 components: (1) a guiding catheter, (2) a non-elastic balloon dilatation catheter filled with liquid contrast medium, and (3) a leading guidewire.

Guiding Catheter

A guiding catheter provides stable access to the coronary ostium and allows the advancement of dilatation equipment. Current guiding catheters are available in different sizes and shapes suitable for specific anatomical situations (Figure 1.1). In addition to the conventional Judkins and Amplatz curves, other speciality guiding

catheter shapes include the multipurpose, hockey stick, Arani, El-Gamal, Voda, vein bypass, and internal mammary artery configurations (Arani, 1985; Voda, 1992). The Stertzer guiding catheter has been the "work horse" guiding catheter via the brachial route, although other preformed catheters can also be used from this approach. Early guiding catheters were made of solid Teflon and were relatively rigid, but modern guiding catheters consist of bonded composites of several layers. The outer layer is made either of polyurethane or polyethylene, which provides stiffness and "memory" (ability to retain preformed shape); the middle layer consists of either epoxy and fibre braid, or a woven wire matrix, for transmission of torque along the catheter shaft; the inner lumen is lined with Teflon to allow smooth passage of the balloon catheter and guidewire. The typical guiding catheter has an outer diameter of 8 or 9 French (2.7 or 3.0 mm), a non-tapered and occasionally tapered soft tip to accommodate the dilatation system and to reduce trauma to the coronary ostium, and a luminal diameter of 0.062 to 0.092 inch (1.5 to 2.3 mm) to deliver contrast medium and for pressure monitoring when the balloon catheter is in place. Preformed side-hole guiding catheters are commercially available although they can also be created with a punch device (Chua et al, 1985; Burch and Wholey, 1985). Their presence may be required to preserve perfusion pressure in the event of coronary wedging but, because they allow contrast spillage into the coronary sinuses, visualisation can be less satisfactory.

Dilatation Catheter

The original Grüntzig balloon consisted of a short segment of guidewire permanently affixed to the catheter tip. In 1982, Simpson introduced a new catheter system with the advantage of having an independently movable, flexible-tipped guidewire within the balloon dilatation catheter system (Simpson et al, 1982). The balloon dilatation catheter was manufactured from 2 concentric pieces of polyolefin

tubing. The outer lumen was contiguous with the balloon wall and the inner lumen accepted a 0.018 inch (0.46 mm) Teflon coated flexible-tipped guidewire. A variety of dilatation catheters are now commercially available with inflated balloon diameters ranging from 1.5 mm to 4.5 mm, and balloon lengths ranging from 10 mm to 40 mm. Preshaped, angled balloons have also been introduced to prevent dissection in lesions on severe bends although they are infrequently used today.

Dilatation Systems. The dilatation catheters that are currently available are of 4 basic types: Fixed-wire, over-the-wire, monorails, and perfusion catheters (Figures 1.2, 1.3, 1.4, and 1.5). With the fixed-wire system, the guidewire is fixed at the distal end of the dilatation catheter. With the over-the-wire system, an independently movable and/or steerable guidewire is present which extends the entire length of the dilatation catheter. With the monorail system, the steerable guidewire is confined to a short segment at the distal end of the dilatation catheter. Perfusion balloon catheters are over-the-wire or monorail systems that have larger central lumens with proximal and distal side holes. The side holes permit passage of blood through the distal end of the catheter, thus allowing passive coronary blood perfusion during balloon inflation.

Balloon Technology. The balloon material affects the distensibility, profile, pressure capability, and conformability of the angioplasty balloon. Polymers that are currently in use include polyvinyl chloride, polyolefin copolymer, polyethylene, and polyethylene terephthalate.

The distensibility depends on the compliance of the polymer (Figure 1.6). Polyolefin balloons are the most compliant, followed by polyvinyl chloride and polyethylene balloons. The diameter of polyvinyl chloride and polyethylene balloons

increases with inflation pressure and can vary by up to 18% over a range of 2 to 10 atmospheres (Jain et al 1986). The advantage is that one can use an undersized balloon to reduce the risk of dissection while leaving scope for an increase in balloon size. Polyethylene terephthalate balloons are the most non-compliant, thus allowing a high inflation pressure, with little over-expansion of the balloon. This has the advantage of delivering great distending forces to stenoses without overdistending the adjacent normal tissue.

The 'profile' of the balloon catheter is defined as the smallest diameter opening through which the deflated balloon can be passed. The lower the profile of the balloon, the greater is the ability to navigate through tortuous anatomy and cross tightly stenotic lesions. Although polyethylene terephthalate balloons are thin walled and have a low profile, they have no "memory", tending to bunch when crossing tight stenoses. The profile characteristics of polyvinyl chloride balloons are also completely altered after an initial inflation. Polyethylene and polyolefin copolymer balloons have better "memory" in that they retain their low profile wrap with serial inflations although the inflation characteristics of polyethylene may change over serial inflations (Penny et al 1989).

The strongest balloon polymer is polyethylene terephthalate, followed by polyolefin copolymer. Because of its intrinsic strength, balloons made from polyethylene terephthalate are thin walled (0.0002 inch) when compared to balloons made from other materials (0.002-0.003 inch). The strength of these balloons allow tough calcified lesions to be dilated with very high inflation pressures of up to 20 bar (Bush et al, 1991; Willard et al, 1991). Polyethylene terephthalate balloons also confer superior conformable properties, and are ideal for treating angulated lesions since they reduce straightening stress and risk of dissection.

Catheter Shaft Technology. The stiffness and size of the shaft, as well as the shaft material, influence the "pushability" (ability to transmit the force applied by the operator to the distal balloon end) and "trackability" (ability to negotiate tortuous anatomy) of the catheter. Catheter shafts are usually made of polyethylene, which is a flexible material providing maximum "trackability", facilitating crossing of tight or occluded lesions especially in tortuous vessels. Polyvinyl chloride shafts are stiffer and provide "pushability" in crossing tight stenoses. Catheters that combine both features are now available with a polyvinyl chloride shaft and a flexible neck behind the balloon.

Fixed-wire dilatation catheters have a single inflation-deflation lumen and have a very low shaft profile, some of which are less than 0.7 mm. These features allow better coronary visualisation during the procedure and enable high grade distal stenoses to be crossed. Over-the-wire dilatation catheters must have a second lumen of sufficient calibre to allow free movement of the guidewire. This allows maintenance of the guidewire across a stenosis and obviates the need to recross the lesion when a larger balloon size is required. The lumens are either eccentrically or concentrically placed. The eccentric design has a larger lumen for the guidewire, therefore allowing distal injection of contrast and measurement of the trans-lesional gradient. These facilities are not available with the concentric design, which is more compact and has a much lower shaft profile.

Guidewire

The original Simpson guidewire was a 0.018 inch Teflon coated wire, to allow free movement in the dilatation catheter and within the coronary tree. Modern guidewires are Teflon, silicon, or microglide coated to enhance the sliding mechanics (ability to move through the guiding catheter and coronary tree). They

are obtainable in diameters ranging from 0.010 to 0.018 inch (0.25 to 0.46 mm), and are specially designed to combine tip softness, radiographic visibility due to the presence of platinum or other heavy metals, and precise torque transmission so that the guidewire can be steered past vascular side branches and tortuous high grade stenotic segments. The 3 essential components of coronary guidewires are: a distal tip weld, which is a smooth surfaced structure that allows the guidewire to travel through the coronary tree avoiding intimal trauma; a flexible spring coil tip that allows for shaping of the guidewire; and a long stiff central core wire that spans the entire length of the guidewire, which at the distal end, undergoes a series of tapered transitions (Figure 1.7). The stiffness of the tip varies depending on whether the stiff wire core extends to the tip (stiff guidewire) or stops 2 to 3 cm short of the tip (floppy guidewire). Stiff guidewires have better axial support and are useful for crossing total occlusions but are liable to damage vascular intima.

Exchange length (300 cm) guidewires are also available to facilitate serial advancement of different size balloons while keeping the guidewire across the stenosis. However, the introduction of extendable guidewires and the monorail system have largely replaced the cumbersome use of extended length guidewires. Other specialised guidewires have been developed for dilating chronic total occlusions (Magnum-Meier system: Meier et al, 1989), or for the predilation of tight stenoses before the balloon catheter is advanced to complete the procedure (dilating guidewire: Rizzo et al, 1989).

(c) ANGIOPLASTY PROCEDURAL GUIDELINES

Patient Preparation

Informed consent must be obtained, including the possible need for emergency coronary bypass surgery. As with most invasive procedures, pre-medication is a matter of personal choice but must be compatible with the possibility of the patient undergoing emergency surgery. Aspirin or other antiplatelet agents must be administered within the previous 12-24 hours to reduce the risk of coronary thrombus formation and peri-procedural myocardial infarction (Barnathan et al, 1987; White et al, 1987a; Schwartz et al, 1988). In the randomised study reported by Mufson et al (1988), there were no differences in ischaemic complications between patients randomised to 80 mg or 1500 mg of aspirin daily starting the day before the procedure. The use of dipyridamole in addition to aspirin is more controversial, with 1 controlled trial showing no added benefit compared to aspirin alone (Lembo et al, 1990). The efficacy of adjunctive dextran has also not been proven, and in fact may occasionally be associated with anaphylactic reactions (Swanson et al, 1984). Although the use of calcium channel blockers and nitrates have not been shown to improve the outcome of angioplasty, these agents are frequently started prior to angioplasty to reduce coronary spasm (Lam et al, 1988; Fischell et al, 1988; Babbit et al, 1988) and to decrease angina (Serruys et al 1983).

Equipment Selection

The selection of the angioplasty equipment and the dilatation strategy will be influenced by individual operator experience, the anatomy of the coronary arteries, the location(s) and morphology of the target lesion(s), the extent of coronary artery disease, and the amount of myocardium placed in jeopardy. Selecting the right equipment is all important in ensuring the best chance of achieving a successful

outcome. Choosing a guiding catheter which provides adequate support especially when dilating tight coronary stenoses, and matching the balloon size to the vessel to reduce the risk of dissection (Roubins et al 1988; Nichols et al 1989) are both critical to the success of the procedure.

Route

The majority of angioplasties are performed from the femoral artery. This route reduces the operators exposure to radiation and is more comfortable for the patient. The brachial artery approach (Dorros et al, 1982) may be preferred in patients with peripheral vascular disease, or when dilating stenoses in shepherd's crook right coronary arteries or other anatomical variants (Timmis, 1990). Some operators routinely insert a venous sheath into the femoral vein for standby ventricular pacing and for rapid administration of drugs.

Anticoagulation

At the start of the procedure, 10,000 units of heparin are routinely administered in order to prevent thrombus formation (Bettman et al, 1987). Further heparin is administered when the procedure is prolonged (Hollman et al, 1983a), or when the anticoagulation level is inadequate, and is monitored by using automated instruments (Hattersley, 1976). The effects of heparin vary considerably from patient to patient and a continuous infusion of heparin throughout the procedure may achieve a more consistent anticoagulation effect (Bull et al, 1975; Rath and Bennett, 1990). In patients with unstable angina, pre-treatment with aspirin and a continuous heparin infusion for 3 to 4 days before angioplasty significantly reduces the likelihood of acute occlusion or angiographically evident mural thrombus (Lukas et al, 1990; Chesebro et al, 1991)

Angioplasty Technique

The guiding catheter is introduced in the coronary ostium and positioned carefully since the large diameter, non-tapered tip, and the relative stiffness increase the risk of ostial injury. However, in high grade stenoses, tortuous arteries, and total occlusions, deep guiding catheter engagement to obtain a stable ostial position may be necessary for adequate support (Carr, 1986). Should catheter wedging and reduction of coronary flow occur, an immediate fall in diastolic pressure will be evident in the pressure tracing recorded from the catheter tip. The resultant pressure tracing, which resembles a recording obtained from the left ventricle, is referred to as being 'ventricularised'. When catheter obstruction results in a further compromise of coronary flow, a drop in both systolic and diastolic pressure occurs and a 'dampened' pressure tracing results (Figure 1.8). If gentle manipulation of the guiding catheter does not resolve the problem, side hole catheters should be used instead. Baseline angiograms are obtained to select the optimal views which allow visualisation of the target stenoses and their relation to side branches. The guiding catheter is than connected to a haemostatic device with side arms (Y-connector). One arm allows continuous monitoring of pressure and the injection of contrast medium through the guiding catheter. The other arm is equipped with a 'Tuohy-Borst' valve through which the dilatation equipment is inserted (Figure 1.9). Fixed-wire systems are advanced directly into the coronary artery. With over-the-wire systems, the steerable guidewire is advanced independently of the dilatation catheter through the target stenosis and into the distal vessel, which then serves as a sliding rail for safe advancement of the dilatation catheter. The position of the dilatation equipment is evaluated using fluoroscopic control and contrast medium injection.

Once the balloon is positioned across the target stenosis, the balloon is inflated progressively until the "waist" of the stenosis is eliminated. The optimal dilatation

pressure is not known, and partly depends on the composition of the stenosis. It has been suggested that higher balloon dilatation pressures are associated with improved haemodynamic outcome (Meier et al, 1984a), but animal studies have shown that vessels exposed to high inflation pressure have a significantly higher incidence of mural thrombus, dissection, and medial necrosis when compared with low inflation pressure (Sarembock et al, 1989). Furthermore, if the burst pressure of the balloon is exceeded, rupture of the balloon catheter in the coronary artery can lead to extensive coronary dissection and rupture. The optimal duration of inflation is still a subject of continued research although inflation periods of 30 to 120 seconds may be more effective than short inflations of 10-15 seconds (Kaltenbach et al, 1984). Furthermore, prolonged inflation periods of over 15 minutes using a perfusion balloon catheter may result in further improvement of success rate but needs prospective evaluation (Tenaglia et al, 1992). A progressive approach towards coronary dilatation using balloons of incremental size may also reduce angioplasty complications (Banka et al, 1993).

Balloon angioplasty of stenoses involving bifurcation of coronary arteries carries a significant risk of permanent occlusion of the branches, especially if the side branch has pre-existing ostial narrowing by extension of plaque from the primary vessel (Meier et al, 1984b; Vetrovec et al, 1985). Side branch occlusion occurs because of the snow-plow effect (in which plaque from the primary vessel is literally plowed into the side branch during dilatation), spasm caused by mechanical irritation of the origin of the side branch, dissection of the primary vessel, or embolisation of thrombus. To protect side branches, especially if they supply significant regional myocardium and would otherwise be bypassed surgically, an additional guidewire is positioned in the side branch at risk ("kissing-wire" technique), and can be used to reopen the vessel if acute closure occurs (Zack and Ischinger, 1984; Pinkerton et al,

1985). Alternatively, 2 balloon catheters, passed through a single or separate guiding catheters ("kissing-balloon" technique), may be inflated sequentially or simultaneously in the main vessel and the side branch to dilate the bifurcation stenosis (Meier et al 1984b; George et al, 1986; Thomas and Williams, 1988; Myler et al, 1989a).

Post-procedural Management

Once an adequate angiographic result is obtained, the balloon catheter and guidewire are all withdrawn into the guiding catheter. The femoral sheaths are usually removed about 4 to 8 hours after the procedure when the heparin wears off spontaneously, or left in place overnight if substantial intimal dissection is evident on the post-angioplasty films. Some recommend routine infusion of heparin for 24 hours after the procedure to prevent thrombus formation at the site of dilatation which can result in acute coronary occlusion (Chesebro et al, 1987a; Gabliani et al, 1988; McGarry et al, 1992). Others suggest that such infusion should be given only when the procedure is complicated by coronary artery dissection (Bredlau et al, 1985a).

1.3 MECHANISM OF BALLOON DILATATION

Despite the therapeutic success of coronary balloon angioplasty, the exact mechanism or mechanisms by which balloon angioplasty improves vessel patency remains unsettled. In their original description, Dotter and Judkins (1964) attributed the mechanism of enlargement of the vessel lumen following transluminal peripheral artery angioplasty to redistribution and compression of intimal atherosclerotic plaque. The concept was universally accepted and supported by Grüntzig (Leu and Gruentzig, 1978; Lee et al, 1980). It was data from experimental studies of transluminal angioplasty in normal animal arteries and in atherosclerotic rabbit models, from angioplasty performed in cadaveric human hearts, from pathological specimens studied after successful angioplasty in human femoral and coronary arteries, and from *in vivo* studies that have helped to delineate the mechanism of angioplasty.

(a) NORMAL ANIMAL ARTERIES

Casteneda-Zuniga et al (1980) argued that since atheromatous material is a solid or sometimes a semiliquid, it is basically incompressible unless empty spaces are present within the atheroma, something which is not found histologically. Furthermore, redistribution of atheromatous material would result in an elongation of the lesion since no material is removed, a phenomenon which has not been observed. In a series of experiments involving balloon inflations in the arteries of dogs and cadavers, Castaneda-Zuniga et al (1980) demonstrated that cracking, dehiscence, and stretching of the intima and media occurred during dilatation, which healed by the formation of a neointima and scar tissue. Using scanning electron microscopy, Pasternak et al (1980) showed that balloon angioplasty of

normal canine coronary arteries caused extensive endothelial denudation, with immediate dense platelet adhesion to the subendothelial matrix and thrombus formation. Similar arterial changes and platelet deposition was also reported by Steele et al (1985) in normal porcine common carotid arteries. These platelets have the ability to release potent vasoconstricting substances (Ellis et al, 1976; Moncada et al, 1979; Vanhoutte and Houston, 1985), causing localised vasoconstriction that may complicate an angioplasty procedure (Cowley et al, 1984a; Steele et al 1985). The correlation *in vivo* between the degree of platelet deposition, and the extent of arterial wall injury and vasoconstriction was first reported by Lam et al (1987) in a porcine preparation, where a reduction of platelet deposition and vasoconstriction by aspirin therapy were also demonstrated.

(b) ATHEROSCLEROTIC RABBIT MODELS

Although the "atherosclerotic" plaques in rabbits are composed of foam cells and differ in composition from human plaques, the pathological changes induced by angioplasty are almost identical to those seen in human coronary arteries. The morphological changes of an *in vivo* atherosclerotic lesion in response to angioplasty was first studied by Block et al (1980). Aorto-iliac stenoses were dilated in hypercholesterolaemic rabbit models of atherosclerosis, and denudation of endothelial cells and deposition of a layer of platelets enmeshed in fibrin were demonstrated. Faxon et al (1982) showed that the degree of fracture in the intima and media were most marked in rabbits with the greatest angiographic involvement. Using the same animal model, Sanborn et al (1983) suggested that the major mechanism of successful transluminal angioplasty is stretching of the vessel, resulting in localised aneurysm formation. Again, intimal and medial compression were not seen in any of these experiments. The early accumulation of platelets after

angioplasty was also demonstrated using ^{51}Cr-labelled platelets, and the degree of deposition was correlated to the extent of dissection (Wilentz et al, 1987).

(c) HUMAN CADAVERIC STUDIES

As early as 1980, Lee et al (1980) described 6 different types of histological changes observed after coronary angioplasty of human cadaver hearts. These included intimal disruption, derangement and disturbance of the components within the tunica media, stretching of the adventitia, and atheroma compression. Furthermore, vessel rupture occurred when dilatation beyond normal coronary diameter was attempted. Similar pathological changes were also described by Freudenberg et al (1981), including atheroma compression. Baughman et al (1981) studied the effect of coronary angioplasty in twelve autopsy human hearts and demonstrated mural disruption with intimal or medial tears, especially in arteries with atherosclerosis and calcification. However, no plaque compression was observed. The relative contribution of these factors towards arterial enlargement during transluminal coronary angioplasty was quantitatively examined by Kinney et al (1984). A series of mechanical tests were conducted on both normal and atherosclerotic artery necropsy specimens. They showed that the majority of the increase in lumen area was due to plaque and arterial disruption, and content extrusion of fluid from the plaque accounted for only 6-12% of the overall lumen area changes.

(d) HUMAN AUTOPSY STUDIES AFTER *IN VIVO* ANGIOPLASTY

Attempts to extrapolate findings from animal models of atherosclerosis and post-mortem tissue to the mechanism of clinically successful angioplasty have been

subjected to the criticism that these tissue may respond differently to angioplasty. Lesions in animal models consist mainly of foamy macrophages and may dilate differently from human lesions, which consist of a heterogeneous combination of cholesterol crystals, fibrous and smooth muscle cells, calcium deposits and thrombotic material. In addition, cadaveric human hearts used to study mechanisms of plaque dilation do not represent the actual physiologic state and therefore may not accurately reflect processes that occur *in vivo* during angioplasty. However, histological sections of human arteries that were studied after successful *in vivo* angioplasty have shown changes similar to those seen in animal models and in human post-mortem coronary specimens.

Pathological Changes in Native Coronary Arteries

The first of such studies was reported by Block et al (1981), who described the pathological changes in 2 patients who died after percutaneous transluminal coronary angioplasty and emergency coronary bypass surgery. Microscopic sections of the left anterior descending artery at the site of angioplasty were obtained in both patients. In 1 patient, the histological sections showed endothelium disruption and splitting of the atheromatous plaque extending into the media. The split was infiltrated with a dissecting haematoma which extended distally from the site of angioplasty. In the second patient, the histological sections showed a split in the thinnest portion of a fibrous atherosclerotic plaque extending into the media with circumferential extension.

The next study came from Mizuno et al (1984), who reported on a patient who died immediately after percutaneous transluminal coronary angioplasty of the left anterior descending artery. Serial histological sections of the treated artery showed intimal and medial splitting, desquamation, and plaque fracture. The untreated

atherosclerotic lesion in the circumflex artery did not reveal any of these histological changes. Similar changes were also described by Soward et al (1985), de Morais et al (1986), and Kohchi et al (1987). The first coronary artery rupture during coronary angioplasty was reported by Saffitz et al (1983), when a balloon larger than the artery was used in a small, rigid calcified right coronary artery. Histological examination showed an atherosclerotic split which extended through the media and adventitia with through-and-through rupture, and occurred opposite a large calcified plaque.

Pathological Changes in Saphenous Vein Grafts

The first report on the morphological changes induced by coronary angioplasty in a saphenous vein aortocoronary bypass graft was by Famularo et al (1983). They described a patient who underwent emergency coronary bypass surgery after an unsuccessful left anterior descending saphenous graft coronary angioplasty. The occluded graft was resected during surgery and microscopic analysis revealed intimal disruption, medial splitting, haemorrhage and dissection into the subadventitia space.

Pathological Changes During Acute Myocardial Infarction

The spectrum of pathology associated with coronary angioplasty during acute myocardial infarction was reported by Colavita et al (1986). They reported on 4 patients who died within 4 days of the procedure. The histological changes observed included intimal haemorrhage, plaque disruption, distal embolisation of plaque elements, and thrombotic occlusion of the coronary artery. These changes were no different from those described in association with elective angioplasty, but may also occur in patients with acute myocardial infarction who have not undergone coronary angioplasty (Davies and Thomas, 1985). In the same year, Düber et al (1986)

reported morphological findings in 6 patients who died 8-52 days after combined thrombolysis and coronary angioplasty for acute myocardial infarction. Again, the predominant findings were intimal splitting, subintimal dissection, medial tears, and submedial dissection. In addition, gaps were found between the ruptured intimal and medial flaps, with patch necrosis of the smooth muscle cells along the whole circumference of the arterial wall. These changes were interpreted as evidence for plastic deformation of the media and adventitia necessary for permanent luminal extension after coronary angioplasty.

The above studies suggest that rupture of the inner portion of the arterial wall, and stretching of the outer arterial diameter (ie formation of an aneurysm) appear to be inevitable and necessary events during successful angioplasty. However, apart from the report by Mizuno et al (1984), most of these studies did not include comparison of the coronary angioplasty treated vessel with control, that is, vessels not treated with coronary angioplasty. Many of the pathological changes described after coronary angioplasty have also been observed in post-mortem coronary arteries which have not been treated by angioplasty (Isner and Fortin, 1982). This, in conjunction with the fact that improved vessel patency after angioplasty may also be seen in the absence of these pathological changes, precludes firm assurance that such changes are the sole basis for successful angioplasty.

(e) *IN VIVO* STUDIES IN HUMANS

Although animal models, human cadaveric studies, and autopsy findings after angioplasty have all provided information about the mechanism of angioplasty, *in vivo* data concerning the mechanisms of lesion dilation are lacking. In truth, the histological appearance of coronary arteries after angioplasty represents the result

rather than the mechanism of coronary lumen dilation. The actual mechanism of coronary angioplasty can be truly ascertained only by *in vivo* studies in humans as they are undergoing the procedure.

Jain et al (1987) measured the pressure-volume relation of the balloon catheter while it is inflated across the coronary stenosis, and described 3 patterns of plaque dilation, each of which predominate in different coronary lesions. The first pattern was stretching of the plaque, in much the same way as Silastic tubing stretches. After dilation, these plaques would recoil and required several inflations to achieve adequate dilation. The second pattern showed small incremental 'jumps' in the pressure-volume curve, in much the same way that Styrofoam would be expected to dilate if the stenosis was made of this substance. This was believed to reflect progressive compaction of the lesion. The third pattern was sudden yielding of the balloon at a given inflation pressure. This form of plaque dilation was compared to the yielding of uncooked macaroni, and was found angiographically to be associated with dissection of the artery at the site of the angioplasty.

Hjemdahl-Monsen et al (1990) used quantitative angiographic techniques to measure the degree of expansion of angioplasty balloons across lesions at incremental pressures, and compared these with the diameter of the lesion before and after angioplasty. These measurements provided a means to quantify the relative 'distensibility' of a coronary lesion and the extent of elastic recoil immediately after angioplasty. It was found that eccentric irregular lesions tended to dilate more fully at low pressures than did non-eccentric irregular lesions, probably as a result of the differences in plaque composition. Furthermore, lesions that were most easily distensible exhibited greater elastic recoil after angioplasty, suggesting that an arc of normal wall was stretched by the balloon and recoiled after deflation. The greatest

degree of correlation between extent of inflation and elastic recoil was for eccentric irregular lesions. This supports the hypothesis that some of the dilation of a coronary lesion can be related to stretching of plaque-free wall segments of eccentric atherosclerotic lesions (Saner et al, 1985; Waller, 1985). The gradual relaxation of this overstretched segment (elastic recoil) may account for the early restenosis seen after initially successful dilatation (Waller, 1989a).

1.4 CLINICAL RESULTS OF CORONARY ANGIOPLASTY

(a) ASSESSMENT OF ANGIOPLASTY SUCCESS

The optimal method of assessing immediate angioplasty success has not been established. The adequacy of the dilatation is assessed either by angiographic evaluation, or by the measurement of the trans-stenotic pressure gradient (measured between the tip of the balloon catheter distal to the stenosis and the tip of the guiding catheter), both of which have been correlated with regional myocardial perfusion using thallium scintigraphy (MacIsaac et al, 1989). Early definitions of angioplasty success required a reduction in the trans-stenotic pressure gradient in addition to improvement in angiographic stenosis severity (Grüntzig et al, 1979; Myler et al, 1987).

Trans-stenotic Gradient Assessment

Although trans-stenotic gradient appears to be a more objective assessment of the adequacy of dilatation, the measurement is complicated by the presence of the dilatation catheter within the stenotic lumen and the small size of the dilatation catheter lumen (Leiboff et al 1983; Busch et al, 1983), and is probably no better than angiographic assessment of the residual stenosis (MacIssac et al 1989). The trans-stenotic gradient is proportional to the fourth power of stenosis with diameter stenosis of up to 60%, but becomes dampened and relatively constant with diameter stenosis of 60% or higher (Anderson et al 1986). The pressure gradient across the stenosis is overestimated in a predictable manner, and is dependent on the ratio of the dilatation catheter diameter to the stenosis diameter (Leiboff et al 1983). With successful angioplasty, although the reduction in pressure gradient and the diameter

stenosis are not linearly related, it is considered a useful indicator of angioplasty outcome (Anderson et al, 1986).

Angiographic Assessment

The current angiographic technique of assessing angiographic success routinely employs visual, calliper, or computer-assisted digital quantitative determination of the residual percent diameter lumen narrowing. According to Poiseuilles's law, a relatively small increase in luminal diameter will result in a significant increase in coronary blood flow. Therefore, early definitions of angiographic success only required a reduction in stenosis severity of 10% to 20% of the normal luminal diameter (Grüntzig et al, 1979; Faxon et al, 1984a), and remains the definition used by the National Heart, Lung, and Blood Institute (Detre et al, 1988). The guidelines published by the American College of Cardiology/American Heart Association defined angiographic success as a ≥20% change in luminal diameter, with the final diameter stenosis <50% (Ryan et al, 1988).

Although the clinical value of contrast coronary cineangiography is well established (Ringqvist et al, 1983), it provides inadequate information about the physiological importance of an obstructive lesion (Klocke, 1983; White et al, 1984; Vogel, 1985), and is prone to inter-observer and intra-observer variations (Zir et al 1976; DeRouen et al 1977; de Cesare et al 1992). Furthermore, immediately after coronary angioplasty, assessment of residual stenosis with both visual and quantitative methods is hampered by lesion eccentricity, and poor luminal definition owing to the diverse angiographic appearances produced by balloon inflation including intimal disruption and perivascular oedema (Holmes et al, 1983; Serruys et al, 1984; Sanz et al, 1987; Katritsis et al, 1988a). These limitations, coupled with the fact that the percent diameter stenosis is only 1 of several factors that

influence the physiological significance of flow resistance and pressure gradient across a given stenosis (Houghton et al, 1990), prompted several investigators to seek other methods of assessing the severity of coronary artery stenosis.

Coronary Flow Reserve Assessment

Animal studies have shown that flow distal to the stenosis remains normal until a critical degree of stenosis (about 80% to 95% reduction in luminal area) is reached (Gould et al, 1974; Elzinga et al, 1975; Furuse et al, 1975; Feldman et al, 1978). Flow is maintained at normal levels by autoregulatory vasodilatation of the distal vascular bed, which enhances the pressure gradient and maintains driving pressure. These findings have also been shown in patients with single vessel coronary artery disease by Nichols et al (1986). They reported that distal regional myocardial blood flow was normal with stenotic lesions ranging from 19% to 84% cross sectional-area reduction, and only decreased when the minimum area was less than 0.8 mm^2, or when area reduction was >85%. Measurement of the coronary flow reserve, which is defined as the ratio of regional blood flow during hyperaemia to regional blood flow during basal conditions (Zijlstra et al, 1988), has therefore been proposed as a better method to evaluate the haemodynamic repercussions of a coronary stenosis (Klocke, 1983; Hoffman, 1984).

Three techniques have been developed to measure regional coronary flow reserve during cardiac catheterisation. The first method is an indicator dilution technique using a platinum-tipped angioplasty guidewire with hydrogen as the indicator (Vogel et al, 1987). The second technique is based on the digitised cineangiographic assessment of myocardial contrast appearance time and density in the resting and hyperaemic state, induced either by contrast agent (O'Neill et al, 1984) or by intra-coronary bolus injection of papaverine (Zijlstra et al, 1988). The third technique

utilises a pulsed-Doppler coronary artery catheter that can measure intra-coronary flow velocity (Wilson et al, 1985; Sibley et al, 1986; Serruys et al, 1988a). Intra-coronary flow velocity during the reactive hyperaemia that occurs immediately after dilatation can be used to calculate an index of coronary flow reserve (Serruys et al, 1988a). Ofili et al (1993) recently reported the use of a 12-MHz Doppler transducer mounted on a 0.018 inch angioplasty guidewire, which allows both proximal and distal coronary flow velocity to be determined. They demonstrated that significant increase in the coronary artery flow velocity, with restoration of a predominant diastolic flow pattern, occurred after endoluminal enlargement with coronary angioplasty and results in a reduction of proximal/distal flow velocity ratio.

These methods are expensive, time consuming, not widely available, and impractical for routine clinical use. Since determination of coronary narrowing by calliper techniques is a readily available methodology that correlates closely with sophisticated computer quantitative methods, it is likely to remain the main objective method of assessing the angiographic result of coronary angioplasty.

(b) ACUTE SUCCESS OF CORONARY ANGIOPLASTY

Early Experience

After Grüntzig's first described case, 50 patients were treated over the subsequent 18 months, with an angiographic success rate of 64% (defined as a reduction in stenosis severity of at least 10%). The mean trans-stenotic gradient was reduced from 58 mmHg to 19 mmHg, and the mean stenosis severity reduced from 84% to 32%. In total, 29 of 46 native coronary arteries and 5 of 7 saphenous vein stenoses were successfully dilated. He concluded that patients with single-vessel disease appear to be most suitable for the procedure (Grüntzig et al, 1979). The technique

was introduced in the United States and several centres started to perform percutaneous transluminal coronary angioplasty (Gruentzig et al, 1978; Stertzer et al, 1979).

During this early period, the success rates achieved ranged from 50% to 66% depending on the definition of angiographic success, and incidence of major complication was up to 14% (Stertzer et al, 1979; Cowley et al, 1981; Alford et al, 1982; Faxon et al, 1984a) (Table 1.1). The procedures were performed with non-steerable systems which did not allow directional control of the dilatation catheter. Early guiding catheters were 9.4 Fr and made of solid Teflon, a material with poor memory and torque control. Many of the initial angioplasty failures were due to the inability to cannulate the target artery with these guiding catheters (Myler et al, 1983). The first publication from the American National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry reported data collected form 34 centres in the United States and Europe. In the first 631 patients enrolled into the registry, the procedure was successful in 59% of 663 vessels dilated (defined as >20% decrease of coronary stenosis). The incidence of emergency coronary bypass surgery was 6%, myocardial infarction was 4%, and in-hospital death was 1% (Kent et al, 1982). The complete National Heart, Lung, and Blood Institute registry (1977-1981) recruited 3,079 patients from 105 participating centres. The angiographic success rate achieved was 67% of 3341 coronary lesions attempted (Faxon et al, 1984a), with an incidence of mortality of 0.9%, myocardial infarction of 5.5%, and emergency coronary bypass surgery of 6.6% (Cowley et al, 1984b, Dorros et al, 1984a). The most common cause of angioplasty failure was the inability to cross the stenosis with the balloon catheter (23%) and inadequate dilatation of the stenosis (8%) (Kelsey et al, 1984).

Impact of New Technology

With the introduction of newer multilayer guiding catheters, independent steerable guidewires (Simpson et al, 1981), and low profile dilatation catheters, the angioplasty success rate dramatically improved. Grüntzig et al (Gruentzig and Hollman, 1982) significantly increased their success rate from 89% to 94% using the steerable guidewire system.

The impact of catheter design on single-vessel coronary angioplasty was also studied in 2,969 patients by Anderson et al (1985). They reported that the introduction of the steerable catheter system was accompanied by improvement in the primary success rate of right coronary artery dilatation from 78% to 88%, and left anterior descending artery dilatation from 90% to 94%. The significant differences in ability to reach and cross lesions among the 3 major coronary arteries also vanished. Furthermore, the incidence of acute complications and the percentage of coronary angioplasty attempts on the left anterior descending artery declined during the same period (Anderson et al, 1985; Bredlau et al, 1985b).

Similar improvement in success rate and changing patterns in coronary angioplasty were also demonstrated in 2677 patients by Tuzcu et al (1989). The primary success rate increased from 73% to 94% after the introduction of steerable catheter systems, although the introduction of low-profile systems did not contribute to any further improvement. In addition, an increasing number of elderly patients, patients with class III or IV angina, distal stenosis, high grade stenosis (90% to 99%), and totally occluded arteries were attempted.

The report from the "second generation" National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry (1985-1986) confirmed the

expanded indications for this procedure and documented the improved success rate in spite of the increased complexity of cases (Detre et al, 1988). Compared to the old National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry (1977-1981), the new-registry patients were older and had a significantly higher proportion of multivessel disease, poor left ventricular function, previous myocardial infarction, and previous coronary bypass surgery. The new-registry also had more complex coronary lesions and angioplasty attempts involve more multivessel procedures. Despite these differences, angiographic success rate per lesion improved from 67% to 88% and clinical success rate (angiographic success in all lesions attempted without death, myocardial infarction, or coronary bypass surgery) from 61% to 78%.

Impact of Operator Experience

The impact of operator experience on the success of coronary angioplasty has also been assessed. A report from the early National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry (1977-1981), which enrolled patients that were treated with non-steerable balloon catheters, revealed that operators who had performed fewer than 50 cases had an angiographic success rate of 55%. However, operators who had performed at least 150 procedures achieved a success rate of 77% (Kelsey et al, 1984). This could be attributed to either better patient selection by the operator or improved skills of the operator.

Meier et al (1984c) also improved their success rate from 63% for the first 30 cases to 79% for the following 58 cases using a non-steerable catheter system. Levin et al (1985) also reported a learning curve with steerable catheter systems, achieving a success rate of 65% in the first 20 cases but 81% for the following 80 cases. Similar improvement in success rates with higher frequency operators was also shown by

Finci et al (1987b). Hamad et al (1988) reported that while low frequency operators performed coronary angioplasty of "simple lesions" with satisfactory results, outcomes with "complex lesions" were better in more experienced hands. In contrast, Harston et al (1986) reported that with the steerable catheter system, high success rates could be achieved even in inexperienced hands without any learning curve. In support of this, Jacob et al (1986) did not find any difference in the success rates between operators who performed 2 or less coronary angioplasties per month and those who performed more than 2 per month.

(c) ACUTE COMPLICATIONS OF CORONARY ANGIOPLASTY

Incidence

In Grüntzig's first 50 cases, of the 18 patients with unsuccessful angioplasty, 7 patients required coronary artery bypass surgery within 24 hours of the procedure, and 10 within 4 weeks. Three patients developed electrocardiographic evidence of acute myocardial infarction. There were no procedure-related deaths (Grüntzig et al, 1979).

The first report of complications from the National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry (1977-81) cited in-hospital deaths, non-fatal myocardial infarction, and emergency coronary bypass grafting as the major complications of coronary angioplasty, and occurred in 9.2% of patients (Dorros et al, 1983). Other complications that were reported included prolonged angina (8.1%), acute coronary occlusion (4.7%), coronary dissection (2.9%), coronary artery spasm (4.2%), and neurological events (0.3%). Vascular complications at the catheter insertion site in the femoral or brachial artery occurred in 1.5% of patients. In the recent "second generation" National Heart, Lung, and

Blood Institute percutaneous transluminal coronary angioplasty registry (1985-1986), at least 1 major complication occurred in 7.2% of patients. Despite a higher incidence of older patients with multivessel disease, a higher incidence of prior bypass surgery, and more left ventricular dysfunction, the overall complication rates were not significantly different from those in the old registry although the incidence of emergency coronary bypass surgery decreased significantly from 5.8% to 3.5%, and coronary spasm decreased significantly from 5.0% to 1.3% (Holmes et al, 1988a). These results clearly demonstrate that advances in technology and operator experience over the past decade have resulted in the use of coronary angioplasty in anatomic situations and patient groups previously considered unsuitable for such intervention.

Other studies have reported procedure-related mortality rates ranging from 0% to 3% (Mata et al, 1985; Levin et al, 1985; de Feyter et al, 1990), myocardial infarction rates ranging from 0.9% to 11% (Cowley et al, 1984a; Disciascio et al, 1988; Vandormael et al, 1991), and emergency coronary bypass surgery rates ranging from 0% to 14% (Alford et al, 1982; Mata et al, 1985; Ernst et al, 1987a) (Table 1.2).

Mechanism of Acute Ischaemic Complications

The ischaemic complications encountered during coronary angioplasty arose frequently as a result of acute occlusion of the coronary artery being dilated, of which the reported incidence ranged from 2.1% to 14.1% (Hollman et al, 1983; Sugrue et al, 1986; Myler et al, 1987; Sinclair et al, 1988; Ellis et al, 1988). The proposed mechanisms responsible for acute vessel occlusion include intimal dissection, thrombus formation, and arterial spasm (Baim and Ignatius, 1988). Shiu et al (1985) reported acute vessel occlusion in 20 of 240 procedures (8%), and

attributed the mechanism to arterial dissection in 6 cases, coronary thrombosis in 4, and persisting arterial spasm in 7. However, definite establishment of the aetiology is confounded by the lack of adequate angiographic distinction between thrombus and dissection, and methods for decision making under these circumstances are relatively crude. In an angiographic study of 109 patients with abrupt vessel closure, Lincoff et al (1992) diagnosed dissection in 28% of patients, thrombus in 20% of patients, a combination of thrombus and dissection in 7% of patients, and were unable to determine the mechanism of acute closure in 45% of patients.

Intimal Dissection. Spasm or thrombus formation is very rarely the principal cause of abrupt closure and typically, the inciting event is a complex dissection with intimal flap formation. Although coronary angioplasty results in an angiographically visible dissection in 20% to 45% of vessels dilated, ischaemic complications occurs in only 4% to 11% of cases (Marquis et al, 1984; Ellis et al, 1988; Ryan et al, 1988; Detre et al, 1990), and may be more common in certain morphological types of dissection defined according to the National Heart, Lung, and Blood Institute criteria (Dorros et al, 1983; Guiteras et al, 1987a; Huber et al, 1991).

Thrombus Formation. Schofer et al (1982) reported 3 patients in whom acute coronary occlusions were successfully treated with intra-coronary infusion of streptokinase, thus suggesting that the occlusion was caused by acute thrombosis. Gulba et al (1990) reported acute thrombotic occlusion in 6% of 447 patients who underwent single vessel angioplasty. Acute thrombotic occlusion was diagnosed if an intraluminal filling defect, or a slowly progressing structure surrounded by contrast medium that finally completely obstructed the vessel lumen, was present. The combination of intra-coronary recombinant tissue-type plasminogen activator

and repeat mild balloon inflations successfully reopened the vessel in 81.5% of patients.

Coronary Spasm. Hollman et al (1983a) reported acute vessel occlusion in 20 of 935 patients who underwent initially successful coronary angioplasty. Eight patients responded to nifedipine or nitrates given via sublingual or intra-coronary route, and in 3 patients, no further invasive therapy were necessary. They concluded that coronary arterial spasm may play an important role in acute vessel occlusion.

Predictors of Acute Ischaemic Complications

Multiple clinical-, angiographic-, and procedure-related variables have been associated with a heightened risk of acute ischaemic complications although conflicting results have been reported. In the recent "second generation" National Heart, Lung, and Blood percutaneous transluminal coronary angioplasty registry study (1985-1986), increased ischaemic complications were associated with severe stenosis of ≥90%, diffuse or multiple discrete disease, presence of thrombus, collateral flow from the lesion, inoperable or high risk status for surgery, recent onset angina, and multivessel coronary artery disease (Detre et al, 1990). Ellis et al (1988) reviewed the Emory University experience of 4772 angioplasty procedures, and identified post-angioplasty residual stenosis, dissection, branch point location, fixed bend point location, other stenoses in the dilated vessel, and prolonged post-angioplasty use of heparin as independent predictors of ischaemic complications. de Feyter et al (1991) reported the Thoraxcentre experience of 1423 consecutive patients, and identified presentation with unstable angina, multivessel disease, and complex lesion as independent predictors of acute vessel closure. Myler et al (1992) reviewed the San Francisco Heart Institute experience and found the presence of thrombus to be the only significant predictor of ischaemic complications.

Other variables that have been identified as predictors of ischaemic complications include **age** (Holmes et al, 1988a; Simpfendorfer et al, 1988), **female gender** (Cowley et al, 1984a; Ellis et al, 1988; Holmes et al, 1988a), **right coronary artery location** (Cowley et al, 1984a; Hermans et al, 1992a), **ostial location** (Topol et al, 1987), **lesion length** (Meier et al, 1983; Ellis and Topol, 1990), **lesion eccentricity** (Meier et al, 1983), **diffuse disease** (Cowley et al, 1984a), **irregular lumen edges** (Ischinger et al, 1986), **intraluminal lucencies** (Ischinger et al, 1986), and **balloon to artery ratio** (Roubin et al, 1988; Nichols et al, 1989).

In response to these observations, the American College of Cardiology/American Heart Association Task Force has proposed an ABC classification scheme based on the morphological characteristics of lesions for estimating the likelihood of acute procedural success and complications (Ryan et al, 1988). According to this classification, lesions are categorised as type A, B, or C depending on their morphological characteristics (Table 1.3). Each category is ascribed an estimated probability of success and risk of complication. Both Ellis et al (1990a) and Myler et al (1992) employed a modification of this system to stratify a patient's risk for complication more adequately following angioplasty. Lesions with a single type B or C characteristic were designated type B1 or C1, respectively. Those lesions with multiple B or C characteristics were designated type B2 or C2, respectively. These lesion classification schemes have assisted operators in selecting appropriate patients for the procedure. However, with the dramatic advances made in angioplasty technology and technique, their validity have been questioned (Faxon et al, 1992a).

Management Of Acute Vessel Occlusion

Traditionally, emergency coronary bypass surgery is recommended for the treatment of acute coronary occlusion to minimise myocardial damage (Murphy et al, 1982).

Coronary artery bypass surgery for failed angioplasty has been associated with relatively low morbidity and mortality, especially when cardiogenic shock is not present pre-operatively (Cowley et al, 1984b; Reul et al, 1984; Killen et al, 1985; Parsonnet et al, 1988). The recent development of several new innovative methods to deal with acute vessel occlusion has improved the safety of coronary angioplasty. The most frequently practised approaches are redilatation with balloon angioplasty and intra-coronary stenting.

Redilatation. A standard approach, which has evolved empirically to "tack-up" the tear, is the use of prolonged inflations with the same size balloon or a larger balloon dilatation catheter at low pressure (Hollman et al, 1983a, Marquis et al, 1984; Bredlau et al, 1985a; Simpfendorfer et al, 1987). This strategy can successfully restore arterial patency in 36% to 56% of cases, and has resulted in the decline in the incidence of emergency coronary bypass surgery observed in some series (Holmes et al, 1988a; Steffenino et al, 1988). In the collective experience of the National Heart, Lung, and Blood percutaneous transluminal coronary angioplasty registry, 49% of patients who suffered peri-procedural occlusion were managed with successful redilatation (Holmes et al, 1988a). Sinclair et al (1988) reported that it was possible to redilate and stabilise antegrade flow in 51% of patients in whom this manoeuvre was attempted. Tenaglia et al (1993) reported successful reopening of abrupt closure in 58% of patients with redilatation. However, they have shown that the long-term adverse events are increased in patients with successfully treated abrupt closure by redilatation compared to those without abrupt closure.

Autoperfusion Balloon Catheter. The autoperfusion balloon catheters allow maintenance of flow to the distal myocardial bed during prolonged inflations, thus reducing myocardial ischaemia (Hinohara et al, 1986; Werter et al, 1988; Sundram

et al, 1989). Leitschuh et al (1991) reported the outcome of prolonged inflations with perfusion balloon catheters in 36 patients with major dissection, and compared the results with those of historical control subjects with similar dissections before the availability of perfusion balloons. Total inflation time was 11.3 minutes over 5.8 inflations for conventional balloon treatment versus 25.9 minutes over 6.5 inflations for perfusion balloon patients, whose mean perfusion balloon time was 18.2 minutes. Angiographic success was 84% in the perfusion balloon group versus 62% in the conventional group ($p<0.05$). The complication rate was also lower in the perfusion balloon group, with 78% remaining free of major adverse events versus 48% in the conventional group ($p=0.014$). Jackman et al (1992) recently reported the outcome, after prolonged balloon inflation of over 20 minutes, in 40 patients with unsuccessful angioplasty despite aggressive angioplasty efforts. Procedural success was achieved in 80% of patients, and improvement in the appearance of filling defects or dissections occurred in 48% of patients. These results suggest that prolonged inflations should be attempted before consideration of bypass grafting or stenting. Van der Linden et al (1993) reported the use of very long inflations (>30 minutes) of an autoperfusion catheter outside the cardiac catheterisation laboratory in 35 patients with refractory acute occlusion. Although the mean duration of dilation was 17 hours, the overall success rate achieved was only 57%, indicating that further prolongation of inflation time of the perfusion balloon to several hours conveyed no additional advantage.

Intra-coronary Stenting. All the intra-coronary stents now under investigation have been shown to be effective in treating acute or threatened vessel closure, including the Medinvent wall stent, Palmaz-Schatz stent, Gianturco-Roubin stent, Strecker stent, and the Wiktor stent (Sigwart et al, 1988; Haude et al, 1991; Roubin et al, 1992; Reifart et al, 1992b; Kiemeneij et al, 1993; Maiello et al,

1993). Within the setting of failed angioplasty, the major drawback of intra-coronary stenting has been the potential for thrombosis. Within such a setting, Herrmann et al (1992) reported a 17% subacute thrombotic event rate for emergency stenting. Vigorous peri- and post-procedural anticoagulation regimens are therefore necessary, which can result in peripheral vascular complications. The **GRACE** trial (Ginaturco Roubin Stent Acute Closure Evaluation), a prospective, randomised trial comparing the immediate and long-term efficacy of bailout stenting, using the Gianturco-Roubin stent with long balloon inflation or other interventional devices, is currently in progress. Results from this trial are eagerly awaited.

Other Therapeutic Strategies. Other reported therapeutic strategies for acute vessel occlusion include laser balloon angioplasty (Jenkins and Spears, 1990), directional coronary atherectomy (Maynar et al, 1989; Lee et al, 1990; Warner et al, 1991; Webb et al, 1992), and the use of intra-aortic balloon pumps (Murphy et al, 1982). Although reducing the need for emergency coronary artery bypass surgery is clearly desirable, none of these strategies is likely to obviate the absolute requirement for back-up, emergency surgical revascularisation.

(d) LONG-TERM RESULTS OF CORONARY ANGIOPLASTY

Patients who underwent coronary angioplasty in the early experience, reflected the selection criteria that Grüntzig applied, which was heavily influenced by the capability of the equipment available at that time. The majority of the patients underwent single-vessel dilatation, usually involving the left anterior descending coronary artery. Although angioplasty has been expanded to more complex patient

subsets in many high volume centres, many operators continue to limit themselves to lesions similar to those originally described by Grüntzig.

Early Experience

The 10-year follow-up data of Grüntzig's original 169 patients treated in Zurich, was recently reported by King and Schlumpf (1993). Single vessel disease was present in 58% of patients, and multivessel disease in 42%. Of the 133 patients who underwent successful angioplasty, the 10-year survival rate was 89.5% for all patients, 95% among patients with single-vessel disease and 81% among those with multivessel disease. Freedom from a cardiac event (death, myocardial infarction or coronary bypass surgery) was 65% for all 133 patients, 74% among patients with single vessel disease and 52% among those with multivessel disease. Furthermore, patients with single vessel disease were less likely to have bypass surgery and were more likely to be angina free at follow-up than were patients with multivessel disease.

The long-term efficacy of coronary angioplasty was also evaluated in a subgroup of 2,272 patients at 65 centres enrolled into the early National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry (1977-1981). All patients were followed for 1 year but few patients beyond 2 years. Within 12 months of successful angioplasty in 1397 patients, 1.6% died, 3% had a myocardial infarction, 12% had coronary artery bypass surgery, and 14% had repeat coronary angioplasty (Kent et al, 1984). The annual mortality rate was $<1\%$ per year in patients with single vessel disease and 3% in patients with multivessel disease. Detre et al (1989) reported the 1-year follow-up results of the 1,801 patients enrolled into the "second generation" National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry (1985-1986). The overall 1-year

mortality was 3.2%, myocardial infarction rate was 7.2%, and coronary artery bypass surgery rate was 13.2%. In the subgroup of patients who underwent successful dilatation without major procedural complications, the corresponding rates were 1.9%, 2.6%, and 6.4%. Comparison of 1 year results between the new and the old registries is confounded by the higher risk profile observed in patients who have undergone more recent angioplasty. Compared to the old registry, the new registry contained more patients with advanced age, unstable angina, multivessel disease, impaired ejection fraction, and history of infarction, bypass surgery, diabetes, hypertension, and congestive cardiac failure at baseline. When adjustments were made to account for these imbalances, the relative risk of mortality, myocardial infarction, or bypass surgery was reduced in favour of the new cohort. Hence, despite the broader application of coronary angioplasty to include patients with more complex coronary artery disease, both the initial success rate (Detre et al, 1988) and the 1-year clinical benefit were sustained.

Single Vessel Disease

There are currently insufficient data to judge if coronary angioplasty offers any advantage over medical therapy in patients with single vessel coronary artery disease. Nevertheless, registry studies from multiple centres have reported excellent long-term prognosis with regard to survival, cardiac symptoms, and functional status in patients with single vessel disease who have undergone successful coronary angioplasty.

Talley et al (1988) reported the 5-year clinical status of 427 patients who underwent coronary angioplasty at Emory University in 1981. Eighty-six percent of patients had single vessel disease, 67% had left anterior descending artery stenosis, and 92% had normal left ventricular function. Angiographic success was achieved in 84%

and clinical success (angiographic success without in-hospital death, myocardial infarction or coronary bypass surgery) in 79%. The 5-year overall survival and cardiac survival was 96% and 98%, respectively. The 5-year overall survival and cardiac survival for patients who had a clinically successful procedure was 97% and 99%, respectively. Five-year freedom from cardiac death, myocardial infarction and coronary artery bypass surgery was 79% for all patients. The excellent survival and low event rates over 5 years supports the concept that coronary angioplasty is safe and effective for carefully selected patients with symptomatic single vessel disease, and well preserved left ventricular function.

The Frankfurt experience in patients with single vessel disease, involving 798 patients followed-up after a mean of 78 months after dilatation, was recently reported by Kadel et al (1992). Angioplasty was immediately successful in 81.2% of patients and 7.1% suffered a major complication. The 8-year overall survival and cardiac survival was 91.7% and 95.5%, respectively. The 8-year freedom from death, myocardial infarction, coronary bypass surgery, and repeat angioplasty was 52.7% for all patients; 62.5% in patients who had successful angioplasty and 14.5% in patients who had unsuccessful angioplasty. Significantly more patients in the successful angioplasty subgroup remained free of angina pectoris and were still working. These results suggest that patients with single vessel disease who have undergone successful dilatation have an excellent long-term prognosis with regard to survival and cardiac symptoms. Furthermore, the long-term prognosis of patients who received medical therapy after failed angioplasty was less favourable than that of patients who had undergone successful dilatation. However, if angioplasty was unsuccessful, bypass surgery improved long-term outcomes in these patients in a way that was similar to that of angioplasty.

Similarly, favourable long-term outcome of coronary angioplasty in patients with single vessel disease was also reported by Henderson et al (1989). Four hundred and twelve patients, who underwent coronary angioplasty at Guy's Hospital in London, were followed for a median of 772 days. Five years after the procedure, overall survival was 93% for all patients and 94.2% for patients with a clinically successful procedure (angiographic success without a major in-hospital complication). The 5-year freedom from cardiac death, myocardial infarction, coronary artery bypass surgery, and repeat angioplasty was 60.2% for all patients and 70.2% for patients with clinically successful procedures.

Mabin et al (1985a) reported the follow-up clinical results of 229 patients who underwent coronary angioplasty at the Mayo Clinic. Single vessel disease was present in 62% of patients and multivessel disease in 38%. At 12 months, freedom from death, myocardial infarction, coronary artery bypass surgery, repeat angioplasty, and angina pectoris occurred in 61% of patients with successful angioplasty and 78% of patients with unsuccessful angioplasty and prompt coronary artery bypass surgery. Complete revascularisation was found to have a positive impact on symptomatic status and event-free survival but other baseline differences between the 2 groups were not taken into consideration.

Multivessel Disease

The preferred method of revascularisation for patients with coronary artery disease is not yet established. The controversy is particularly relevant in patients with multivessel disease, who now represent a large segment of the group undergoing balloon angioplasty. Several registry studies have addressed the role of coronary angioplasty in this subset of patients. High primary success rates have been

reported, ranging from 85% to 95%, with favourable long-term clinical outcome (Cowley et al, 1985; Deligonul et al, 1988a; O'Keefe et al, 1990).

An early study by Cowley et al (1985) reported long-term results in 44 patients who underwent successful multivessel angioplasty. After a mean follow-up of 26 months, freedom from death, myocardial infarction, coronary artery bypass surgery, and repeat angioplasty, was 64%.

Deligonul et al (1988a) reported follow-up results in 373 patients who underwent successful multivessel angioplasty. After a mean follow-up period of 27 months, 79% were free of death, nonfatal myocardial infarction or coronary artery bypass grafting. They also showed an increased incidence of late coronary artery bypass grafting in patients with incomplete versus complete revascularisation.

More recently, longer-term follow-up studies have also been reported. O'Keefe et al (1990) followed 700 patients who underwent multivessel coronary angioplasty at the Mid-America Heart Institute for a mean period of 54 months. The overall actuarial 1 and 5 years survival rates was 97% and 88%, respectively. Freedom from death, Q-wave myocardial infarction, and coronary artery bypass surgery at 1 and 5 years was 90% and 74%, respectively. Using multivariate analysis, they identified age $\geq$ 70 years, ejection fraction $\leq$40% and prior coronary artery bypass surgery as independent predictors of long-term mortality. Impaired left ventricular function, diabetes mellitus, and age $\geq$65 years were also identified as adverse predictors of long-term cardiac survival by Vandormael et al (1991).

Two studies have specifically addressed the long-term efficacy of triple-vessel angioplasty. DiSciascio et al (1988) followed 50 patients who had successful triple

vessel angioplasty for a mean of 18.4 months. Actuarial survival and survival free of death, myocardial infarction, or bypass surgery at 2 years was 96% and 90%, respectively. Warner et al (1992) reported the long-term follow-up data in 103 patients who underwent triple vessel angioplasty. Actuarial survival and survival free of death, myocardial infarction, or bypass surgery at 4 years was 89% and 78%, respectively.

These results suggest that coronary angioplasty of multiple vessels is a safe and effective therapy in selected patients with severe multivessel disease. Nonetheless, the specific indications for coronary angioplasty in the wide spectrum of patients with multivessel disease remain undefined. Rigorous scrutiny of randomised trials, including analyses of nonrandomised patients entered into a registry, may help clarify some of the issues.

Influence of Degree Of Revascularisation

The value of complete versus incomplete revascularisation in patients undergoing coronary angioplasty is still controversial. The impact of the degree of revascularisation has been specifically examined in several studies.

Vandormael et al (1985) followed up 135 patients who underwent multilesion coronary angioplasty for a minimum of 6 months. They showed that the need for a second revascularisation procedure was significantly more common in patients who had incomplete revascularisation.

Follow-up data at a mean duration of 26.2 months from the early National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry (Reeder et al, 1988) showed that although the need for coronary artery bypass

grafting was greater for patients with incomplete revascularisation, their lower risk for having repeat angioplasty resulted in an overall similar risk of requiring a second revascularisation procedure. A higher incidence of coronary artery bypass grafting and a lower risk of repeat angioplasty, during follow-up in 1023 patients who were incompletely revascularised, were also reported by Shaw et al (1990b).

Bell et al (1990) also demonstrated a lower risk of coronary artery bypass grafting, and occurrence of severe angina, in patients with complete revascularisation, in a follow-up study involving 867 patients with multivessel coronary artery disease.

However, considerable differences in baseline characteristics existed in patients with and without complete revascularisation in these studies. Reeder et al (1988) argued that studies associating higher late event rates to incomplete revascularisation were flawed, in that the differences found were due to the poorer prognosis of the incomplete revascularisation group prior to the angioplasty procedure. The occurrence of late events were attributable to other risk factors, such as poor left ventricular function and prior myocardial infarction. Reeder et al found that after adjusting for these baseline differences, the degree of revascularisation was no longer strongly predictive of any long-term cardiac event, such as the occurrence of late death or myocardial infarction.

Some investigators have argued that it is the functional significance of the residual disease that determines the long-term outcome of patients. Faxon et al (1992b) stratified patients with incomplete revascularisation into those with functionally adequate revascularisation (successful dilatation of all 70% stenoses in vessels that were >1.5 mm in diameter, and that served viable myocardium) and those with functionally inadequate revascularisation. This study demonstrated that patients with

incomplete but functionally adequate revascularisation have long-term results that are comparable with those of patients with complete revascularisation. In support of this, studies of exercise testing with or without thallium-201 imaging have shown that a positive test after coronary angioplasty is predictive of a greater need for subsequent revascularisation (Atwood et al, 1990; Breisblatt et al, 1988). Breisblatt et al (1988) reported that evidence of ischaemia by thallium-201 imaging in a vascular distribution separate from the territory fed by the "culprit" lesion, predicted a greater need for subsequent revascularisation. Deligonul et al (1989a) showed that an abnormal exercise treadmill finding within 1 month of successful coronary angioplasty is predictive of subsequent cardiac events in patients who have multivessel disease. These studies emphasise the need for better assessment of the functional importance of coronary stenoses in assessing their contribution to long-term prognosis of patients with incomplete revascularisation.

(e) CORONARY ANGIOPLASTY VERSUS CORONARY ARTERY BYPASS SURGERY

Despite a tremendous increase in utilisation of coronary angioplasty, little data exist that allow comparison of the results obtained with coronary artery bypass grafting. The role of these 2 techniques in the treatment of coronary artery disease remains undefined and many questions regarding indications, patient selection, safety, and long-term efficacy remain controversial. There are patients with coronary artery disease in whom coronary angioplasty is a reasonable first treatment option; there are other patients in whom coronary artery bypass surgery is a better therapeutic choice. However, there remains a large number of patients in whom either therapeutic approach may be chosen and consequently, the choice remains open to question.

Non-randomised Studies

Multiple non-randomised studies have attempted to compare the efficacy of coronary artery bypass grafting and percutaneous transluminal coronary angioplasty as a treatment strategy.

Hochberg et al (1989) matched 125 consecutive patients who underwent angioplasty with 125 consecutive patients who underwent coronary artery bypass surgery, so that both groups had similar distributions of single and double vessel disease. At 3 year follow-up, no significant difference in mortality was found between the matched groups but better symptom control was achieved in the surgically treated patients. Better symptomatic improvement with bypass surgery was also reported by Finci et al (1987c), who compared 80 patients undergoing angioplasty with 80 patients undergoing coronary artery bypass surgery for multivessel disease.

Atkins et al (1989) compared the late clinical results of angioplasty in 389 patients with a cohort of 1000 surgically treated patients. The 5-year actuarial event-free rates showed a significantly greater freedom from subsequent myocardial infarction, coronary angioplasty, coronary artery bypass grafting, and all combined morbidity and mortality, for the coronary artery bypass surgery patients compared with the angioplasty patients.

Kramer et al (1989) compared the late follow-up results of 413 patients who underwent angioplasty, with 368 patients who underwent coronary bypass surgery for an isolated obstruction in the left anterior descending artery. Five year freedom from death, myocardial infarction, bypass grafting, and angioplasty was significantly higher for surgical patients when compared to angioplasty patients (93% versus 62%, $p=0.0001$).

Vacek et al (1992) compared the outcomes of 152 patients undergoing multivessel angioplasty with those of 134 patients undergoing multivessel bypass surgery. Although the occurrence of death and myocardial infarction was similar in both groups, the need for repeat interventions including cardiac catheterisation, angioplasty, and bypass surgery occurred significantly more often in patients undergoing angioplasty as opposed to those undergoing surgery during ≤4 years of follow-up.

The long-term outcomes of 415 patients undergoing angioplasty, and 454 patients undergoing bypass surgery, for 2-vessel coronary artery disease at Emory University were also compared (Weintraub et al, 1993a). Again, there was no difference in the 5-year overall survival and incidence of myocardial infarction after coronary surgery or angioplasty but a significantly greater incidence of additional revascularisation procedures after angioplasty than after surgery.

However, all these studies were retrospective and nonrandomised, and many had limited statistical power due to the relatively small sample size. Even when Grüntzig introduced coronary angioplasty in 1977, he urged that "a prospective randomised trial will be necessary to evaluate its usefulness in comparison with surgical and medical management" (Grüntzig et al, 1979).

Randomised Trials

Several randomised trials of coronary angioplasty versus coronary artery bypass surgery are in progress in the United States (**BARI, EAST**), South America (**ERACI**), and Europe (**RITA, CABRI, GABI**). Early and medium term results from some of these trials have now been reported.

Randomised Intervention Treatment of Angina Trial. The Randomised Intervention Treatment of Angina trial (**RITA**) is the British multicentre trial comparing the long-term effects of coronary angioplasty and coronary artery bypass surgery in patients with 1, 2, or 3 diseased coronary arteries, in whom equivalent revascularisation was deemed achievable by either procedure (RITA Trial Participants, 1993). A total of 1011 patients were randomised to coronary angioplasty (n=510) or bypass surgery (n=501). In 97% of bypass surgery patients all intended vessels were grafted. However, dilatation of all treatment vessels was only attempted in 87% of coronary angioplasty patients, with an angiographic success rate per vessel of 87%. One month post procedure, there were fewer physically active patients, in those who had undergone bypass surgery compared to those who had undergone coronary angioplasty (38% versus 52%, $p<0.001$), although there was no evidence of a treatment difference thereafter. After a mean follow-up of 2.5 years, there was no significant difference in risk of death (3.1% versus 3.6%) or myocardial infarction (9.8% versus 8.6%), between coronary angioplasty and bypass surgery patients. At 6 months, 31.6% of coronary angioplasty patients had anginal symptoms compared with 11.0% of bypass surgery patients ($p<0.001$). At 2 years, the prevalence of angina in the bypass surgery group had increased to 21% but this was still significantly less than the 31% for coronary angioplasty patients ($p=0.007$). The repeat coronary angiography rate was 4 times more common in coronary angioplasty than in bypass surgery patients (31% versus 7%, $p<0.001$). Within 2 years of randomisation, 38% of the coronary angioplasty group and 11% of the bypass group had experienced either death, myocardial infarction, further bypass surgery or coronary angioplasty ($p<0.001$). These results suggest that recovery after bypass surgery takes longer than after coronary angioplasty. However, those treated with bypass surgery were less likely to have persistent angina, to require anti-anginal medications, and to need additional

diagnostic and therapeutic interventions in the first 2 years than coronary angioplasty. There was no significant difference in risk of death or myocardial infarction after a mean of 2.5 years' follow-up, although the results of 5 years' follow-up is still awaited.

Argentine Coronary Angioplasty versus Bypass Surgery Trial. The smaller Argentine Coronary Angioplasty versus Bypass Surgery Trial (**ERACI**) have also reported 1- and 3-year follow-up results (Rodriguez et al, 1993a; Rodriguez et al, 1994). Patients with multivessel disease were randomised if the choice of a revascularisation approach remained open to question, and if lesions were considered suitable for either coronary angioplasty or bypass surgery. Only 127 patients were randomised, to either coronary angioplasty (n=63) or bypass surgery (n=64) at the Anchorena Hospital (Buenos Aires, Argentina). Complete revascularisation was achieved in only 51% of the coronary angioplasty group compared to 88% for the bypass surgery group. There were no differences in in-hospital deaths (1.5% versus 4.6%), frequency of peri-operative myocardial infarction (6.3% versus 6.2%), or need for emergency revascularisation procedures (1.5% versus 1.5%) between coronary angioplasty and bypass surgery patients. At 1-year follow-up, there were no differences in mortality (3.2% versus 0%), or in the incidence of myocardial infarction (3.2% versus 1.8%) between coronary angioplasty and bypass surgery patients. However, bypass surgery patients were more frequently free of angina ($p<0.02$), reinterventions (96.8% versus 68%, $p<0.001$), and combined cardiac events (83.5% versus 63.7%, $p<0.005$). In-hospital cost and cumulative cost 1-year follow-up were greater for the bypass surgery than for the coronary angioplasty group. These 1-year findings were sustained at 3-years follow-up. At 3-years, patients treated with bypass surgery were more frequently free of angina than patients treated with coronary angioplasty

(80.4% versus 59.7%, $p<0.001$). The need for new revascularisation procedures remained higher in coronary angioplasty then bypass surgery patients (37% versus 3.2%, $p<0.001$). As before, the overall survival and freedom from myocardial infarction were similar between both groups. These results were similar to those reported by the **RITA** trial.

German Angioplasty Bypass-Surgery Investigation. The German Angioplasty Bypass-Surgery Investigation (**GABI**) is a multicentre trial to compare coronary angioplasty and bypass surgery in patients with symptomatic multivessel coronary artery disease (Hamm et al, 1994). Patients were included, if complete revascularisation was considered necessary and technically feasible in at least 2 major coronary vessels supplying different myocardial territories. A total of 359 patients were randomised to coronary angioplasty ($n=182$) or bypass surgery ($n=177$). After bypass surgery, hospitalisation was longer (median, 19 days, as compared with 5 for coronary angioplasty), and Q-wave myocardial infarction in relation to the procedure was more frequent (8.1%, as compared to 2.3% after coronary angioplasty, $p=0.022$), whereas in-hospital mortality did not differ significantly between the 2 groups (2.5% in bypass surgery group and 1.1% in the coronary angioplasty group). During the first year of follow-up, re-interventions were necessary in 44% of the patients in the coronary angioplasty group (repeat coronary angioplasty in 23%, bypass surgery in 18%, and both in 3%) but in only 6% of the patients in the bypass surgery group (repeat bypass surgery in 1% and coronary angioplasty in 5%; $p<0.001$). At 1 year, 74% of the patients in the bypass surgery group and 71% of those in the coronary angioplasty group were free of angina. Angina class III or IV was present in 7% of patients in the bypass surgery group and 8% of those in the coronary angioplasty group ($p=0.82$). These results suggest that in patients with multivessel disease, bypass surgery and coronary

angioplasty as initial treatments resulted in equivalent improvement in angina after 1 year. However, in order to achieve similar clinical outcomes, the patients treated with coronary angioplasty were more likely to require further interventions, whereas patients treated with bypass surgery were more likely to sustain an acute myocardial infarction at the time of the procedure.

Emory Angioplasty versus Surgery Trial. The Emory Angioplasty versus Surgery Trial (**EAST**), which was performed at a single centre, was designed to determine whether initial revascularisation with coronary angioplasty in patients with multivessel disease is a viable alternative to bypass surgery (King et al, 1994). The primary end point was a composite of death, Q-wave myocardial infarction, and a large ischaemic defect on thallium scanning at 3 years. A total of 392 patients with multivessel disease were randomised to coronary angioplasty ($n=198$) and bypass surgery ($n=194$). The primary end point occurred in 27.3% of the bypass surgery group and 28.8% of the coronary angioplasty group ($p=0.81$). At 3 years, the proportion of patients in the bypass surgery group who required repeat bypass surgery (1%) or coronary angioplasty (13%) were significantly lower than the proportion in the coronary angioplasty group (22% and 41%, respectively; $p<0.001$). Angina was also more frequent in the coronary angioplasty group (20%) than in the bypass surgery group (12%; $p=0.039$). This trial suggest that bypass surgery and coronary angioplasty did not differ significantly with respect to the occurrence of the composite end point, although patients treated with coronary angioplasty were more likely to suffer recurrence of angina and require further interventions.

Coronary Angioplasty Bypass Revascularisation Investigation Trial. The Coronary Angioplasty Bypass Revascularisation Investigation Trial (**CABRI**) is a

multicentre trial supported by the European Society of Cardiology. The aim was to compare strategies of primary angioplasty or primary surgery for the management of patients with symptomatic multivessel coronary artery disease, in whom equivalent symptom relief could be expected by either intervention procedure (Rickards, 1994). One thousand and sixty patients were randomised to coronary angioplasty (n=541) and bypass surgery (n=519). The 1-year follow-up result showed no significant difference in outcome judged either in survival (2% versus 4.1%), risk of myocardial infarction (3.0% versus 3.0%), or symptomatic terms (angina class II/III, 15% versus 9%) between coronary angioplasty and bypass surgery. Again, the rate of early re-interventions was higher with coronary angioplasty patients (repeat angioplasty 20%, and bypass surgery 26%) than with bypass surgery patients (coronary angioplasty 7%, and repeat bypass surgery 1.4%; $p<0.001$).

Bypass Angioplasty Revascularisation Investigation. The Bypass Angioplasty Revascularisation Investigation (**BARI**) is the largest of the coronary intervention studies, supported by the National Institutes of Health (Anonymous, 1991). It is a 14 centre trial, the primary aim is to test the hypothesis that an initial strategy of coronary angioplasty compared with bypass surgery, in patients with multivessel disease, does not compromise clinical outcome during a 5-year follow-up period. The study focuses on the treatment of patients who have multivessel disease and severe angina or ischaemia, those who require revascularisation, and those who are suitable for either procedure. Two thousand eight hundred patients have been enrolled. The primary study end point is mortality at 5 years. Other major end points include myocardial infarction, angina status, repeat revascularisation, resource use, and quality of life. The extent of revascularisation and left ventricular function will also be angiographically assessed at the 5-year follow-up, so that the

condition of bypass conduits and dilated segments can be evaluated. Results of the **BARI** trial are eagerly awaited.

The variations between the coronary intervention trial protocols reflect differences in coronary angioplasty practice. **RITA** and **GABI** exclude patients in whom intervention is likely to result in incomplete revascularisation, and **GABI** and **EAST** exclude patients with chronically occluded coronary arteries. By contrast, in **CABRI,** treatment is directed towards effective symptomatic relief rather than full myocardial revascularisation. With the exception of **RITA,** the trials exclude patients with single vessel disease, which supports the widely held but unproven view that coronary angioplasty is the treatment of choice for these patients.

These trials have shown that patients who underwent bypass surgery had less angina, required less anti-anginal medication, and were less likely to need another revascularisation procedure. However, the higher relative rate of re-interventions appeared to expose coronary angioplasty patients to no additional risk of death or serious cardiac events. The findings of these randomised trials are not surprising since restenosis is more likely in the first 6 months after coronary angioplasty, whereas failure of saphenous vein graft tends to occur late. Hence, cross-over from angioplasty to surgery tends to occur early (mean 21 months) because of restenosis, while surgical problems due to graft sclerosis or native vessel disease progression resulting in cross-over to angioplasty tend to occur later (mean 76 months). Therefore, in any randomised trial of coronary angioplasty and bypass surgery, premature reports will include most angioplasty untoward results, especially the need for repeat revascularisation, but may exclude late surgical problems. Obviously, long-term follow-up is necessary for more valid comparisons (Myler et al, 1989b).

Whereas these randomised studies will go a long way towards improving our ability to make decisions, many patients with complex multivessel disease are not being studied in these trials. In fact, more patients were excluded from these trials than were included, especially those with single-vessel disease, total occlusions, left-main stenosis, and very poor left ventricular function. Decisions on coronary angioplasty or bypass surgery on these patients will have to rely on clinical judgement in the absence of any future randomised trials.

(f) CORONARY ANGIOPLASTY VERSUS MEDICAL THERAPY

Comparisons of coronary angioplasty with medical treatment for single- and double-vessel coronary disease with left anterior descending coronary involvement, was first reported by Ellis et al (1989a). The 3- to 5-year clinical outcomes of 627 consecutive patients treated with coronary angioplasty at Emory University were compared with 865 patients treated with medical therapy in the Coronary Artery Surgery Study with similar coronary artery disease involvement. Coronary angioplasty was successfully achieved in 91.8% of patients, with a 4.1% incidence of emergency bypass surgery, and a 1.4% incidence of procedure-related myocardial infarction. The 5-year actuarial survival for all patients treated medically did not differ from that for all patients treated with angioplasty (93% versus 95%, $p=0.36$). The 5-year actuarial rate of non-fatal myocardial infarction was also not significantly different between the coronary angioplasty group and the medically treated group (12% versus 10%). However, patients with a left ventricular ejection fraction of less than 50% and patients with double-vessel disease, had improved survival if treated by angioplasty. Furthermore, patients whose worst left anterior descending artery stenosis was 90% to 99% had a trend toward lessened risk of infarction when angioplasty was performed. The likelihood of late bypass surgery

was increased after angioplasty (19% versus 16%, p=0.002) but the level of angina was dramatically reduced for patients treated with initial angioplasty as compared to medical therapy: 61.4% of the angioplasty patients had no angina after 3 years compared to only 13.9% of the medically treated patients ($p<0.0001$). These results suggested that coronary angioplasty compared to medical therapy was associated with improved functional status and may decrease the risk of death and infarction in certain patient subsets. However, the results also suggested that angioplasty was associated with an increased likelihood of subsequent bypass surgery. Although this study is limited by its non-randomised, non-concurrent data accrual study design, it brings ancillary data to an area of particular health interest, with many important, but yet unresolved, issues.

Randomised trials comparing medical therapy with coronary angioplasty are also in progress. The effects of coronary angioplasty and medical therapy on angina and exercise tolerance were compared in the Angioplasty Compared With Medicine Trial (**ACME**). Patients with 70% to 90% stenosis of 1 epicardial coronary artery and have evidence of exercise-induced myocardial ischaemia were randomised to undergo percutaneous transluminal coronary angioplasty or to receive medical therapy. A total of 107 patients were assigned to medical therapy and 105 to coronary angioplasty. Coronary angioplasty was clinically successful in 80 of the 100 patients who actually had the procedure. Two patients required emergency coronary artery bypass surgery and 4 had an acute myocardial infarction. During follow-up, of the patients assigned to coronary angioplasty, no death occurred, 1 had a myocardial infarction, 5 had bypass surgery, and 19 underwent repeat angioplasty procedures. Of the patients assigned to medical therapy, 1 died, 3 had a myocardial infarction, none had bypass surgery, and 11 underwent coronary angioplasty. At 6-months follow-up, 64% of the patients in the coronary angioplasty

group were free of angina as compared with 46% of the medically treated patients ($p<0.01$). Although both groups of patients had an increase in duration of exercise, the coronary angioplasty group were able to increase their total duration of exercise more than the medical patients (2.1 minutes versus 0.5 minutes, $p<0.0001$) and were able to exercise for longer without angina on treadmill testing ($p<0.01$). Quality of life, general health and vitality were also better in the angioplasty group than the medical therapy group ($p<0.01$). These results suggested that for patients with single-vessel coronary artery disease, coronary angioplasty offered more complete relief of angina than medical therapy and was associated with better performance on the exercise test. This was at the expense of higher initial complications in patients treated with coronary angioplasty, especially emergency coronary artery bypass surgery (Parisi et al, 1992). However, of the 9573 patients screened over a period of 37 months, 96% did not satisfy the clinical or angiographic requirements for enrolment. Of the 371 remaining patients, only 212 were included in the study, representing 2% of all patients who underwent coronary angiography in the participating laboratory. As a result, this trial did not have the statistical power to detect differences in mortality or rates of infarctions between the 2 treatments. Furthermore, since the exclusion criteria included multivessel disease, previous bypass surgery or angioplasty, and ongoing unstable angina, the conclusions from this study should not be generalised beyond clinically stable patients with subtotal stenosis of a single coronary artery.

A randomised comparison of coronary angioplasty and medical therapy in the treatment of patients with asymptomatic single-vessel disease, was also reported by Sievers et al (1993). Eighty-eight patients with single vessel disease of a major coronary artery and no angina in daily life under medical therapy with aspirin, nitrates, beta-blockers, and/or calcium antagonists were randomised to coronary

angioplasty (n=44) or medical therapy alone (n=44). Procedural success was achieved in all patients that were randomised to coronary angioplasty. Two years after randomisation, 32 patients of each group were still asymptomatic with unchanged exercise tolerance from baseline assessment. Angina developed in 11 patients of the medical therapy group and revascularisation was necessary in 9 patients (7 coronary angioplasty and 2 bypass surgery). Nine patients in the angioplasty group developed symptoms and revascularisation was necessary in 7 patients (5 repeat angioplasty and 2 bypass surgery, not significant). A myocardial infarction occurred in 1 patient of the medical therapy group (who also died), and 2 patients of the angioplasty group (not significant). These results suggested that the clinical outcome of patients with asymptomatic single-vessel disease is not different with medical therapy alone as compared with coronary angioplasty. Hence, delaying coronary angioplasty, in those patients who have asymptomatic single-vessel disease on medical treatment, until such time when symptoms developed seems justified.

In the United Kingdom, a major trial comparing treatment strategies of coronary angioplasty and medical care (**RITA-II**) is currently recruiting patients, and should further define the role of coronary angioplasty in the management of patients with coronary artery disease.

(g) IMMEDIATE CORONARY ANGIOPLASTY FOR ACUTE MYOCARDIAL INFARCTION

After an acute myocardial infarction, early coronary artery recanalisation reduces infarct size and improves survival. Recanalisation can be achieved by either intravenous thrombolytic agents (ISIS-2 Collaborative Group, 1988; ISIS-3 Collaborative Group, 1992) or immediate percutaneous transluminal coronary

angioplasty, first introduced by Hartzler et al (1983). Many patients have contraindications to thrombolytic therapy, and even after successful thrombolysis, most patients are left with a high-grade stenosis that may limit flow, impair subsequent myocardial recovery, and increase the risk of reinfarction (Chesebro et al, 1987b). Recent studies have shown that there is no place for routine angioplasty after thrombolysis (The TIMI Study Group, 1989; SWIFT Trial Study Group, 1991). On the other hand, multiple non-randomised studies have suggested that immediate angioplasty can result in a high rate of reperfusion that is associated with a low rate of in-hospital mortality and an increase in the ejection fraction (Table 1.4). O'Keefe et al (1989a) reported a primary success rate of 94% with an in-hospital mortality rate of 7.2% in 500 patients who underwent immediate angioplasty for acute myocardial infarction. The ejection fraction increased from 53% to 59%, especially in those with markedly impaired left ventricular function. Rothbaum et al (1987) reported, in a series of 151 patients, a primary success rate of 87% and an in-hospital mortality rate of 9%. An improvement was also noted in the ejection fraction, by 13%±12% in the anterior myocardial infarction group, and 10±12% in the inferior myocardial infarction group.

Three recent prospective, randomised studies have addressed the place of angioplasty versus thrombolysis in acute myocardial infarction. In these studies a total of 645 patients with acute myocardial infarction received aspirin and heparin, and were then randomised to receive either thrombolytic drugs or angiography with a view to immediate angioplasty without thrombolysis. Coronary arteriography and first balloon inflation on average occurred 60 minutes after randomisation. The primary success rates were excellent, with 93-98% of patients having a patent artery at the end of the procedure with no procedure-related deaths (Grines et al, 1993; Gibbons et al, 1993; Zijlstra et al, 1993). Although these authors found that

immediate angioplasty was no more effective than thrombolytic therapy in preserving myocardium, assessed using radionuclide ventriculography, it was more effective in restoring patency and preventing reocclusion of the infarct-related artery. Furthermore, patients who underwent immediate angioplasty had a shorter hospital stay, fewer bleeding complications, lower follow-up costs, and fewer readmissions than those who received thrombolytic therapy. They also had a lower incidence of recurrent ischaemia, reinfarction, and death than those treated with thrombolytic therapy.

It appears that immediate angioplasty is a technically feasible, safe, and effective treatment for acute myocardial infarction. In addition to the expense of performing immediate angioplasty in preference to intravenous thrombolytic therapy, there are several drawbacks. Experienced physicians, nurses, technicians, and surgical back-up must be available immediately so that coronary angiography and angioplasty can be performed rapidly without delay. Few centres have access to coronary angiography, and those centres with the necessary facilities would find it difficult to provide 24 hour access to a cardiac catheterisation laboratory and back-up surgery without disrupting their routine work. Moreover, the risks and complications associated with cardiac catheterisation and immediate angioplasty for acute myocardial infarction are greater than those of elective coronary angioplasty for chronic angina (Topol, 1990). In a cost-conscious and budget-orientated health service, immediate angioplasty should only be implemented if larger randomised studies show clear cost and clinical benefits over thrombolytic therapy, and if more resources and facilities can be provided to support such a programme. At the moment, the marginal benefits of immediate angioplasty in the routine management of acute myocardial infarction do not justify a massive investment programme. Careful case selection is therefore essential. It may be the preferred strategy for

patients with contraindication to thrombolytic therapy (Himbert et al, 1993) and high risk patients with evolving myocardial infarction complicated by cardiogenic shock, where improvement in short- and long-term outcome have been shown.

(h) CORONARY ANGIOPLASTY IN PATIENTS WITH CARDIOGENIC SHOCK

In 1954, Griffith et al (1954) reported an 80% in-hospital mortality rate for patients with cardiogenic shock after acute myocardial infarction. O'Keefe et al (1989a), in a series of 500 patients who underwent immediate angioplasty for acute myocardial infarction, reported a mortality rate of 41% in the sub-group of patients who had cardiogenic shock complicating myocardial infarction. In a series of 151 patients reported by Rothbaum et al (1987), 39% of the patients in cardiogenic shock died. Despite the dramatic advances in cardiac care over the last decade, Goldberg et al (1991) have found little improvement in this gloomy prognosis. Given the high mortality rate with conventional care, an aggressive approach to the management of cardiogenic shock seems justified, but the efficacy of any new intervention still needs to be validated in clinical trials.

Many reports have evaluated the treatment of cardiogenic shock with coronary angioplasty (Brown et al, 1985; Sahni et al, 1986; Heuser et al, 1986; Laramee et al, 1988; Landin et al, 1988) (Table 1.5). These early reports have demonstrated an improvement in survival which was clearly linked to reperfusion status. Lee et al (1991) attempted to define subgroups with different survival rates further in a multicentre registry experience. They have shown that patients with multivessel disease had a 62% mortality and patients with unsuccessful reperfusion

had an 80% mortality. Coronary angioplasty achieved successful reperfusion in 71% of cases.

More recently, 3 studies have again supported the emerging role of coronary angioplasty as the optimal therapy for cardiogenic shock. Gacioch et al (1992) reported the results of 48 patients in cardiogenic shock treated with angioplasty therapy, and 20 patients treated with conventional therapy over a 5-year period. Haemodynamic support devices were used in 12 patients. Successful angioplasty was achieved in 73% of patients. After 30 days, the mortality rate was 39% in the group of patients successfully treated with angioplasty versus 93% for patients with failed angioplasty. Patients who had no attempt at angioplasty had a 30-day mortality rate of 86%. Moosvi et al (1992) reported the effect of revascularisation, either by angioplasty or bypass surgery, in 81 patients with cardiogenic shock complicating acute myocardial infarction. The in-hospital survival was 56% in patients with successful revascularisation and only 8% in patients treated without revascularisation. This survival difference persisted after a mean follow-up period of 21 months. However, the criteria for the selection of some patients for aggressive approach and others for conventional care was not defined in the study. Selection bias may have occurred and may explain the favourable results reported. Hibbard et al (1992) reviewed the recent Mayo Clinic experience and demonstrated that successful angioplasty in patients with cardiogenic shock has beneficial short- and long-term effects. Of 45 patients, 62% underwent successful dilatation of the infarct-related artery, with a 71% in-hospital survival rate as compared with a 29% survival rate in patients in whom angioplasty failed. The value of haemodynamic support was not considered in this study. The mean follow-up period 2.3 years is especially significant, extending previous observations in documenting an excellent

prognosis and a relatively high quality of life after hospital discharge (Lee et al, 1991).

These consistently encouraging results of angioplasty in cardiogenic shock, and the knowledge that patients treated with conventional therapy have a 90% chance of early death, appears to make a randomised trial unethical. However, it may be that only studies with a positive outcome are being reported. In addition, much more information is required about case selection, adjunctive support therapy, and the role of emergency bypass surgery in this group of patients.

1.5 RESTENOSIS: BASIC AND CLINICAL CONSIDERATIONS

The term "restenosis" has been applied simultaneously to describe local neointimal hyperplasia at the site of dilatation (histological restenosis), the development of significant luminal narrowing at the treatment site (angiographic restenosis), and the late recurrence of signs or symptoms of ischaemia after an initially successful angioplasty (clinical restenosis). Although the incidence of initial success and complications with coronary angioplasty has improved steadily since the procedure's inception, the frequency of restenosis has not changed (Detre et al, 1988), and remains the major problem limiting the long-term efficacy of the procedure (David et al, 1982; Vlietstra et al, 1983; Holmes et al, 1984). In the first 133 patients in whom coronary angioplasty was successfully performed, Grüntzig reported a 6-months' angiographic follow-up in 93% of the patients and a restenosis rate of 31%, defined as a recurrence of a ≥50% diameter stenosis at a previously successfully dilated site (Gruentzig et al, 1987).

(a) BASIC CONSIDERATIONS OF RESTENOSIS

The exact pathophysiological mechanisms that lead to restenosis remains unclear, although pathological observations and experimental models have allowed the sequence of events to be elucidated.

Pathological Observations

Post-mortem studies in patients dying at various intervals after percutaneous transluminal coronary angioplasty, have demonstrated intimal proliferation of smooth muscle cells as the explanation for the development of restenosis. Essed et al (1983) were the first to describe intimal fibrous hyperplasia at the site of coronary

angioplasty. They reported proliferation of fibrocellular tissue filling the dissected media and covering the atherosclerotic plaque in a patient who died 5 months after coronary angioplasty of the left anterior descending artery.

Austin et al (1985) described the necropsy findings in 3 patients who died 5, 17, and 62 days after percutaneous transluminal coronary angioplasty. Focal proliferation of smooth muscle cells was prominent on neointimal surfaces of the coronary artery from the patient who died 17 days after angioplasty. However, extensive proliferation of smooth muscle cells distributed over the entire circumference of the intimal surface, as well as within gaps in the old atherosclerotic plaques, was seen in the patient who died 62 days after the procedure.

Similar findings were shown by Giraldo et al (1985) and Waller et al (1987) in patients who died 96 days and 123 days respectively, after successful angioplasty. Recently, Waller et al (1991) reported the necropsy findings of 20 patients entered into the Cardiovascular Pathology Registry who had died late after successful coronary angioplasty (range 1.6 to 24.1 months, mean 8.2 months). Intimal hyperplasia was observed in 60% of restenotic lesions. Furthermore, Klein et al (1990) had shown that restenosis is morphologically dissimilar to the original pre-angioplasty stenosis. These studies suggest that the reparative processes post-angioplasty are of critical importance in determining the occurrence of restenosis. Hence, it appears that restenosis after successful percutaneous transluminal coronary angioplasty is due to fibrocellular tissue proliferation.

However, these observations in human vessels were essentially descriptive. Whilst they have given insight into the time course of restenosis after angioplasty, they

have been of little value in providing an understanding of the basic pathophysiology and cellular mechanisms in restenotic neointimal formation. Much of the understanding came from work done in animal models.

The "Response to Injury" Hypothesis

The prevalent view of spontaneous atherosclerosis is the "response to injury" hypothesis based on early proposals made by Virchow (1856) and subsequently modified by Ross (1986) more than a century later. Restenosis after percutaneous transluminal coronary angioplasty can be considered to be an accelerated version of this proliferative process. Type II (endothelial denudation and intimal damage) or type III (endothelial denudation with damage of both intima and media) vascular injury after angioplasty appears to be the critical initiating event in the pathogenesis of restenosis, followed by intense platelet involvement and thrombus formation, leading to an initial predominant process of smooth muscle cell proliferation (Faxon et al, 1984b; Lam et al, 1986; Chesebro et al, 1987a; Ueda et al, 1991). However, the precise relation between these processes remains uncertain.

In a pig model of restenosis, Steele et al (1985) demonstrated that immediately after balloon catheter injury to the carotid arteries, complete endothelial denudation and varying degrees of medial injury were induced. Using radioactive labelled platelets in animal models, Lam et al (1986) and Wilentz et al (1987) both demonstrated rapid platelet aggregation and accumulation over the site of endothelial denudation. Within 10 minutes of balloon injury, the exposed and highly irregular intimal connective tissue of elastin fragments and vascular basement membrane, is covered by a monolayer of fibrin and platelet deposition, which extends pseudopods into the connective tissue layer (Stemerman, 1973). The degree of platelet deposition was also correlated to the extent of dissection (Wilentz et al, 1987). By 3 hours, the

entire de-endothelialised surface is covered by a carpet of platelets and fibrin strands, with some polymorphonuclear leucocytes appearing (Stemerman, 1973).

Earlier studies have provided evidence that fibrin clots may stimulate smooth muscle hyperplasia in the organisation of arterial thrombi in pigs (Jorgensen et al, 1967), rats (Poole et al, 1971), and rabbits (Sumiyoshi et al, 1973). The most rapid rate of smooth muscle cell replication in human atherosclerotic plaques has also been shown to occur at a site around an area of haemorrhage (Gordon et al, 1990). It is postulated that smooth muscle regrowth is activated by platelet-derived growth factor (PDGF) and other mitogens released from the α-granules of platelets, endothelial cells, and smooth muscle cells (Kohler and Lipton, 1974; Westermark and Wasteson, 1976; Witte et al, 1978; Forrester et al, 1991). Goldberg and Stemerman (1980) have shown that within 30 minutes of balloon injury, platelet factor IV, 1 of the constituents in the α-granules, can be detected throughout the intima and media. By extrapolation, since PDGF and other mitogens also reside in the α-granules, they also enter the vessel wall after denudation has occurred. An increased PDGF activity and reduced prostacyclin production, have also been shown in patients with restenosis after percutaneous transluminal coronary angioplasty (Kanaka et al, 1988). Stemerman (1973) showed that platelets furthest away from the vessel wall retained more intra-cytoplasmic granules, suggesting that the degranulation process is more intense with platelets adhering to the subendothelial surface. Hence, the amount of growth factor delivered to the injured site depends not on the intensity of platelet accumulation, but on the size of the surface area of smooth muscle exposed to platelets caused by denudation, dissection, or fissuring (Liu et al, 1989).

Role of PDGF and Other Growth Factors

PDGF is a basic glycoprotein, and the most potent mitogen found in serum for cells of mesenchymal origin, including smooth muscle cells. It is also chemotactic for smooth muscle cells, macrophages, and neutrophils (Harker, 1987; Liu et al, 1989), and may be responsible for attracting smooth muscle cells from the media into the intima as well as for the subsequent intimal proliferation. Using ^{3}H-thymidine labelled smooth muscle cells, Clowes and Schwartz (1985) have demonstrated cellular migration from the media into the intima within days of endothelial denudation of rat carotid arteries. Similar migration has also been demonstrated in human coronary arteries, using electron microscopy, as early as 1 week after coronary angioplasty (Ohara et al, 1988).

PDGF is also a "competence factor" in that it makes cells competent to enter the cell cycle by moving the cell from the arrest stage (G0 phase) to active cell cycling (G1 phase). Further exposure to "progression factors" (eg epidermal growth factors, basic fibroblast growth factor, interleukin-1, and somatomedin-C) initiates DNA synthesis and cell division (S phase) (Schwartz et al, 1986; Liu et al, 1989). Smooth muscle cell proliferation is an acute event related to the initial injury and is virtually completed within 7 days (Clowes and Schwartz, 1985). Any further increase in intimal thickness thereafter is due to increased cell volume and synthesis of extracellular matrix and connective tissue (Clowes et al, 1983). This view is further substantiated by the findings of Ohara et al (1988), who observed that smooth muscles migrating and proliferating within the intima exhibited ultrastructural and functional properties of synthetic phenotype cells as opposed to contractile phenotype cells. Nobuyoshi et al (1991) performed histopathological examination in 20 patients undergoing antemortem coronary angioplasty. They showed that in lesions examined within 6 months of the procedure, proliferating smooth muscle

cells were predominantly of the synthetic type and the extracellular matrix composed chiefly of proteoglycans. However, in lesions examined between 6 months and 2 years, contractile smooth muscle cells were dominant and extracellular matrix was composed chiefly of collagen. Hence, the population of medial smooth muscle recruited for this proliferative process determines the degree of hyperplasia (Liu et al, 1989), which is in turn modulated by the extent of vascular injury (Schwartz et al, 1992a).

Extent of Vascular Injury and the Restenosis Process

Animal experiments suggest that simple denudation is insufficient to initiate marked intimal proliferation, and that direct injury to smooth muscle cells is essential for this process (Gebrane et al, 1982; Walker et al, 1983; Cole et al, 1987; Tada and Reidy, 1987). Furthermore, Schwartz et al (1992a) demonstrated that the severity of vessel injury strongly correlated with neointimal thickness 4 weeks after tantalum coil implantation into porcine coronary arteries. Similarly, morphometric analysis of histological sections from patients who have undergone antemortem coronary angioplasty, revealed that the extent of intimal proliferation was significantly greater in lesions with evidence of medial or adventitial tears, than in lesions with no or only intimal tears (Nobuyoshi et al, 1991). Since splitting, fissuring, and dissection of plaque and media are commonly produced after angioplasty of an atherosclerotic lesion, a much greater number of smooth muscle cells are directly exposed to platelets. This could lead to an intense smooth muscle cell proliferation, and ultimately determine the likelihood of clinical restenosis.

Other Proposed Mechanisms of Restenosis

Other mechanisms may also contribute towards the restenosis process, although it is unknown to what extent. These include coronary spasm (Hollman et al, 1983b;

Fischell et al, 1988; Bertrand et al, 1989), elastic recoil (Sanders, 1985, Powelson et al, 1987; Waller, 1989b), and incorporation of the mural thrombus into the arterial wall (Steele et al, 1985; Düber et al, 1986). Recently, Schwartz et al (1992b) proposed an alternative cellular mechanism for restenosis. They suggested that mural thrombus may determine the volume of neointima early after angioplasty by providing an absorbable matrix into which smooth muscle cells proliferate

(b) CLINICAL CONSIDERATIONS OF RESTENOSIS

Restenosis, the phenomenon of renarrowing of the vessel after coronary angioplasty, can be defined using histological, angiographic, or clinical terms. The choice of these definitions in turn dictates the analytical techniques that are used to assess restenosis. Because of the imprecise nature of clinical signs and symptoms and the overwhelming evidence that late term failure following coronary angioplasty is caused by luminal renarrowing at the treatment site, the coronary angiogram became attractive as a standard analytical end-point for evaluating coronary restenosis. Furthermore, the coronary angiogram could distinguish coronary restenosis from progression or persistence of disease at other sites as the cause of recurrent clinical symptoms. However, angiographic definitions of restenosis may not correlate well with the clinical recurrence of angina (Holmes et al, 1984).

Incidence and Definitions

The true incidence of angiographic restenosis after coronary angioplasty is unknown. The variability of the reported incidences of restenosis (ranging from 12% to 49%) reflects the differences in the definitions used, in the methods used to assess restenosis, and in the angiographic follow-up rates (ranging from 57% to 100%). At present, there are at least 14 definitions, all of which are arbitrary (Table

1.6 and Table 1.7). Furthermore, comparison between studies may be difficult because it is not possible to take account of differences in baseline and procedural variations. These factors are responsible for most of the confusion surrounding the concept of restenosis after coronary angioplasty.

In the initial National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry, 4 arbitrary definitions were used: i) an increase in ≥ 30% from the immediate post-angioplasty stenosis to the follow-up stenosis (NHLBI 1); ii) an initial <50% stenosis after angioplasty that increased to 70% at follow-up angiography (NHLBI 2); iii) an increase in stenosis at follow-up angiography of up to ≥10% below the pre-dilation stenosis (NHLBI 3); iv) a loss of ≥50% of the initial gain achieved by angioplasty (NHLBI 4) (Holmes et al, 1984). When all 4 angiographic definitions were utilised, 33.6% of patients were identified as having restenosis. However, when each definition was considered separately, the restenosis rate ranged from 21.7% (NHLBI 2) to 32.8% (NHLBI 4). Similar variations, in the incidence of restenosis which was clearly dependent on the definition used, were also shown in the Frankfurt University experience (Kaltenbach et al, 1985), the Emory University experience (Leimgruber et al, 1986), and the Thoraxcenter experience (Serruys et al, 1988b).

Reiber et al (1985) reported that repeat angiographic measurement of the same coronary segment using quantitative angiography (CAAS system) over a 90-day interval was associated with a 0.36 mm standard deviation due to inter- and intra-observer variation. The Rotterdam group therefore popularised another definition of restenosis in which coronary restenosis was considered to be present whenever more than 0.72 mm absolute luminal loss (twice the standard deviation) was evident between the intervention and the 6-month angiogram (Serruys et al, 1988b). Any of

these definitions when taken to their extremes may be flawed, and the different definitions identified different patient populations making risk factor determination difficult (Holmes et al, 1984; Serruys et al, 1988b).

Techniques Used for Assessing Angiographic Restenosis

Nearly all the early reports on angiographic restenosis after angioplasty relied on visual or user dependent analysis of cineangiograms (Meyer et al, 1983; Holmes et al 1984; Fleck et al, 1984; Thornton et al, 1984; Corcos et al, 1985; Leimgruber et al, 1986). Inter-observer and intra-observer variability of visual assessment has been shown to vary from 7% to 18% (Detre et al, 1975; Zir et al, 1976; DeRouen et al, 1977; Scoblionko et al, 1984; Vas et al, 1985). Flemming et al (1991) found that visual estimation tends to fall into 3 discrete categories of mild, moderate, and severe lesions. To reduce inter-observer and intra-observer variability and to improve accuracy of visual interpretation, investigators have either obtained a consensus reading of multiple angiographers (Detre et al, 1975; Sanmarco et al, 1978; Fisher et al, 1982; Brensike et al, 1984) or routinely used electronic or manual callipers (Vandormael et al, 1985; Leimgruber et al, 1986; Katritsis et al, 1988b; Grigg et al, 1989; Savage et al, 1991a). Others have employed computer assisted quantitative coronary angiography (Brown et al, 1977; Nichols et al, 1984; Reiber et al, 1984; Mancini et al, 1987; Strauss et al, 1991), which has shown less over- or under-estimation when compared to visual interpretation (Serruys et al, 1984; Bove et al, 1985; Arce et al, 1986; Beauman et al, 1990; Fleming et al, 1991). Computer assisted detection of arterial contour facilitates luminal diameter measurement. However, it becomes unreliable in tortuous coronary arteries with overlapping side-branches, and in asymmetrical coronary stenosis (Serruys et al, 1984). On the other hand, cinevideodensitometry assesses luminal cross sectional area from a single angiographic projection, and is not directly dependent on the

precise definition of the vessel contours, hence overcoming some of the deficiencies of arterial contour measurements (Nichols et al, 1984).

However, quantitative angiography is not widely available. In addition, recent studies to validate the use of these systems in Europe and North America have shown marked variability in performance between systems, with such wide ranges in accuracy and precision that results between laboratories could not be reliably compared (Keane et al, 1993). Furthermore, recent studies have demonstrated that visual assessment supplemented by hand-held or electronic callipers can improve accuracy of measurements (Scoblionko et al, 1984), especially when performed by angiographers already trained in quantitative analysis (Waters et al, 1990; Lespérance et al, 1990).

Another problem encountered in the assessment of restenosis stems from the unit of measurement used, which is percentage diameter stenosis. This is calculated by assuming a normal diameter value for the adjacent coronary segment proximal or distal to the stenosis and using it as a reference. This assumption is flawed because there is virtually always diffuse intimal or subintimal thickening in the adjacent reference coronary artery segments (Arnett et al, 1979; Nissen et al, 1991) as well as age related or compensatory ectasia (Glagov et al, 1987). Furthermore, the adjacent coronary artery segments may also be subjected to the restenosis process, which will tend to underestimate the incidence of restenosis when it is defined using luminal diameter expressed as a percent of the reference diameter (Brayden et al, 1983; Beatt et al, 1988; Nobuyoshi et al, 1988; Smucker et al, 1991). The use of absolute measurements such as mean luminal diameter, minimal luminal diameter, or the minimal cross sectional area of stenosis may provide more reliable and

meaningful information on the haemodynamic significance of an obstructive coronary lesion (Wijns et al, 1985a; Serruys et al, 1986; Zijlstra et al, 1987).

There is further confusion as to whether the restenosis process is inherently a dichotomous outcome (in which lesions either do or do not cross a threshold of angiographic luminal renarrowing), or a continuous outcome (in which restenosis reflects variation in a pathological response that occurs to some degree in all mechanically injured coronary segments). In a recent study, King et al (1991) reported that the percent diameter stenosis at follow-up angiography after coronary angioplasty followed a bimodal distribution. This finding seems to support that the restenosis process is an all or none event, occurring in some lesions but not in others.

This view was not supported by Rensing et al (1992), who studied 1,445 successfully dilated lesions using quantitative angiography before and after coronary angioplasty and at 6-months follow-up. They demonstrated that the process of lumen narrowing after coronary angioplasty was normally distributed, with few lesions showing regression, most showing no change, and a considerable number showing progression. This finding has also been demonstrated by Kuntz et al (1992) in patients undergoing atherectomy or stent implantation. Restenosis can thus be viewed as the tail end of a Gaussian distribution, with some lesions crossing an arbitrary angiographic cut-off point, rather than a separate disease entity that occurs in some lesions but not in others.

Two earlier studies lend support to this view and had shown that luminal renarrowing occurred to some degree in all lesions that are dilated and that it is a continuous, time-related phenomenon. Both Nobuyoshi et al (1988) and Serruys et

al (1988b) prospectively studied the temporal sequence to restenosis using quantitative angiography to assess angiographic findings at predetermined intervals after coronary angioplasty. Early lesion progression was observed as early as day 1 in 16% of lesions dilated, although these early findings on progression did not correlate well with those on late restenosis. In contrast, Rodriguez et al (1993b) demonstrated that early worsening of obstruction, which was seen in 30% of lesions at 24 hours after coronary angioplasty, was highly predictive of restenosis at follow-up. The early reduction of luminal diameter was also shown by Sanders et al (1985), who reported that exacerbation of stenosis was already observed 30 minutes after coronary angioplasty, and Powelson et al (1987), who reported that 10% of lesions showed evidence of restenosis 2 days after angioplasty. However, these earlier studies failed to correlate these changes with late restenosis. Possible mechanisms include early arterial wall elastic recoil, arterial spasm, or thrombus formation (Serruys et al, 1988b; Hjemdahl-Monsen et al, 1990; Rensing et al, 1990; Hanet et al, 1991, Ardissino et al, 1993).

Regression of luminal narrowing was common between the first post-procedural day to 1 month after coronary angioplasty, although lesion progression occurring during this period was highly correlated with late restenosis. In the majority of patients, progression was most prevalent between 1 and 3 months, and reached a plateau thereafter. After 3 months, the trend for progression was no longer observed and restenosis rarely occurs beyond this period (Nobuyoshi et al, 1988; Serruys et al, 1988b). The finding that luminal renarrowing rarely occurs after 3 to 6 months was also supported by other studies (Holmes et al, 1984; Kaltenbach et al, 1985; Roubin et al, 1987; Cequier et al, 1988; Kent et al, 1988). This finding made it possible for a single 6-month angiogram to serve as the "gold standard" for evaluating restenosis.

Predictors of Restenosis

Despite an extensive number of studies examining the clinical-, lesion-, and procedure-related factors associated with an increased risk of restenosis, our understanding of the problem remains incomplete.

Clinical-related Variables. Clinical-related variables that have been associated with an increased risk of restenosis include **age** (Hamm et al, 1985; Leimgruber et al, 1986; Weintraub et al, 1993b), **male gender** (Holmes et al, 1984; Leimgruber et al, 1986; Vandormael et al, 1987; Black et al, 1988; Lambert et al, 1988), **prior myocardial infarction** (Holmes et al, 1984), **angina grade** (Holmes et al, 1984; Weintraub et al, 1993b), **unstable or recent onset angina** (Meyer et al, 1983; Holmes et al, 1984; Leimgruber et al, 1986; Myler et al, 1987; Ruprecht et al, 1987; MacDonald et al, 1990), **vasospastic angina** (David et al, 1984; Bertrand et al, 1986b; Guiteras et al, 1987a; Bertrand et al, 1989), **smoking** (Myler et al, 1987; Galan et al, 1988; Fleck et al, 1988), **diabetes mellitus** (Margolis et al, 1984; Myler et al, 1987; Vandormael et al, 1987; Lambert et al, 1988; Weintraub et al 1993b; Rensing et al, 1993), **hypertension** (Lambert et al, 1988; Fleck et al, 1988; Ellis et al, 1989b; Weintraub et al, 1993b), and **hyperlipidaemia** (Hamm et al, 1985; Galan et al, 1986; Myler et al, 1987).

Lesion-related Variables. Pre-procedural lesion-related variables that have been associated with higher restenosis rates include **multivessel disease** (Mata et al, 1985; Guiteras et al, 1987a; de Feyter et al, 1988), **multivessel or multilesion dilatation** (Roubin et al, 1986; Hollman et al, 1986; Le Feuvre et al, 1994), **proximal lesion location** (Whitworth et al, 1985; Vandormael et al, 1987; Roubin et al, 1987), **dilatation of left anterior descending coronary artery lesions** (Mata et al, 1985; Leimgruber et al, 1986; Hollman et al, 1986; Vandormael et al, 1987;

Roubin et al, 1987; de Feyter et al, 1988; Hirshfeld et al 1991; Weintraub et al, 1993b), **dilatation of saphenous vein graft lesions** (Holmes et al, 1984; Dorros et al, 1984b; Kussmaul, 1988; Plakto et al, 1989), **lesion severity** (Holmes et al, 1984; David et al, 1984; Mata et al, 1985; Myler et al, 1987; Black et al, 1988; Pepine et al, 1990; Hirshfeld et al, 1991), **lesion length** (Hall et al, 1984; Uebis et al, 1986; Vandormael et al, 1987; Ellis et al, 1988; Pepine et al, 1990, Bourassa et al, 1991; Rensing et al, 1993), **lesion eccentricity** (Scholl et al, 1981; Mata et al, 1985; Guiteras et al, 1987b; Hirshfeld et al, 1991; Weintraub et al, 1993), **lesion calcification** (Scholl et al, 1981; Mata et al, 1985; Guiteras et al, 1987a), **lesion angulation** (Ellis et al, 1989c), **arterial diameter** (Hirshfeld et al, 1991; Ghazzal et al, 1991; Foley et al, 1992), and **presence of collateral vessels** (Probst et al, 1985; de Feyter et al, 1988).

Post-procedural lesion-related variables that have been associated with an increased restenosis rate include **residual stenosis severity** (David et al, 1984; Levine et al, 1985; Mata et al, 1985; Leimgruber et al, 1986; Hollman et al, 1986; Guiteras et al, 1987a; Lambert et al, 1988; Pepine et al, 1990, Renkin et al, 1990; Bourassa et al, 1991; Weintraub et al, 1993b), **residual trans-stenotic pressure gradient** (Holmes et al, 1984; Marantz et al, 1984; Leimgruber et al, 1986, Hodgson et al, 1986; Bourassa et al, 1991), and **presence of thrombus after angioplasty** (Rensing et al, 1993). The presence of an **angiographically visible intimal tear** at the angioplasty site has been associated with a reduced risk of restenosis (Cowley et al, 1984a; Leimgruber et al, 1985; Bredlau et al, 1985a; Levine et al, 1985; Hollman et al, 1986; Galan et al, 1986; Matthews et al, 1988; Weintraub et al, 1993b) although this finding has not been substantiated by other studies (Fleck et al, 1988; Hermans et al, 1992a)

Procedure-related Variables. Procedure-related variables that have been associated with an increased risk of restenosis include **inflation frequency** (Clark et al, 1986; Guiteras et al, 1987a; Glazier et al, 1989a; Uebis et al, 1989; Hearn et al, 1991), **inflation pressure** (Marantz et al, 1984; Levine et al, 1985; Clark et al, 1986; Myler et al, 1987), **inflation duration** (Stack et al, 1988; Quigley et al, 1989) and **balloon to artery lumen ratio** (Duprat et al, 1984; Mata et al, 1985; von Essen et al, 1985; Guiteras et al, 1987a; Roubin et al, 1988; Nichols et al, 1989).

Many of the earlier studies were based on retrospective data although some of the recent studies allow the influence of these factors to be assessed prospectively (Macdonald et al, 1990; Renkin et al, 1990; Bourassa et al, 1991; Hirshfeld et al, 1991, Hermans et al, 1992a, Rensing et al, 1993). Despite the large number of variables evaluated, studies diverge on the significance of many and concur on the significance of few factors. Hence, it is not possible to predict with a high degree of certainty which patients, vessels, or lesions are likely to undergo restenosis. Possible explanations for the discrepancies include the different angiographic criteria of restenosis used in the various studies which identified different patient populations (Holmes et al, 1984; Serruys et al, 1988b), the wide dissimilarity in the angiographic restudy rate, and the different methods used to assess angiographic lesions.

"Relative Gain" and "Relative Loss". Recently, the concept of "relative gain" (a measure of vessel wall injury) and "relative loss" (a measure of the restenosis process) was introduced for assessing the restenosis process, by relating the absolute change in minimal luminal diameter after intervention (acute gain) and during follow-up (late loss) to the interpolated reference diameter of the coronary segment in question. According to this new paradigm, the ultimate net gain produced by

coronary angioplasty reflects the difference between acute gain and net loss (Figure 1.10). Using this concept, the Thoraxcentre investigators have shown that the greater the relative gain in minimal luminal diameter achieved by dilatation, the greater the subsequent relative loss, hence the phrase "the more you gain, the more you lose" (Beatt et al, 1992; Rensing et al, 1992; Hermans et al, 1992b). This probably reflects the combination of deep arterial injury and reversible stretch imposed on the diseased wall, both of which are known stimuli for smooth muscle cell proliferation. However, Kuntz et al (1993) have shown that the procedures that provided the largest acute gains had the lowest restenosis rates, hence the phrase "the bigger, the better". The apparently paradoxical relationship between these 2 views of restenosis can be explained by examining the relationship between absolute acute gain and late loss. For coronary balloon angioplasty, the increment in late loss is only a fraction, that is about 50%, of the immediate gain for balloon angioplasty. This relationship implies that for every 1 mm of gain seen following coronary angioplasty, a corresponding 0.5 mm of late loss in luminal diameter can be expected. While large acute gains would thus be associated with more absolute late loss, further improvement in immediate gain should result in improved net gain and thus better late results (Kuntz and Baim, 1993).

Detection of Restenosis

Although the majority of patients with restenosis after coronary angioplasty present with recurrent angina, the positive predictive value of symptoms for predicting restenosis have been shown to range from 44% to 92% (Holmes et al, 1984; Mabin et al, 1985a; Levine et al, 1985; Zaidi et al, 1985; Gruentzig et al, 1987; Simonten et al, 1988). Symptom recurrence also lacks specificity since angina may also be due to vasospasm, incomplete revascularisation, new disease, or non-cardiac chest

pain (Quyyumi et al, 1986; Joelson et al, 1987). Furthermore, up to 25% of those without recurrent symptoms have restenosis (Holmes et al, 1984).

The value of a non-invasive test that could accurately and reliably detect coronary restenosis is obvious. However, the reported value of a non-invasive test depends greatly on the completeness of angiographic follow-up data, and is confounded by inadequate stress yielding low exercise heart rates, the presence of drugs that are known to influence test results, and the extent of disease in vessels other than those dilated (Hlatky et al, 1988). Nevertheless, exercise treadmill testing (Scholl et al, 1982; Ernst et al, 1985; El-Tamimi et al, 1990; Bengtson et al 1990a), exercise radionuclide angiography and thallium scintigraphy (Scholl et al, 1982; DePuey et al, 1984; Wijns et al, 1985b; Breisblatt et al, 1988), exercise echocardiography (Bengtson et al, 1990b; Rowland et al, 1990), and dipyridamole echocardiography (Picano et al, 1989) have all been shown to improve the detection of restenosis. In general, a positive test result is only moderately accurate in identifying patients with angiographically defined restenosis (positive predictive value) whereas a negative result provides a high level of assurance that restenosis is absent (negative predictive value). Since patients with angiographic restenosis who remain asymptomatic and who have no evidence of exercise induced ischaemia have a benign course, with occurrence of symptoms well before a clinical event, conservative management in these patients seems justified (Wijns et al, 1985b; Gruentzig et al, 1987; Rosen et al, 1987; Popma et al, 1988; Hernandez et al, 1992; Le Feuvre et al, 1994).

(c) STRATEGIES FOR THE PREVENTION OF RESTENOSIS

Despite substantial basic and clinical efforts to address the problem of restenosis, effective preventive therapies have not yet been developed after a decade of intensive clinical and pharmacological research.

Pharmacological Approaches

Despite the extensive theoretical basis, the influence of pharmacological treatment on restenosis in humans remains unproven. Randomised clinical trials assessing the effect of **antiplatelet agents** (Thornton et al, 1984; White et al 1987b; Mufson et al, 1988; Dyckmans et al, 1988; Kitazume et al, 1988; Schanzenbacher et al, 1988; Finci et al, 1988; Schwartz et al, 1988; Chesebro et al, 1989; Taylor et al, 1991), **anticoagulants** (Thornton et al, 1984; Urban et al, 1988; Ellis et al, 1989d; Hirshfeld et al, 1991; Faxon et al, 1992c), **calcium antagonists** (Corcos et al, 1985; Whitworth et al, 1986, Hoberg et al, 1990; Unverdorben et al, 1992), **corticosteroids** (Rose and Beauchamp, 1987; Stone et al, 1989; Pepine et al, 1990), **lipid lowering agents** (Hollman et al, 1989; Sahni et al, 1992; Weintraub et al, 1992), **omega-3 fatty acids** (Slack et al, 1987; Dehmer et al, 1988; Grigg et al, 1989; Reis et al, 1989; Milner et al, 1989; Nye et al, 1990; Bairati et al, 1992; Jacobs et al, 1994), **platelet derived growth factor antagonists** (Okamoto et al, 1992, Nishikawa et al, 1992; Starc Study Group, 1993), **angiotensin converting enzyme inhibitors** (Mercator Study Group, 1992; Faxon, 1992d; Desmet et al, 1992), **antiproliferatives** (Faxon et al, 1992c; O'Keefe et al, 1992), **prostacyclin** (See et al, 1987; Raizner et al, 1988; Knudtson et al, 1990), **thromboxane A2 receptor antagonists** (Yabe et al, 1989; Savage et al, 1991a, Serruys et al, 1991a; Pepine et al, 1992), **serotonin antagonists** (Klein et al, 1989; Heik et al, 1992),

and **somatostatin analogues** (Amtorp et al, 1993; Eriksen et al, 1993; Emanuelsson et al, 1994) have been conducted.

Although some of these pharmacological agents have shown promise, the published results are conflicting, and the majority have failed to reduce the restenosis rate. There is no conclusive evidence that any current drug treatment is effective for preventing restenosis. Many of the early trials have been flawed by statistical and design problems, including inadequate dose and administration route, small sample sizes and incomplete angiographic follow-up, and lack of standardised clinical and angiographic outcomes (Popma et al, 1991). Moreover, with the realisation that the vascular injury response is initiated immediately following angioplasty, there may have been too little attention paid to having these agents "on board" before the onset of angioplasty. However, multiple trials are currently underway to evaluate new pharmacological agents that have an adequate planned sample size and improved attention to these methodological parameters.

Non-pharmacological Approaches

New devices for percutaneous coronary recanalisation were introduced in an attempt to reduce the amount of intimal hyperplasia compared with balloon angioplasty, by producing a less reactive luminal surface and providing a larger post treatment lumen diameter. Although these newer devices (endoluminal coronary stent implantation; directional, extractional, or rotational atherectomy; laser balloon angioplasty; and excimer laser) do provide in a larger acute gain in lumen diameter, the restenosis process, resulting in late loss of lumen diameter, appears to be greater than that seen after conventional balloon angioplasty (Kuntz et al, 1992). However, the increment in late loss is only a fraction, that is about 50%, of the immediate gain after stenting and directional atherectomy (Kuntz et al, 1993), as well as for

excimer laser followed by adjunctive balloon dilation (Bittl et al, 1992a). Therefore, further improvement in immediate gain should result in improved net gain and thus better late results, even though the absolute late loss is increased, although this favourable relationship between late loss and acute gain has not been confirmed by other studies (Umans et al, 1993). However, apart from primary stent implantation, most of these devices have, up to now, failed to provide better long-term outcome than balloon angioplasty (Karsch et al 1990; Serruys et al 1991b; Bittl et al, 1992b; Buchwald et al, 1992; Bertrand et al, 1992; Strauss et al, 1992; Umans et al, 1993; Stertzer et al, 1993; Feld et al, 1993).

Coronary Angioplasty Versus Excisional Atherectomy Trial. The **CAVEAT** study (Coronary Angioplasty Versus Excisional Atherectomy Trial) is a multicentre randomised trial comparing directional coronary atherectomy versus balloon angioplasty (Topol et al, 1993). A total of 1012 patients were randomly assigned to either atherectomy (n=512) or angioplasty (n=500). Patients underwent repeat coronary angiography at 6 months which were assessed using computer-assisted quantitative methods. Although directional atherectomy had a significantly greater procedural success rate than balloon angioplasty (89% versus 80%, $p<0.001$), atherectomy also led to more complications than did angioplasty, including death, myocardial infarction, emergency bypass surgery, and abrupt vessel closure (11% versus 5%, $p<0.001$). Overall event-free survival rates at 6-months were virtually indistinguishable in the 2 treatment groups but the probability of death or myocardial infarction was higher in the atherectomy group (8.6% versus 4.6%, $p=0.007$). The frequency of angiographic restenosis, as defined by the occurrence of stenosis of >50% of the vessel's diameter after 6-months of follow-up, was only marginally lower with atherectomy (50% versus 57%, $p=0.06$). Most of the reduction in the rate of restenosis was confined to lesions in the proximal left

anterior descending artery, but this difference was not associated with improvement in clinical outcome.

Canadian Coronary Atherectomy Trial. The **CCAT** study (Canadian Coronary Atherectomy Trial) is another multicentre randomised trial comparing directional atherectomy with balloon angioplasty for lesions in the proximal segment of the left anterior descending artery (Adelman et al, 1993). Of 274 patients randomised, 134 were assigned to atherectomy and 136 to angioplasty. At a median of 5.9 months, 97% of patients underwent follow-up angiography. Computer-assisted quantitative methods were used for assessing coronary angiograms. Although directional atherectomy enlarged the luminal diameter more than did balloon angioplasty (1.45 $\pm$ 0.47 mm versus 1.16 $\pm$ 0.44 mm, $p<0.001$), the initial rates of angiographic success (94% versus 88%), complications (5% versus 6%), restenosis (46% versus 43%), and event-free survival rates at 6-months (71% versus 71%) were not significantly different between the 2 groups.

The results from these studies suggest that the clinical outcomes after directional atherectomy and balloon angioplasty are similar. The role of coronary atherectomy in the treatment of coronary artery disease is yet to be defined although stenoses of bypass grafts, stenoses at the coronary ostia, and highly eccentric lesions, may be better treated with directional atherectomy (Hinohara et al, 1991).

Benestent Study. The **Benestent** study is a multicentre trial comparing stent implantation using the Palmaz-Schatz device (n=262) versus balloon angioplasty (n=258) in 520 patients with stable angina and a *de novo* lesion in a native coronary artery (Serruys et al, 1994). The primary end-points were death, the occurrence of a cerebrovascular accident, myocardial infarction, the need for coronary artery bypass

surgery, or a second percutaneous intervention involving the previously treated lesion, either at the time of the initial procedure or during the subsequent 7 months. The primary angiographic end-point was the luminal diameter at follow-up, as determined by quantitative coronary angiography.

There was an increased incidence of the combined primary end-point, in patients randomised to angioplasty compared to those randomised to stent implantation (30% versus 20%, $p=0.02$). The restenosis rate was also significantly higher in patients randomised to angioplasty compared to those randomised to stent implantation. The minimal luminal diameters at follow-up were 1.82 ± 0.64 mm in the stent group and 1.73 ± 0.55 mm in the angioplasty group ($p=0.09$). This corresponds to a restenosis rate (defined as a diameter stenosis of ≥50%) of 22% in the stent group versus 32% in the angioplasty group ($p=0.02$). However, peripheral vascular complications necessitating surgery, blood transfusion, or both were more common in the stent group compared to the angioplasty group (13.5% versus 3.1%, $p<0.001$). The mean hospital stay was significantly longer in the stent group than in the angioplasty group (8.5 days versus 3.1 days, $p<0.001$).

Stent Restenosis Study. The **STRESS** (Stent Restenosis Study) trial is another multicentre study comparing balloon angioplasty ($n=203$) versus single Palmaz-Schatz stents placement ($n=207$) in 410 patients with symptomatic coronary disease, and a *de novo* lesion in a native coronary artery with a vessel diameter of ≥ 3 mm (Fischman et al, 1994). The primary end-point was angiographic evidence of restenosis, defined as at least 50% stenosis on the follow-up angiogram. The secondary clinical end-point was a composite end-point, defined as whichever of the following occurred first: death, myocardial infarction, coronary artery bypass surgery, and the need for repeated angioplasty within the first 6 months.

Procedural success was achieved in 96.1% of stent procedures versus 89.6% of angioplasty procedures ($p=0.011$). There was no difference in the occurrence of any early major cardiac event (death, myocardial infarction, coronary artery bypass surgery, or repeated angioplasty within 14 days after the procedure) between the stent and angioplasty patients (5.9% versus 7.9%, $p=0.41$). Bleeding and vascular complications occurred more commonly in the stent group than in the angioplasty group (7.3% versus 4.0%, $p=0.14$). The hospital stay after the procedure was longer in the stent group (5.8 days versus 2.8 days, $p<0.001$).

At 6 months, the patients with stented lesions have a larger luminal diameter (1.74 $\pm$ 0.60 mm versus 1.56 $\pm$ 0.65 mm, $p=0.007$) and a lower rate of restenosis (31.6% versus 42.1%, $p=0.046$) than those treated with angioplasty. Fewer patients in the stent group underwent symptom-driven revascularisation of the target lesion by bypass surgery or angioplasty (10.2% versus 15.4%, $p=0.06$). Event-free survival was 80.5% in the stent group, as compared with 76.2% in the angioplasty group ($p=0.16$).

Although these preliminary results from *de novo* stent implantation are encouraging, the risks associated with stenting are substantial. The need for intensive anticoagulant therapy requires prolonged hospitalisation, and results in bleeding problems, manifesting as a need for transfusions or major peripheral vascular complications. There is also a 3% to 4% risk of subacute thrombosis of the stent, which can result in myocardial infarction or death. Furthermore, stent implantation is expensive, and the long-term results are not known. Further results should be awaited before drawing final conclusions on the merits of primary stenting.

1.6 OBJECTIVES OF THIS STUDY

The efficacy and safety of percutaneous transluminal coronary angioplasty have been enhanced by continuing refinement in technique, greater operator experience, and equipment evolution. Currently, experienced centres achieve successful dilatation in approximately 90% of lesions in which coronary angioplasty is attempted (Anderson et al, 1985). As a result, coronary angioplasty has increasingly been extended to patients with more complex coronary artery disease, although patients with "unprotected" left main stem stenosis are specifically contraindicated because of the catastrophic risk of complications and late restenosis (Gruentzig et al; 1979, Stertzer et al, 1985; O'Keefe et al, 1989b). Coronary angioplasty is increasingly performed in more challenging arteries including those with tortuous segments, multiple branches, ectopic origins, distally located stenoses, or other complex lesion morphology. Nonetheless, considerable controversy remains about its application in certain patient and morphological subsets. A difference of opinion continues regarding management of patients with coronary ostial stenoses, old saphenous vein grafts, chronic total occlusions, and unstable angina pectoris because of the unfavourable acute results and higher restenosis rates. Because of the significantly higher acute complication rates, the use of coronary angioplasty in lesions with certain morphological features (eg lesions that are long, angulated, calcified, markedly ectatic, located at bifurcations, or contain thrombus) remains uncertain. Furthermore, the role of coronary angioplasty in the management of elderly patients with symptomatic coronary artery disease, and repeated angioplasty in patients with recurrent restenosis, are topics of continuing debate. This thesis has aimed to examine the feasibility of percutaneous transluminal coronary angioplasty in many of the aforementioned patient and lesion morphological subsets. It has also

aimed to provide data in assisting the selection of patients or lesions for this procedure so as to ensure continued improvement in acute and long-term outcome.

This thesis has studied the acute success and complication rates, and long-term results of coronary angioplasty of chronic total occlusions. A multiple logistic regression model has been described which incorporates clinical and angiographic data to predict the probability of procedural success for a particular lesion. Evaluation has also been made of the impact of a successful procedure on follow-up clinical events.

This thesis has evaluated the acute success and complication rates, and long-term results of coronary angioplasty of ostial stenoses. Since the technical requirements, procedural success, complication and restenosis rates differ among aorta ostial, non-aorta ostial, and branch ostial stenoses, these data have been examined separately for each of these anatomical species of ostial disease.

Evaluations have also been made of acute and long-term results of coronary angioplasty for patients with prior coronary artery bypass grafting, for elderly patients aged 70 years and older, and for patients with left anterior descending artery 'tandem lesions'.

The feasibility of a third coronary angioplasty procedure for a second restenosis has been examined, and the correlates of clinical restenosis after a third angioplasty procedure have been determined.

Assessment has been made of clinical and lesion morphological determinants of acute coronary angioplasty success and complications. Previously reported

American College of Cardiology/American Heart Association ABC lesion classification scheme and its modifications have been validated. Multiple logistic regression models that incorporate lesion specific morphological characteristics to predict acute angioplasty outcomes have been developed, in the expectation that they may contribute to any new classification schemes that may emerge in the future.

Finally, examination of the angiographic findings when chest pain recurs after successful coronary angioplasty has been undertaken. The ability to predict the angiographic findings on the basis of baseline clinical-, angiographic-, and procedure-related factors has been assessed, since this may have important implications for the selection of patients for repeat coronary angiography when chest pain recurs after successful angioplasty. Whether accelerated development of atherosclerosis can occur as a complication of coronary balloon angioplasty has also been systematically evaluated.

Table 1.1. Selected Studies Addressing Acute Success Rates of Coronary Angioplasty (At Lest 1 Lesion Successfully Dilated).

First author (year)	Patients (number)	Multivessel disease (%)	Success rate (%)	Definition of success
Grüntzig (1979)	50	40	64	Reduction in DS ≥10% Reduction in TSPG ≥10%
Stertzer (1979)	70	67	56	NR
Cowley (1981)	25	24	56	Reduction in DS ≥20% Reduction in TSPG ≥50%
Alford (1982)	50	8	50	NR
Vlietstra (1983)	100	100	72	Reduction in DS ≥40% No CABG
Detre (1984)	768	100	63	Reduction in DS ≥20%
Faxon (1984a)	3079	28	66	Reduction in DS ≥20%
Faxon (1984a)	3079	28	51	Reduction in DS ≥40%
Kober (1985)	1000	27	77	Reduction in DS ≥20%
Valeix (1985)	1247	9	69	NR
Bredlau (1985b)	3500	19	90	Reduction in DS ≥20%
Cowley (1985)	100	100	95	Reduction in DS ≥20% Clinical improvement
Mata (1985)	74	100	85	Reduction in DS ≥20% Residual DS ≤60%
Mabin (1985a)	229	38	67	Reduction in DS ≥40% No Emergency CABG
Levin (1985)	100	NR	78	Reduction in DS ≥20% Residual DS ≤60%

To be continued

Table 1.1 (continued). Selected Studies Addressing Acute Success Rates of Coronary Angioplasty (At Lest 1 Lesion Successfully Dilated).

First author (year)	Patients (number)	Multivessel disease (%)	Success rate (%)	Definition of success
Harston (1986)	100	NR	95	Reduction in DS ≥20%
Bertrand (1986)	813	100	78	NR
Myler (1987)	494	100	85	Reduction in DS ≥35% Residual DS ≤50% TSPG ≤15 mmHG No major complication
Finci (1987d)	100	100	85	Residual DS ≤50% less gradient No major complication
Ernst (1987a)	1352	30	86	Reduction in DS ≥20% No major complication
Tuzcu (1988)	2677	NR	93	Reduction in DS ≥20% Residual DS ≤50% No major complication
Detre (1988)	2892	53	91	Reduction in DS ≥20%
Detre (1988)	963	100	91	Reduction in DS ≥20%
Perry (1988)	280	9	86	Residual DS ≤50% No major complication
Deligonul (1988a)	470	100	85	Reduction in DS ≥30% Residual DS ≤50% No major complication
Disciascio (1988)	50	100	93	Reduction in DS ≥20% Residual DS ≤50% Clinical improvement
Hamad (1988)	781	NR	88	Residual DS ≤50%

To be continued

Table 1.1 (continued). Selected Studies Addressing Acute Success Rates of Coronary Angioplasty (At Lest 1 Lesion Successfully Dilated).

First author (year)	Patients (number)	Multivessel disease (%)	Success rate (%)	Definition of success
Steffinino (1988)	500	NR	86	Residual DS ≤50% Improved gradient No major complication Clinical improvement
Akins (1989)	389	40	83	Reduction in DS ≥20% Residual DS ≤50%
Hochberg (1989)	125	30	88	NR
Henderson (1989)	412	0	80	Residual DS ≤50% No major complication
Hubner (1990)	3666	NR	87	Residual DS ≤50% No major complication
Richardson (1990)	540	9	82	Reduction in DS ≥50%
de Feyter (1990)	1398	39	92	Residual DS ≤50%
O'Keefe (1991)	3186	100	96	Residual DS ≤40%
Vandormael (1991)	637	100	83	Reduction in DS ≥30% Residual DS ≤50% No major complication
Warner (1992)	103	100	95	Reduction in DS ≥20% Residual DS ≤50%
Kadel (1992)	798	0	81	Reduction in DS ≥20% No major complication
Le Feuvre (1993)	203	100	91	Reduction in DS ≥20% Residual DS ≤50% No major complication

CABG=coronary artery bypass surgery; DS=diameter stenosis; NR=not reported; TSPG=transtenotic pressure gradient.

Table 1.2. Selected Studies Addressing Acute Complication Rates of Coronary Angioplasty.

First author (year)	Patients (number)	Multivessel disease (%)	Major complications (%)	Death (%)	MI (%)	Emergency CABG (%)
Grüntzig (1979)	50	40	NR	0.0	6.0	14.0
Alford (1982)	50	8	14.0	2.0	NR	14.0
Vlietstra (1983)	100	100	10.0	0.0	2.0	6.0
Cowley (1984a)	3079	28	9.4	0.9	5.5	6.6
Kober (1985)	1000	27	NR	0.4	NR	5.2
Valeix (1985)	1247	9	NR	0.9	5.8	8.9
Bredlau (1985b)	3500	19	4.1	0.1	2.7	2.7
Cowley (1985)	100	100	NR	NR	5.0	4.0
Mata (1985)	74	100	1.3	0.0	1.3	0.0
Mabin (1985a)	229	38	NR	0.4	3.0	10.0
Levin (1985)	100	NR	10.0	3.0	NR	7.0
Harston (1986)	100	NR	3.0	0.0	3.0	1.0
Bertrand (1986)	813	100	NR	2.2	5.8	4.5
Myler (1987)	494	100	3.8	0.4	3.0	2.8
McEnierny (1987)	3696	NR	NR	0.2	NR	4.2
Finci (1987d)	100	100	8.0	0.0	5.0	5.0
Ernst (1987a)	1352	30	NR	0.7	3.6	2.6
Perry (1988)	280	9	NR	1.1	6.4	2.9
Holmes (1988a)	2892	53	7.2	1.0	4.7	3.4
Deligonul (1988a)	470	100	7.2	2.8	2.1	6.4

To be continued

Table 1.2 (continued). Selected Studies Addressing Acute Complication Rates of Coronary Angioplasty.

First author (year)	Patients (number)	Multivessel disease (%)	Major complications (%)	Death (%)	MI (%)	Emergency CABG (%)
Disciascio (1988)	50	100	NR	0.0	11.0	1.8
Hamad (1988)	781	NR	NR	0.1	1.2	2.2
Steffinino (1988)	500	NR	NR	0.2	4.8	1.6
Hochberg (1989)	125	30	NR	3.0	4.0	10.0
Henderson (1989)	412	0	6.8	0.5	5.6	2.2
Hubner (1990)	3666	NR	NR	0.8	2.4	2.7
Richardson (1990)	540	9	NR	0.9	NR	2.2
de Feyter (1990)	1398	39	3.6	0.4	2.5	2.5
O'Keefe (1991)	3186	100	2.9	1.0	1.5	1.0
Vandormael (1991)	637	100	NR	1.4	0.9	6.9
Warner (1992)	103	100	5.8	0.0	5.8	0.0
Kadel (1992)	798	0	7.1	0.3	2.8	5.9
Le Feuvre (1993)	203	100	6.4	0.0	6.4	1.5

CABG=coronary artery bypass surgery; MI=myocardial infarction; NR=not reported.

Table 1.3. Characteristics of Type A, B, and C Lesions According to the American College of Cardiology/American Heart Association Task Force.

Type A Lesions (High Success, >85%; Low Risk)

Discrete (<10 mm length)
Concentric
Readily accessible
Non-angulated segment, <45°
Smooth contour
Little or no calcification
Less than totally occlusive
Not ostial in location
No major branch involvement
Absence of thrombus

Type B Lesions (Moderate Success, 60 to 85%; Moderate risk)

Tubular (10 to 20 mm length)
Eccentric
Moderate tortuosity of proximal segment
Moderately angulated segment, >45°, <90°
Irregular contour
Moderate to heavy calcification
Total occlusions <3 months old
Ostial in location
Bifurcational lesions requiring double guide wires
Some thrombus present

Type C Lesions (Low Success, <60%; High Risk)

Diffuse (>20 mm length)
Excessive tortuosity of proximal segment
Degenerated vein grafts with friable lesions
Total occlusion >3 months old
Extremely angulated segments >90°
Inability to protect major side branches

Modified Schemes

Ellis et al (1990a): Type B1 lesion = 1 adverse type B characteristic; Type B2 lesion= ≥2 adverse type B characteristics.

Myler et al (1992): Type C1 lesion = 1 adverse type C characteristic; Type C2 lesion = ≥2 adverse type C characteristics.

Table 1.4. Direct Coronary Angioplasty Trials.

First author (year)	Patients (number)	Successful PTCA (%)	Early mortality (%)	Emergency CABG (%)	Early reocclusion (%)
Holmes (1985)	11	91	0	0	0
Linnemeier (1985)	31	87	NR	0	NR
Hartzler (1986)	222	91	7	4	10
O'Neill (1986)	29	85	7	0	4
Topol (1986)	47	86	6	0	3
Kimura (1986)	58	88	NR	NR	14
Marco (1987)	43	95	9	0	10
Sriram (1988)	8	87	0	0	0
O'Keefe (1989)	500	94	7	2	9
Kahn (1990)	250	95	1	1	NR

CABG=coronary artery bypass surgery; NR=not reported; PTCA=percutaneous transluminal coronary angioplasty.

Table 1.5. Impact of Coronary Angioplasty on Survival in Cardiogenic Shock.

First author (year)	Patients (number)	Overall survival (%)	Reperfusion (%)	Survival with reperfusion (%)	Survival without reperfusion (%)
O'Neill (1985)	27	70	88	75	3
Brown (1985)	28	43	61	58	18
Sahni (1986)	9	66	66	83	0
Heuser (1986)	10	70	60	100	25
Lee (1988)	24	50	54	83	25
Laramee (1988)	39	59	86	NR	NR
O'Keefe (1989)	40	59	NR	NR	NR
Verna (1989)	7	86	100	86	0
Kaplan (1990)	88	42	61	65	29
Brodie (1991)	22	50	68	NR	NR
Lee (1991)	69	55	71	69	30
Eltchaninoff (1991)	33	64	76	76	25
Moosvi (1992)	38	NR	78	56	8
Gacioch (1992)	48	NR	73	61	7
Hibbard (1992)	45	56	62`	71	29

NR=not reported

Table 1.6. Commonly Employed Definitions of Restenosis

(1) A loss of ≥30% diameter stenosis from post-PTCA to follow up (NHLBI-1).

(2) An initial stenosis of <50%, increasing to ≥70% at follow up (NHLBI-2).

(3) A return to within 10% of the predilation stenosis (NHLBI-3).

(4) A loss of ≥50% of the gain achieved by PTCA (NHLBI-4).

(5) A loss of ≥20% diameter stenosis from post-PTCA to follow up.

(6) A post PTCA stenosis of <50% increasing to ≥50% at follow up.

(7) A diameter stenosis of ≥50% at follow up.

(8) A diameter stenosis of ≥70% at follow up.

(9) A diameter stenosis of ≥75% at follow up.

(10) A diameter stenosis of <20% below pre-PTCA diameter stenosis.

(11) Loss of ≥0.72 mm in minimal luminal diameter from post-PTCA to follow up.

(12) Loss of ≥0.5 mm in minimal luminal diameter from post-PTCA to follow up.

(13) Loss of ≥1 mm^2 in stenosis area from post-PTCA to follow up.

(14) Area stenosis of ≥85% at follow up.

(15) Diameter stenosis of >50% at follow up (defined as diameter stenosis <50% and a gain of >10% in luminal diameter immediately after PTCA). Lesions with a <10% increase in diameter stenosis since PTCA are not included.

NHLBI=National Heart, Lung, and Blood Institute definition. PTCA=Percutaneous transluminal coronary angioplasty.

Table 1.7. Selected Studies Addressing the Incidence of Coronary Restenosis

First Author (Year)	Patients (number)	Angiographic follow-up (%)	Interval PTCA to follow-up (months)	Restenosis (%)	Restenosis Criterion According to Table 1.1
Meyer (1983)	70	90	6	20	14
Thornton (1984)	248	72	6-9	31	4
Holmes (1984)	665	84	6.2	33.6	4
Fleck (1984)	51	100	6	42	13
Kaltenbach (1985)	356	94	5.6	12	10
Levine (1985)	100	92	6	40	4
Corcos (1985)	92	100	8.2	18.5	2
Zaidi (1985)	184	100	-	48	-
Leimgruber (1986)	1758	57	7	30.3	7
Bertrand (1986a)	229	-	7	32	4
Uebis (1986)	100	89	5.9	24.8	4
Vandormael (1987)	129	62	7	33	5
Ernst (1987a)	1163	63	4.5	24	4
Finci (1987d)	85	91	12	51	7
Guiteras (1987a)	181	98	4.7	29	1
Deligonul (1988a)	397	56	7	50	7
de Feyter (1988)	179	88	5.1	32	4
Serruys (1988b)	400	85	1	0.9	11
			2	12.4	11
			3	22.6	11
			4	25.5	11
Nobuyoshi (1988)	185	81	24 Hours	14.6	4
	229	100	1	12.7	4
	219	96	3	43.0	4
	149	65	6	49.4	4
Honan (1989)	144	88	2-11	40	9
Bengtson (1990)	303	92	6	36	9
Le Feuvre (1993)	203	78	-	37.2	15

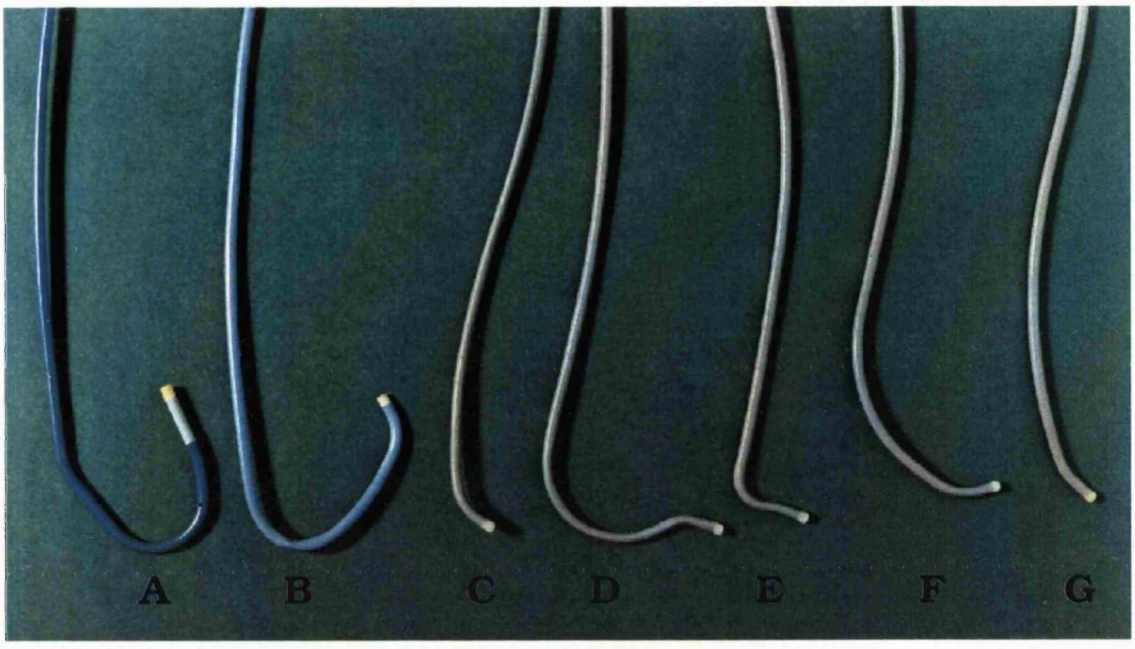


FIGURE 1.1. Commonly used guiding catheters.
A=Left Voda; B=Left Judkins; C=Right Judkins; D=Left Amplatz;
E=Right Amplatz; F=Left coronary bypass; G=Right coronary bypass.

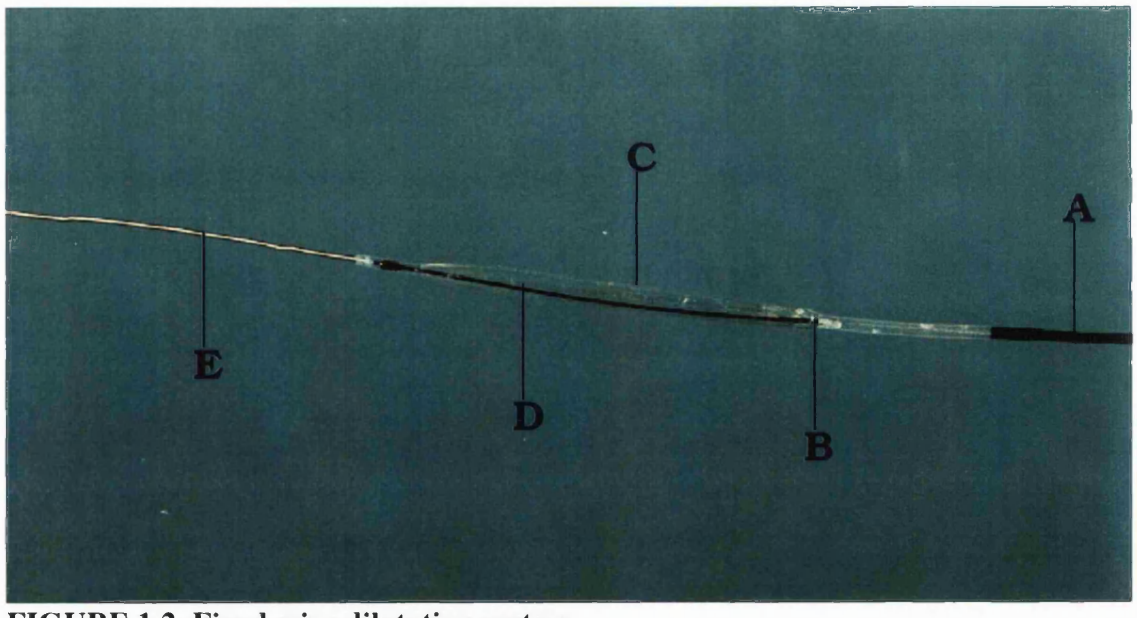


FIGURE 1.2. Fixed-wire dilatation system.
A=Catheter shaft; B=Radiopaque marker; C=Balloon; D=Tapered core wire;
E=Fixed radiopaque distal wire.

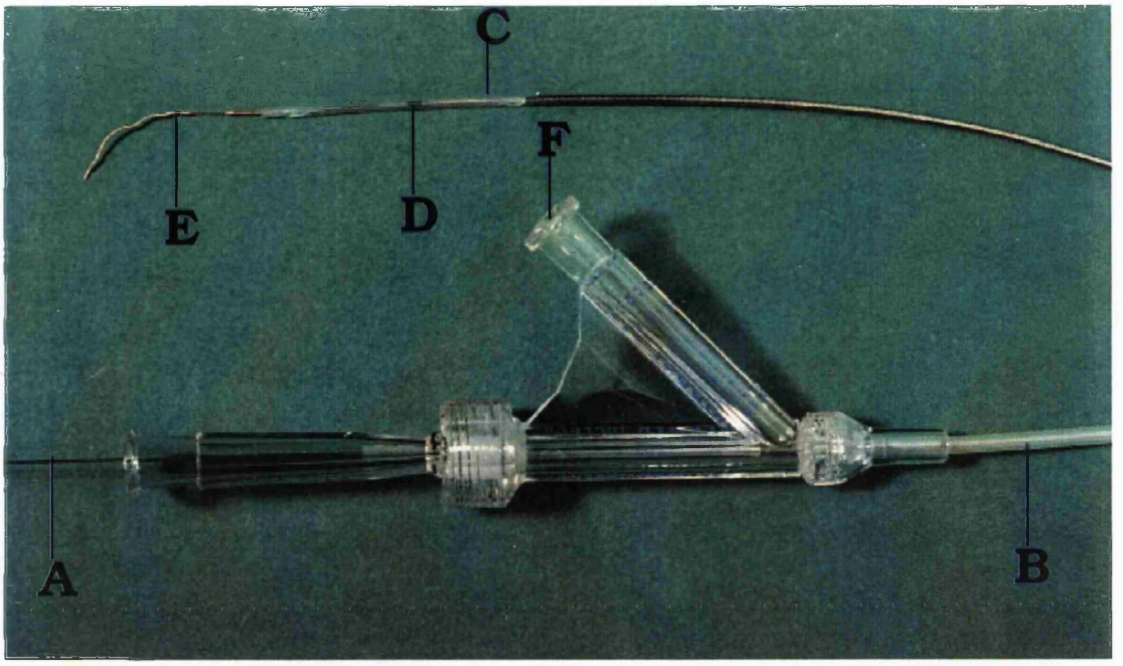


FIGURE 1.3. Over-the-wire dilatation system
A=Guidewire; B=Catheter shaft; C=Balloon; D=Radiopaque marker;
E=Continuation of guidewire; F=Inflation/deflation lumen.

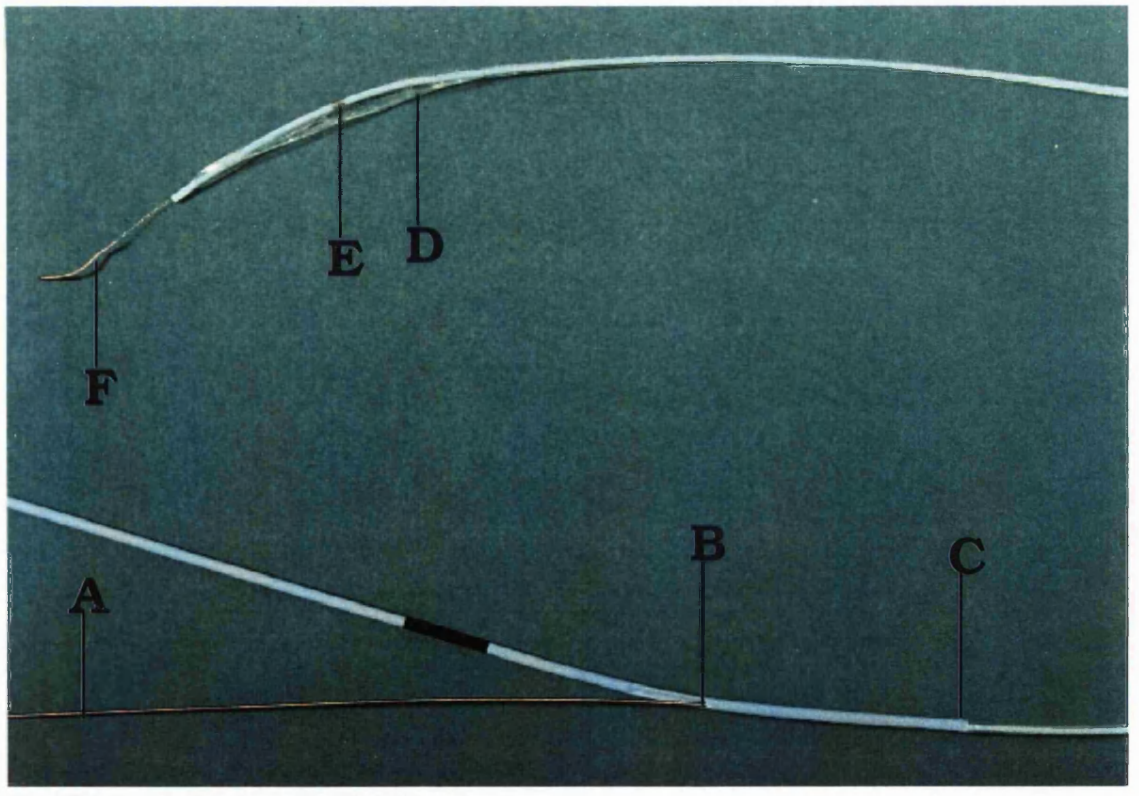


FIGURE 1.4. Monorail dilatation system.
A=Guidewire; B=Point where guidewire exits the catheter; C=Monorail shaft;
D=Balloon; E=Radiopaque marker; F=Continuation of guidewire.

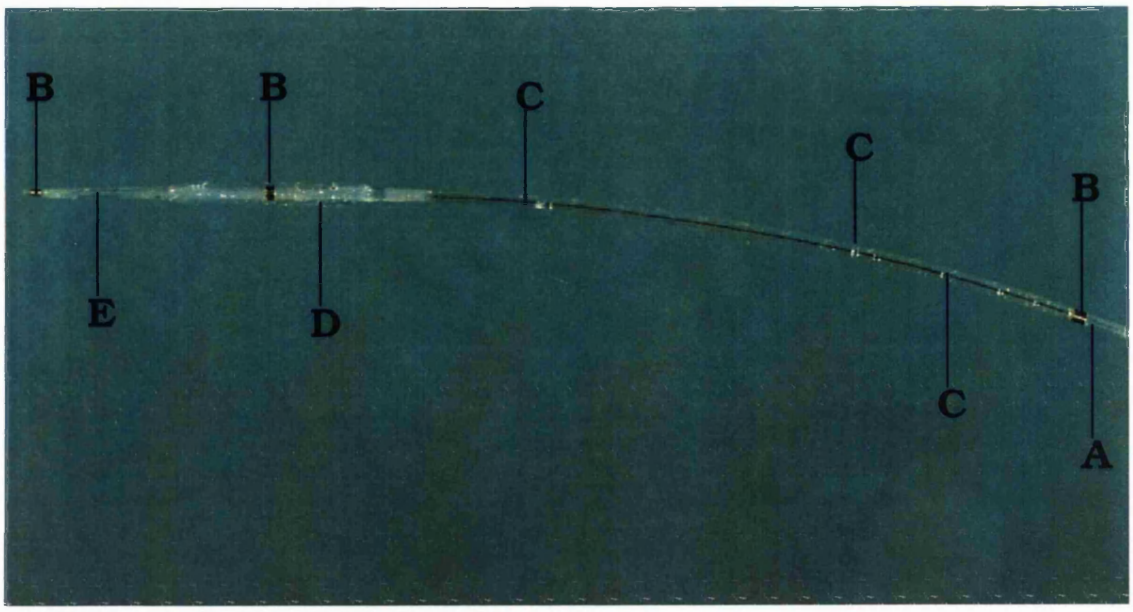


FIGURE 1.5. Autoperfusion dilatation system.
A=Catheter shaft; B=Radiopaque markers; C=Proximal perfusion ports;
D=Balloon; E=Distal perfusion ports.

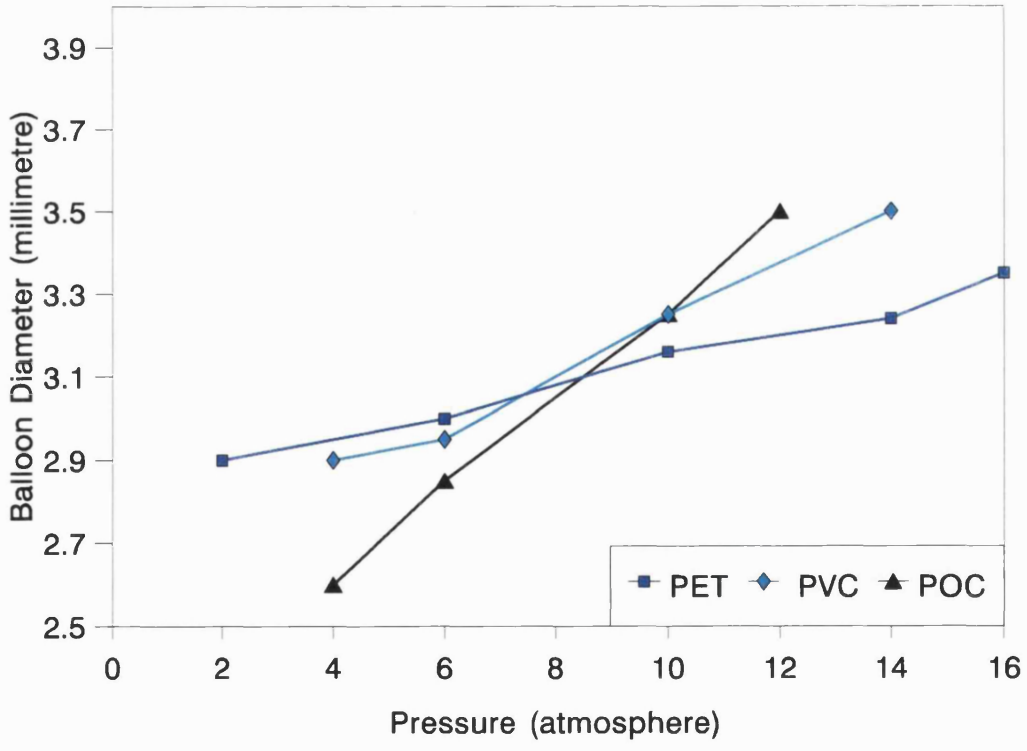


Figure 1.6. Typical compliance characteristics for a 3-mm angioplasty balloon.
POC=polyolefin copolymer; PVC=polyvinyl chloride;
PET=polyethylene terephthalate.

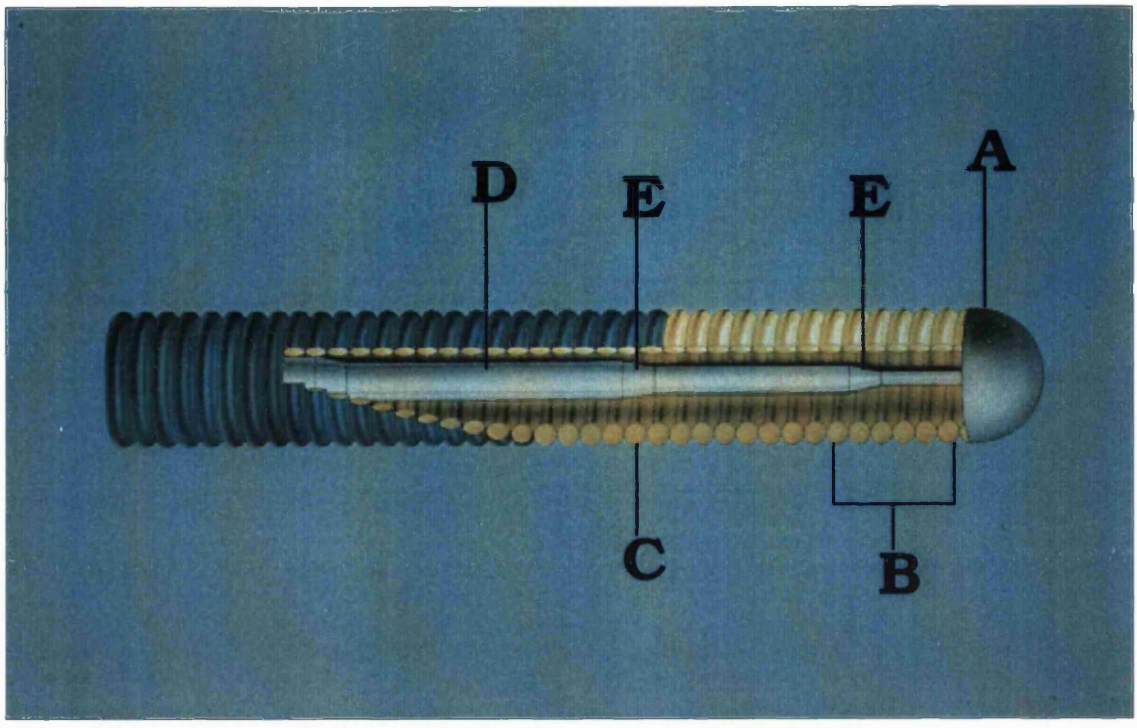


FIGURE 1.7. The major components of a guidewire.
A=Distal tip weld; B=Spring coil; C=Full Teflon coating;
D=Tapered central wire core; E=Transitional zones in wire core.

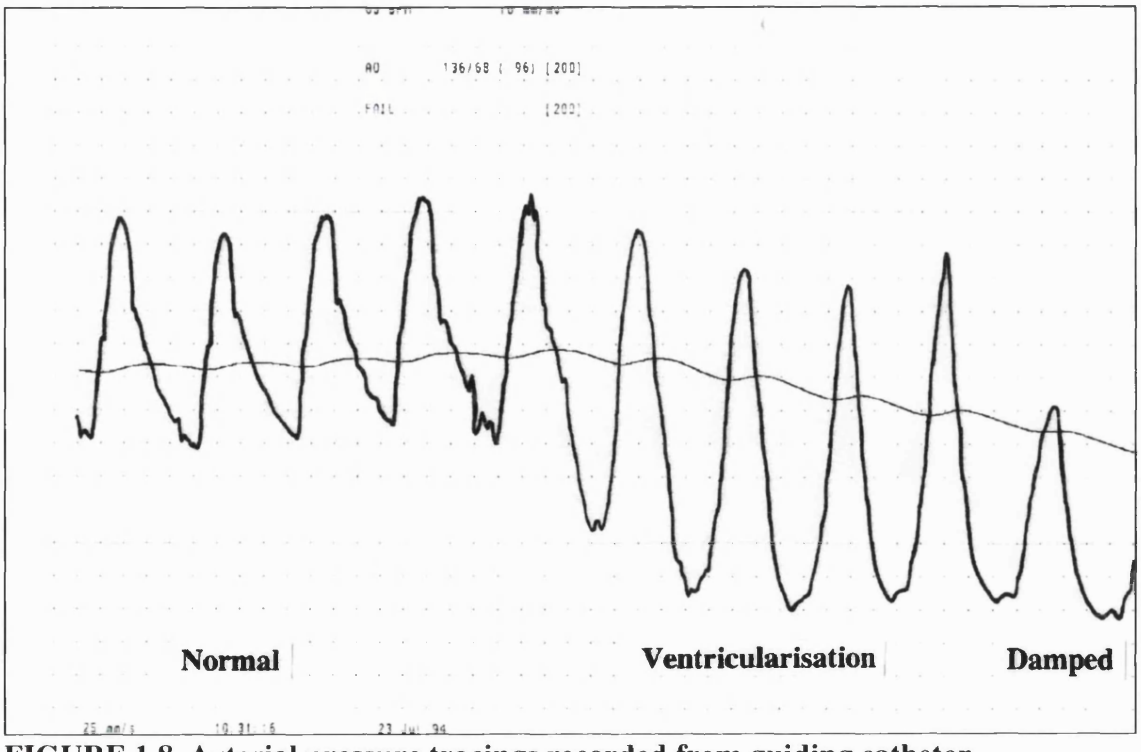


FIGURE 1.8. Arterial pressure tracings recorded from guiding catheter.

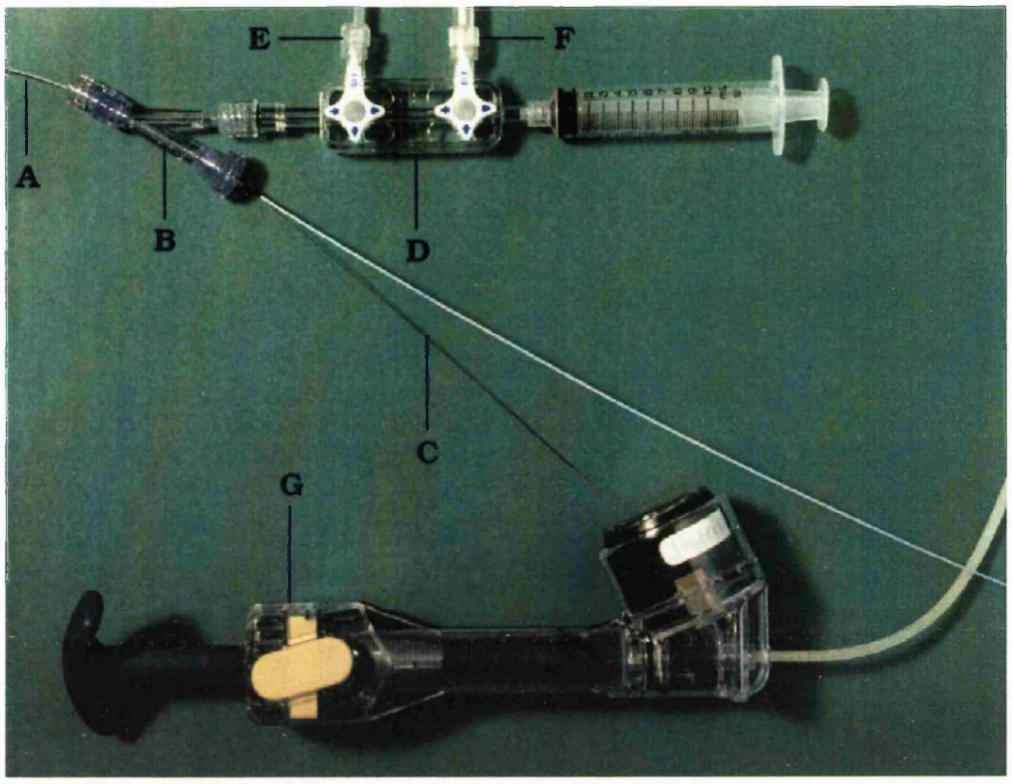


FIGURE 1.9. Basic angioplasty equipment and setup.
A=Dilatation catheter; B=Y-connector; C=Guidewire; D=Manifold;
E=Arterial pressure monitoring; F=Contrast; G=Inflation device.

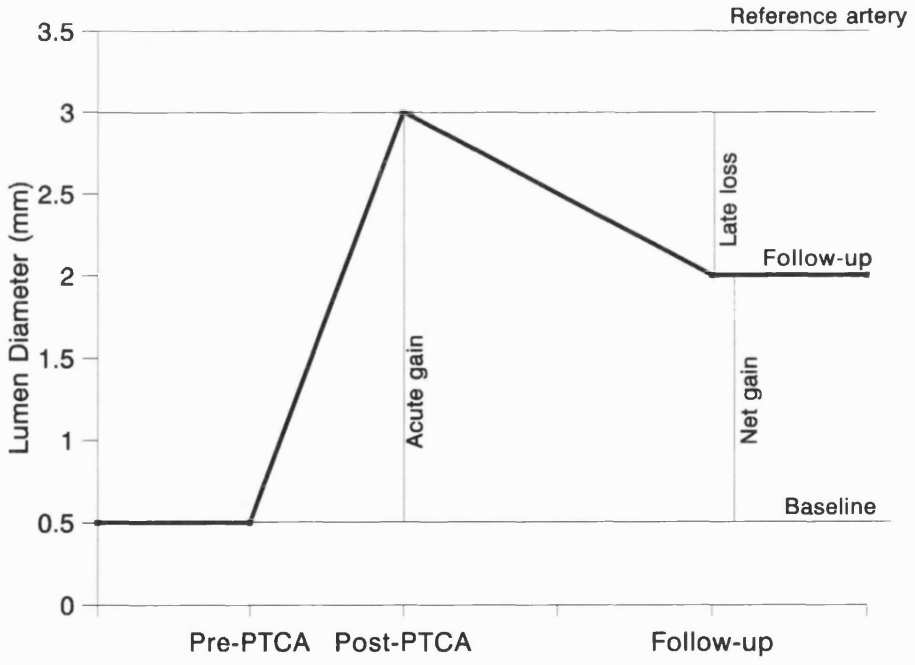


Figure 1.10. Schematic diagram showing changes in luminal dimensions over time after coronary angioplasty (PTCA).
Relative gain=acute gain/vessel size; Relative loss=late loss/vessel size;
Net gain index=net gain/vessel size.

2. *PATIENTS AND METHODS*

2.1 Patients

2.2 Study Methods

(a) Angioplasty Procedure

(b) Data Collection

(c) Definitions

(d) Statistical Methods

Figures and Tables

2.1 PATIENTS

All patients included in this thesis underwent percutaneous transluminal coronary angioplasty in the Department of Cardiology, Guy's Hospital, London, between 1981 and 1993. The following groups of patients were investigated:

(i) Three hundred and twelve consecutive patients who underwent a first coronary angioplasty procedure of a chronic total occlusion between 1981 and 1992 (chapter 3).

(ii) One hundred and ninety-eight consecutive patients, who underwent a first coronary angioplasty of aorta ostial (34 patients), non-aorta ostial (48 patients), or branch ostial stenoses (116 patients), between 1987 and 1993 (chapter 4).

(iii) One hundred and two consecutive patients, who underwent a first 'tandem lesion' coronary angioplasty of 2 separate stenoses (204 lesions) in the left anterior descending artery, between 1981 to 1991 (chapter 5).

(iv) One hundred and sixty-three consecutive patients aged 70 years or older, who underwent a first coronary angioplasty, between 1981 and 1993 (chapter 6).

(v) Sixty-two consecutive patients, who underwent a third coronary angioplasty of a single coronary arterial segment at which restenosis had occurred after 2 previous angioplasty procedures, between 1986 and 1992 (chapter 7).

(vi) One hundred and forty consecutive patients with previous coronary artery bypass surgery, who underwent a first coronary angioplasty procedure, between 1981 and 1991 (chapter 8).

(vii) Seven hundred and twenty-nine consecutive patients, who underwent coronary angioplasty, between 1990 and 1992 (chapter 9).

(viii) Five hundred and sixty-nine patients, who underwent repeat coronary arteriography between 1981 and 1992, due to recurrence of chest pain after an initially successful coronary angioplasty procedure (chapter 10).

Percutaneous transluminal coronary angioplasty was considered in all patients on clinical grounds alone. Patients were selected for the procedure when revascularisation was deemed necessary and 1 or more coronary stenoses were considered suitable for balloon dilatation.

2.2 STUDY METHODS

The study methods used throughout this thesis are described below. Variations to these general methods are described in the relevant chapters

(a) ANGIOPLASTY PROCEDURE

Angioplasty was carried out according to methods described by Grüntzig (Gruentzig et al, 1979) and subsequently modified throughout the series as new techniques and equipment were introduced. Initially, patients were treated with non-steerable balloon catheters until 1983 when steerable guidewire systems were used in all patients thereafter (Simpson et al, 1982). Throughout the study period, adaptations were made to accommodate technical advances. Several operators with varying degrees of experience contributed cases to the study population, and the dilatation strategy differed depending on the operator.

Prior to the procedure, written, informed consent to coronary angioplasty and emergency coronary bypass surgery was sought and gained. Patients were fasted overnight and received oral aspirin and vasodilators. Most of the procedures were performed via the femoral route whereby arterial access was gained using the Seldinger technique (Seldinger, 1953) followed by insertion of an arterial sheath. The brachial approach by antecubital cutdown and arteriotomy was used when femoral arterial puncture was contraindicated, usually as a result of peripheral vascular disease. Prior to the procedure, patients were premedicated with intravenous diazepam and at the start of the procedure, 10,000 units of intra-arterial heparin were administered. Subsequent boluses were given to maintain an activated clotting time of >300 seconds, or if the procedure was prolonged. Apparatus

produced by several different manufacturers was used, and the choice of equipment differed depending on operator preference. Balloon size was selected to approximate the diameter of the adjacent normal segment of the coronary artery.

Once the guiding catheter was engaged into the coronary ostium, single or multiple radiographic projections of the coronary arteriogram were obtained to delineate coronary morphology. A high quality video tape with freeze frame facilities, or a digital recording system allowed instant recall of the images recorded during the procedure and provided a 'road map' for operators to work with. The dilatation catheter was primed with radiographic contrast medium diluted 50% with heparinised saline solution. Inflations were administered until contrast injections showed wide dilatation of the stenosis or, in patients in whom the trans-stenotic gradient was measured, when the gradient had been effectively eliminated. After removal of the dilatation apparatus, a final coronary arteriogram was recorded. After angioplasty, the femoral sheath was left in place for 4 to 6 hours, and an intravenous infusion of heparin (1,000 units per hour) and nitrate (2-10 mg per hour) continued for 24 hours. Although drug therapy was not standardised, patients were usually discharged on oral nifedipine and a long acting nitrate for the first 4 to 6 weeks, and oral aspirin indefinitely.

In the event of an abrupt vessel closure occurring during or early after the angioplasty procedure, immediate redilatation was usually attempted. If this failed, or if evidence of severe coronary dissection was evident, patients with clinical or electrocardiographic evidence of myocardial ischaemia, or evolving myocardial infarction, were referred for emergency coronary artery bypass surgery. Recently, prolonged inflations using autoperfusion balloons, and coronary stents, have also been used successfully to treat abrupt vessel occlusions and coronary dissections.

Procedure-related myocardial infarction was diagnosed when new pathological Q-waves appeared on a predischarge electrocardiogram.

(b) DATA COLLECTION

All angiographic details were assessed by 2 independent observers without knowledge of procedural outcome. If there was any disagreement, the opinion of a third cardiologist was obtained. Hand-held callipers were used for making quantitative measurements from the projected angiographic film using the guiding catheter for magnification scaling. A protractor was used for measuring lesion angulation.

Where relevant, lesion complexity was scored as type A, B, or C according to the guidelines published by the American College of Cardiology/American Heart Association Task Force (Ryan et al, 1988). Type B and C lesions were further subcategorised as suggested by Ellis et al (1990a) and Myler et al (1992) (Table 1.3).

Baseline and procedural data were recorded prospectively on a computerised database. Follow-up information was obtained at routine clinic visits, from the referring physicians, and by telephone interview with the patients. Clinical status, employment status, medication and the occurrence of new cardiac events (defined as death, myocardial infarction, coronary artery bypass grafting or coronary angioplasty) were recorded up to the date of census. Angina was graded using the Canadian Cardiovascular Society functional classification (Campeau, 1976) (Table 2.1). In all cases of death the cause was established and classified as cardiac or non-cardiac. The cause of in-hospital deaths was established by review of the hospital records, death certificate, and post-mortem report when available. For out of

hospital deaths the cause of death was established by direct contact with the general practitioner, notes obtained from the local family practitioner committee, and by review of a post-mortem report if available. When the cause of death could not be established from these sources, copies of the death certificate were obtained from the office of Population Censuses and Surveys. A diagnosis of new myocardial infarction was made during follow-up when new pathological Q-waves appeared on a follow-up electrocardiogram, or when a documented clinical event was associated with other serial electrocardiographic changes and a 2-fold increase in the serum level of at least 1 cardiac enzyme (creatinine phosphokinase, aspartate transaminase, or lactate dehydrogenase).

Patients were followed closely after angioplasty by functional testing for the development of symptoms or signs of myocardial ischaemia. The indication for follow-up coronary angiography was strictly clinical: recurrence of angina pectoris or a positive symptom-limited treadmill exercise test performed routinely during out-patient visits.

(c) DEFINITIONS

The following definitions were used.

Complete revascularisation. Clinically successful angioplasty with no lesions greater than 50% diameter stenosis in any major epicardial vessel.

Epicardial vessel. Either the left anterior descending artery and its large diagonal branches, or the left circumflex artery and its large obtuse marginal branches, or a balanced or dominant right coronary artery.

Left ventricular dysfunction. Left ventricular function was categorised as abnormal if the ejection fraction was estimated to be $<45\%$, assessed visually from a contrast ventriculogram in the right anterior oblique projection.

Significant stenosis. A 50% or greater diameter stenosis in at least 2 radiographic views, or 70% diameter stenosis in 1 view.

Single vessel disease. A significant stenosis or stenoses in a single major epicardial vessel or its large branches. **Multivessel disease.** Involvement of at least 2 major epicardial vessels or their large branches.

Unstable angina pectoris. Angina occurring at rest requiring intravenous medical therapy, and included patients with post-infarction angina pectoris.

(d) STATISTICAL METHODS

All baseline, angiographic, and procedural data were collected and entered into a microcomputer. The Microsoft Excel software was used for storing and organising data in the form of a spreadsheet. Data analysis was performed by exporting data for analysis by external programmes.

Simple Statistical Methods

The standard statistical descriptive terms of mean, median, standard deviation, standard error, and interquartile range are used throughout this thesis in describing most results. All categorical variables were analysed using the Chi-squared test (using Yates' correction for continuity), Fisher's exact test, or the Chi-squared test for linear trend. Continuous variables were compared using the unpaired t test, the

Kruskal-Wallis test, or the Mann-Whitney U-test. A p value of <0.05 was considered statistically significant.

Multiple Logistic Regression Analysis

The statistical technique of multiple regression was used to analyse data in chapters 3, 8 and 9. This technique allows the development of a model that uses the combination of the values of a group of explanatory variables to predict the probability of an individual having the outcome of interest. Because the outcome of interest is a binary variable, transformation of this probability is needed to avoid prediction of impossible probabilities outside the range 0 to 1. The transformation used is the logit transformation, written logit(p), and the approach used is called multiple logistic regression. If p is the probability of a patient having a particular outcome of interest, then 1−p is the probability that they do not have that outcome, and the ratio p/(1−p) is the odds. The log odds is therefore:

$$\mathbf{logit(p) = \log_e(p/1\text{-}p).}$$

If $\mathbf{y = logit(p)}$,

where **y** is a linear function based on the presence or absence of certain characteristics in a given patient, then

$$\mathbf{e^y = p/1\text{-}p}, \text{ and thus}$$

$$\mathbf{p = e^y/(1+e^y).}$$

Single variable analyses and the backwards stepwise selection procedure were used to select variables that independently predict the outcome of interest significant at the 1% level. First, all variables that were significantly related to the outcome by

univariate analysis were entered into the model. Unimportant variables were then removed 1 at a time until each of the remaining variables in the model contributed significantly and independently to the final model. At each step, the variable with the smallest contribution to the model was removed as long as that p value was greater than the chosen level. The value of y can simply be obtained by adding the regression coefficients corresponding to all those characteristics that are present in the patient and the regression coefficient of the constant.

Fisher's Stepwise Discriminant Analysis

The assignment technique of Fisher's stepwise discriminant analysis was used to analyse data in chapter 10 for producing classification functions to allow allocation of new patients to 1 of 4 possible outcome groups. The forwards stepwise selection procedure was used to select variables that independently predicted the outcome of interest significant at the 1% level. With this method, the simple relation between each potential explanatory variable and the outcome variable of interest is examined ignoring all the other variables. The single variable that has the strongest association with the dependent variable is found and entered into the model. The variable among those not in the model, when added to the model so far obtained explained the largest amount of the remaining variability, is then identified and entered into the model. This is repeated until the addition of an extra variable is not statistically significant at the chosen level. To predict which group a patient belongs to, one calculates the classification function for each of the 4 groups, and the largest of the 4 values will indicate the patient's most likely group.

Jacknife or "Leave-one-out" Method

The performance of the derived classification rules on the data were assessed by the jacknife method to compensate for the fact that the same data were being used to

test the prediction rule as had been used to derive it. Also called the 'leaving one out method', the classification rule is derived on the basis of (n−1) individuals and used to classify the individual not included, the whole process being repeated for each individual.

Kaplan-Meier Method and Logrank Test

Cumulative overall and event-free survival probabilities, and the corresponding standard errors and 95% confidence intervals were analysed using the Kaplan-Meier method, computed from the time of coronary angioplasty (Kaplan and Meier, 1958; Peto et al, 1977; Machin and Gardner, 1988). Using this analysis, the proportion surviving a given length of time is calculated by multiplying the probabilities of surviving each successive time period up to that time. Only the times on which there is an event need to be considered. Hence, if P_k is the probability of surviving K days, R_k is the number of subjects still at risk (ie still being followed up) immediately before the Kth day, and F_k is the number of observed events on day K, then

$$P_k = P_{k-1} \times (R_k - F_k/R_k).$$

The number of patients still at risk, R_k, is changed both when patients suffer an event, and when patients reach the end of their follow-up period (ie when they are censored). The cardiac end points that were analysed included death, cardiac death, non-fatal myocardial infarction, coronary artery bypass surgery, and repeat coronary angioplasty. The survival times between different independent subgroups were compared with the logrank test. This is a non-parametric method for testing the null hypothesis that the groups being compared are samples from the same population as regards survival experience. The principle of the test is to divide the

survival time scale into intervals according to the distinct observed survival times, ignoring censored survival times. The logrank test produces for each group an observed (O) and an expected (E) number of events. These are then compared by obtaining the value of X^2, calculated by the sum of

$$(O-E)^2/E,$$

and comparing this value to a χ^2 distribution to obtain the probability value.

Cox Multiple Proportional Hazards Regression Analysis

The survival analysis in chapter 7 used the Cox multiple proportional hazards regression analysis to identify which prognostic factors independently influenced long-term survival and the time to cardiac events during follow-up; prognostic factors were again selected using the backwards stepwise procedure (Cox, 1972, Christensen, 1987). This is a semi-parametric approach which allows the effects of several variables on survival to be investigated at the same time. Although no particular type of distribution is assumed for survival times, a strong assumption is made that the effects of the different variables on survival are constant over time and are additive in a particular scale. Although the overall hazard may change over time, changes in the hazard of any individual must be proportional to changes in the hazard of any other individual, and to changes in the underlying hazard (h_0). For an individual with several independent variables of interest, say X_1 to X_p, the instantaneous hazard of an event at time t, h(t), can be expressed as

$$h(t) = h_0(t) \times \exp(b_1X_1 + b_2X_2 + \ldots b_pX_p),$$

where h_0 is the baseline hazard function (corresponding to the hazard when all the variables are zero), and b_1 to b_p are regression coefficients. The instantaneous hazard gives the risk of an event at time t. Hence, the cumulative hazard, H(t), of an event between time 0 and time t can be obtained by adding up all the hazards up to time t, and is defined as

$$H(t) = H_0(t) \times \exp (b_1X_1 + b_2X_2 + \ldots b_pX_p),$$

where $H_0(t)$ is the cumulative underlying hazard function. The survival probability for any individual with specific values of the variables in the model can thus be estimated.

Software Packages

These statistical analyses were performed using commercially available statistical software programmes (SPSS for windows, BMDP programs 1L and 2L, BMDP program LR).

Table 2.1. Angina Grade According to the Canadian Cardiovascular Society Functional Classification.

Grade I.	Angina occurs during strenuous or rapid or prolonged exertion at work or recreation. Ordinary physical activity, such as walking or climbing stairs, does not cause angina.
Grade II.	Slight limitation of ordinary physical activities. Angina may be precipitated by walking or climbing stairs rapidly, walking uphill or stair climbing after meals, or in cold, or in wind, or other emotional stress, or only during the few hours after awakening.
Grade III.	Marked limitation of ordinary physical activity. Angina may be precipitated by walking on the level, or by climbing 1 flight of stairs at a normal pace, and in normal conditions.
Grade IV.	Inability to carry out any physical activity without discomfort. Angina may occur when patient is at rest.

3. *CORONARY ANGIOPLASTY OF CHRONIC TOTAL OCCLUSION*

3.1 INTRODUCTION

Percutaneous transluminal coronary angioplasty of chronic total occlusions is performed for lifestyle-limiting angina, decreased exercise capacity, silent ischaemia, or a large area of hibernating myocardium. The procedure was first described by Savage et al (1982) and Heyndrickx et al (1982). This procedure is recognised as having a lower primary success rate ranging from 53% to 73% (Kereiakes et al, 1985; Hamm et al, 1990; Bell et al, 1992), and contributes to the failure to achieve complete revascularisation among many patients with multivessel disease (Bell et al, 1990, Shaw et al, 1990b; Deligonul et al, 1988a; Bourassa et al, 1992). Despite this relatively low initial success rate, re-canalisation of chronic total occlusions by coronary angioplasty has become an accepted procedure, and the prevalence has increased from about 2% to 10% of the total number of coronary angioplasties performed in large centres (Detre et al, 1988).

At present, the ability to predict the likelihood of procedural success for a particular lesion is poor. Various clinical and angiographic parameters have been shown to be related to procedural success rates, although previous reports have reached conflicting conclusions (DiSciascio et al, 1986a; LaVeau et al, 1989; Stone et al, 1990). If a statistical model was available that could accurately predict the probability of procedural success on the basis of simple clinical and angiographic factors, this would have important implications for the selection of lesions for coronary angioplasty.

Furthermore, there is a paucity of information regarding the long-term clinical outcome of patients undergoing this procedure. Even if angioplasty is technically feasible, the procedure must be associated with long-term symptomatic

improvement to be judged clinically successful. This is particularly true for angioplasty of chronic total occlusion in view of the complexity of the procedure, relatively low initial success rates, high equipment costs, long periods of exposure to fluoroscopy, increasing number of chronic total occlusions attempted with angioplasty, and relatively high restenosis rates that have been reported to range from 43% to 75% (Serruys et al, 1985; Melchior et al, 1987a; Ellis et al, 1989b; Warren et al, 1990).

The study presented in this chapter reports on the acute success and complication rates of coronary angioplasty of chronic total occlusions on 312 patients. It also describes a multiple logistic regression model incorporating clinical and angiographic data to predict procedural success probability for a particular lesion. Data on long-term clinical outcome, and the impact of a successful procedure on follow-up clinical events, are also presented.

3.2 PATIENTS AND METHODS

(a) PATIENTS

Between 1981 and 1992, 312 consecutive patients underwent a first coronary angioplasty procedure of a chronic total occlusion. Patients having had a myocardial infarction within 2 weeks of coronary angioplasty were excluded. The decision to dilate a chronically occluded lesion was based on the expectation that restoring antegrade flow would improve ischaemic symptoms or left ventricular function. This implied the presence of viable myocardium, usually the result of collaterals that are capable of maintaining tissue viability. Total occlusion was defined as 100% luminal diameter narrowing with absence of a visible intraluminal channel. This included vessels with no opacification of the distal segment and vessels with faint distal opacification via antegrade or retrograde collaterals.

The mean age was 55 years (SD 9, range 31 to 79 years) and 267 (86%) were male (Table 3.1). The median duration of occlusion was 6 months (range up to 156 months). The estimated duration of occlusion was less than 3 months in 87 patients (28%), between 3 and 6 months in 66 patients (21%), between 6 and 12 months in 66 patients (21%), more than 12 months in 62 patients (20%), and could not be established in 31 patients (10%) (Figure 3.1). Two hundred and five patients (66%) had a history of previous myocardial infarction and 137 (44%) had impaired left ventricular function. Twenty-one patients (7%) had previous coronary artery bypass grafting. Prior to intervention, 197 patients (63%) suffered grade III or IV angina. Risk factors that were present in the patients included smoking (61%), diabetes mellitus (7%), hypertension (24%), and hypercholesterolaemia (44%).

Multivessel coronary angioplasty was performed in 127 patients (41%) and multilesion coronary angioplasty in 134 patients (43%). The occluded vessel was the left anterior descending coronary artery in 162 patients (52%), the circumflex coronary artery in 43 (14%), the right coronary artery in 100 (32%) and a saphenous vein graft in 7 patients (2%). The lesion location involved the proximal segment of the coronary artery in 40%, the middle segment in 48% and the distal segment in 12%.

(b) ANGIOPLASTY PROCEDURE

Coronary angioplasty was performed according to the protocol described in Chapter 2. More than 60% of the procedures were performed by a single operator. The technique used to dilate total coronary occlusions differed depending on the operator but essentially consisted of using movable guidewires of increasing stiffness and low profile dilatation balloons, which were exchanged for larger balloons as necessary. In some cases, 'balloon-on-the-wire' or the Magnum-Meier system were used (Meier et al, 1989). Axial strength and stability were improved by advancing the balloon catheter to the point of occlusion to splint the guidewire. Deep guiding catheter engagement to obtain a stable ostial position was frequently necessary for adequate support. Once the guidewire was across the occluded segment, its intraluminal course beyond the occlusion was confirmed by either its easy manoeuvrability or antegrade contrast flow around the guidewire. If the position was still uncertain, contralateral angiography was performed by the left femoral approach. During multivessel coronary angioplasty, the occluded vessel was usually attempted first.

(c) STUDY METHODS

The baseline clinical characteristics on all 312 patients were recorded. Angiographic details from the pre-procedural angiograms on 264 patients (85%) were assessed by 2 independent observers without knowledge of procedural outcome.

The clinical parameters analysed as possible determinants of procedural success included age, gender, angina grade, extent of coronary artery disease, left ventricular function, estimated duration of occlusion, and whether multivessel or multilesion coronary angioplasty was performed. The duration of occlusion was estimated either from the date of myocardial infarction in the distribution of the occluded vessel, abrupt worsening of angina pectoris, or information provided by sequential angiograms. Other clinical factors considered were a history of smoking, hypertension, diabetes mellitus, hypercholesterolaemia, previous myocardial infarction, prior coronary artery bypass surgery, and the presence of a family history.

The angiographic parameters analysed included lesion location, vessel diameter, length of occlusion (estimated in 246 patients in whom the distal extremity of the occlusion could be defined by collateral contrast filling), morphology of the occlusion (a tapered entry configuration at the occlusion as opposed to an abrupt cut-off), distance of the occlusion from the coronary orifice, the presence of diffuse disease (at least 1 significant stenosis of $>50\%$ proximal to the occlusion), vessel tortuosity (presence of at least 1 bend of $>45°$ proximal to the occlusion), calcium at the site of the occlusion (radio-opacity present prior to contrast injection), thrombus at the site of the occlusion (presence of intraluminal filling defect or contrast staining within the lumen), a side branch at the point of occlusion, presence

of bridging collaterals (multiple small collateral channels bridging the angiographic gap found outside the perceived lumen of the vessel), and whether distal vessel opacification was present.

Complete follow-up data were available on all 312 patients on or after the census date. Information on vital status, current angina status, and the occurrence of new cardiac events was obtained up to July 31st, 1993.

Procedural success was defined as less than 50% residual diameter stenosis at the dilated site without a major in-hospital complication (defined as the occurrence of either death, myocardial infarction, or emergency coronary artery bypass grafting). Angiographic restenosis was defined as a recurrence of a $>50\%$ diameter stenosis at a previously successfully dilated site. Clinical restenosis was defined as the recurrence of anginal symptoms or evidence of reversible ischaemia associated with angiographic evidence of restenosis.

(d) STATISTICAL METHODS

Continuous variables are expressed as mean (SD) except estimated duration of occlusion due to its highly skewed distribution.

The study patients were divided into sub-groups according to procedural outcome. The angiographic and clinical variables analysed as possible determinants of procedural success were compared between these patient groups. Categorical variables between patient groups were compared using the chi-squared test or Fisher's exact test, and continuous variables were compared with the unpaired t test.

The chi-squared test for trend was used to test for an association between time-period and procedural success rate.

All variables found to be significantly related to procedural outcome by univariate analysis were included in a multiple logistic regression analysis. The backwards stepwise selection procedure was used to identify independent predictors of procedural outcome significant at the 1% level. An equation was developed that best classified the chances of procedural success. The observed procedural success rates were examined separately for patients whose predicted probability of success was low ($<30\%$), intermediate (30% to 69%), or high ($\geq 70\%$). Predicted probabilities of success were estimated by the jacknife method to compensate for the fact that the same data were being used to test the prediction rule as had been used to derive it. Life table analyses were performed using the Kaplan-Meier method computed from the time of coronary angioplasty and the logrank test was used to assess differences between group outcomes.

3.3 RESULTS

(a) ACUTE RESULTS

Procedural success was achieved in 191 lesions (61.2%) and did not differ significantly by location of the occlusion (p=0.06, Table 3.2, Table 3.3). The procedural success rate was 56% for the first 104 cases, 57% for the second 104 cases, and 71% for the third 104 cases (p=0.02). The most common cause of failure was inability to pass the guidewire across the occlusion (96 of 121 lesions). Failure to cross the lesion or dilate it with a balloon catheter accounted for 25 of the failures. The procedural success rate was highest for occlusions less than 3 months old (74%), intermediate for occlusions between 3 and 12 months old (64%), and least for occlusions greater than 12 months old (47%).

Six patients (1.9%) suffered 1 or more major in-hospital complications. One procedural death (0.3%) occurred in a patient who had an apparently uncomplicated coronary angioplasty to the left anterior descending artery and the right coronary artery which was chronically occluded. He developed ST segment elevation in the anterior chest leads 12 hours after the procedure followed by recurrent ventricular fibrillation and failed to respond to intensive resuscitation. Five patients (1.6%) proceeded to emergency coronary artery bypass grafting after failure to recanalise the occluded vessel; 3 suffered coronary dissection (left anterior descending artery in 2 patients and left main coronary in 1) as a result of guide catheter or guidewire trauma, and 2 developed cardiac tamponade from coronary artery perforation. Of these, 1 (0.3%) also suffered a Q-wave myocardial infarction.

(b) DETERMINANTS OF PROCEDURAL OUTCOME

The clinical characteristics (Table 3.3) and angiographic data (Table 3.4) were analysed to assess their association with procedural outcome. Univariate analysis of 27 clinical and angiographic factors showed that procedural outcome was significantly related to 6 variables. Procedural success was less common in patients with multivessel disease than in those with single vessel disease (53% versus 75%, $p<0.001$), with lesions occluded for more than 3 months than those occluded for less than 3 months (59% versus 74%, $p=0.02$), with vessels less than 3 mm than those greater than 3 mm in diameter (48% versus 73%, $p<0.001$), with occlusions without a tapered entry configuration (43% versus 69%, $p<0.001$), with lesions with side branches at the point of occlusion (53% versus 69%, $p=0.01$), and with lesions with bridging collaterals (20% versus 70%, $p<0.001$).

Multiple stepwise logistic regression analysis identified the presence of bridging collaterals ($p<0.001$), the absence of a tapered entry configuration ($p<0.001$), duration of occlusion of greater than 3 months ($p=0.001$), and vessel diameter of less than 3 mm ($p=0.003$) as independent predictors of procedural failure (Table 3.5; Figures 3.2 to 3.4). Neither of the other variables analysed contributed significantly to this regression model. Using this model, the estimated probability of procedural success (p) is:

$$p = e^y/(1+e^y)$$

where $e = 2.72$, and $y = (-2.56 \times \text{bridging collaterals}) + (1.29 \times \text{tapered entry configuration}) + (-1.35 \times \text{duration of occlusion}) + (1.00 \times \text{vessel diameter}) + 0.82$.

Bridging collaterals were scored 1 for presence and 0 for absence; tapered entry configuration was scored 1 for presence and 0 for absence; duration of occlusion was scored 1 for >3 months and 0 for ≤ 3 months; vessel diameter was scored 1 for >3 millimetres and 0 for ≤ 3 millimetres.

The estimated probability of procedural success from the logistic regression model was used to classify patients into groups of high, intermediate, and low probability of procedural success using cut-off points of 70% and 30% (Table 3.6). With the jacknife method, the predictive value for procedural success (where the probability for success ≥70%) was 91% (95% confidence interval 83% to 96%) and predictive value for procedural failure (where the probability for success <30%) was 81% (95% confidence interval 64% to 92%). One hundred and five patients (44%) had an intermediate predicted probability of success (where the probability for success 30% to 69%). Thus the model successfully identified 2 groups, accounting for 56% of the lesions, as having an unusually high (≥70%) or low (<30%) likelihood of procedural success.

(c) LONG-TERM RESULTS

The median duration of follow-up was 48 months ranging from 11 to 143 months (SD 25 months). During the follow-up period, 14 patients (4.4%) died, 5 (1.6%) suffered non-fatal myocardial infarction, and 42 (13.5%) underwent elective coronary artery bypass grafting. Forty-four patients (14.1%) underwent a repeat angioplasty procedure for restenosis or new coronary lesions. Overall, a second revascularisation procedure was necessary in 85 patients (27.2%). The 14 late deaths included 12 cardiac deaths (myocardial infarction 8, sudden death 1,

revascularisation procedure 2, heart transplant 1) and 2 non-cardiac deaths (cerebrovascular accident and renal adenocarcinoma).

The overall mortality in this group of patients was low, with a cumulative probability of survival for all 312 patients of 97.4% (SE 0.9) and 94.8% (SE 1.4) at 1 and 5 years, respectively (Table 3.7). Patients with procedural success had 1 and 5 year cumulative survival rates of 97.4% (SE 1.2) and 96.7% (SE 1.4), respectively. The 1 and 5 year rates for freedom from death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty was 74.5% (SE 2.5) and 66.9% (SE 2.8), respectively. The 1 and 5 year cumulative event-free survival rates are shown in Table 3.7 for all patients and patients with an initially successful angioplasty procedure (Figure 3.5).

At census, of the 297 survivors, 163 (55%) were asymptomatic, 110 (37%) had mild (grade I or II) angina, and only 24 (8%) complained of severe (grade III or IV) angina ($p<0.001$) (Figure 3.6). No significant difference in the incidence of severe angina (grade III or IV) was found between patients with successful versus unsuccessful procedures (6% versus 12%, $p=0.08$).

The effect of the initial outcome of balloon angioplasty on long-term outcome was assessed by comparing the outcome of patients with successful dilation with those of failed dilation of the total occlusion. The freedom from death at 5 years of patients who had an initially successful procedure was not significantly different from those patients who had an unsuccessful procedure (Figure 3.7). There was also no significant difference in the freedom from myocardial infarction or repeat angioplasty between patients with or without a successful procedure (Figures 3.8 and 3.9). The only significant difference between the 2 groups in terms of long-term

outcome was in the freedom from coronary artery bypass graft surgery in patients with an initially successful angioplasty procedure (Figure 3.10); after 5 years, the probability of undergoing coronary artery bypass graft surgery in this group was 5% compared with 28% for those with unsuccessful dilation ($p<0.001$). Most referrals to coronary bypass surgery occurred within 10 months after angioplasty in both groups. In the group with successful procedures, referrals for coronary bypass surgery occurred sporadically over the first 12 months. In the failed group, most referrals for coronary bypass surgery occurred in the first 4 months after the procedure.

(d) RESTENOSIS

Repeat coronary angiography was performed in 76 of the 191 patients (40%) who had initially successful procedures for recurrence of angina pectoris or reversible ischaemia documented on symptom-limited treadmill exercise tests. Continued success was present in 34 patients (34/74=46%), and angiographic restenosis was present in 40 patients (40/74=54%). Overall, the clinical restenosis rate was 21% (40/191).

3.4 DISCUSSION

During the early years of percutaneous transluminal coronary angioplasty, a total occlusion was considered an absolute contraindication to the procedure (Kent et al, 1982). Despite the presence of well developed collaterals, which maintain myocardial viability under basal conditions, these inter- and intra-coronary networks may become functionally insufficient during periods of increased oxygen demand, resulting in lifestyle-limiting angina. Evidence that left ventricular function may improve after re-canalisation of chronic total occlusions (Melchior et al, 1987b), and the perception that procedural failure is not associated with an adverse outcome (Melchior et al, 1987a), has provided the impetus for its increasing application. In the most recent coronary angioplasty registry report from the National Heart, Lung, and Blood Institute, chronic total occlusions accounted for 10% of all attempted coronary angioplasties during the period 1985-1986 (Detre et al, 1988).

Acute Results

The procedural success rate per lesion of 62.1%, mortality rate of 0.3%, myocardial infarction rate of 0.3% and incidence of emergency coronary artery bypass grafting of 1.6% reported in this study are comparable with previous studies (Table 3.8). Other studies have reported procedural success rates ranging from 47% to 73% depending on the inclusion criteria (Kereiakes et al, 1985; Bell et al, 1992; Hamm et al, 1990; Stewart et al, 1993), mortality rates ranging from 0% to 2% (Bell et al 1992; Stone et al, 1990; Melchior et al, 1987a), myocardial infarction rates ranging from 0% to 18% (Serruys et al, 1985; Bell et al, 1992; Hamm et al, 1990; Ivanhoe et al, 1992), and emergency bypass surgery rates ranging from 0% to 9% (Bell et al, 1992; Melchior et al, 1987a; Ivanhoe et al, 1992). The differences in the success rates between the various studies probably reflect differences in the

selection criteria of patients for coronary angioplasty of chronic total occlusion. A lesion would have been selected only if the operator felt that the occlusion could be re-canalised with a reasonable chance of success. Hence the success rates reported may have differed if dilatations of all total occlusions were attempted. In the present study, the most common causes of failure include inability to pass the guidewire across the occlusion (79%), and failure to cross the lesion or dilate it with a balloon catheter (21%), consistent with the findings of other investigators (Bell et al, 1992; Ruocco et al, 1992).

Although the procedural success rate was lower than coronary angioplasty of non-occluded lesions, re-canalisation of chronic total occlusion was associated with fewer complications. This low risk of acute complication has also been shown by previous studies (Bell et al, 1992; Stone et al, 1990; Melchior et al, 1987a). Only the largest series report in-hospital deaths, which occurred largely secondary to problems with dilated sites other than the total occlusions (Stone et al, 1990; Ivanhoe et al, 1992; Bell et al, 1992). However, the safety is neither absolute nor a consistent finding. The most recent report from the National Heart, Lung and Blood Institute demonstrated a similar incidence of major complications occurring during coronary angioplasty of total and sub-total occlusions (Ruocco et al, 1992). In the present study, complications frequently occurred directly as a result of the procedure itself, either from guide catheter or guidewire trauma causing coronary dissection or perforation. The 1 procedural death was related to acute vessel closure in a non-occluded vessel after an uncomplicated multivessel coronary angioplasty in a patient with impaired left ventricular function.

Improved success rate was observed with the last 104 cases attempted in this study. Similar improvements of success rate with subsequent attempts at dilating chronic

total occlusions have been reported by other investigators (Stone et al, 1990). This may be attributed to improved case selection, improved operator experience and angioplasty technique, and equipment evolution. These developments occurred in parallel and it would be difficult to attribute the improved success rate to any single parameter.

Improved patient selection may have arisen as a result of knowledge gained from previous published reports on coronary angioplasty of chronic total occlusion. In the present study, more than 60% of the procedures were performed by a single operator, who also frequently assisted more junior operators when they failed to recanalise the occluded artery. Therefore, the impact of operator experience on success rate cannot be assessed accurately although Stone et al (1990) have shown no clear correlation between the number of total occlusion dilatations attempted and the procedural success rate. Despite the introduction of new angioplasty technology, such as laser angioplasty (Bowes et al, 1989) and low-speed rotational angioplasty (Kaltenbach et al, 1988), the approach to coronary angioplasty of a total occlusion has remained essentially unchanged at our institution. The majority of procedures in the present study were performed using conventional systems. The combination of improved balloon angioplasty equipment (guide catheters with better support, guidewires of varying stiffness, and low profile balloon catheters) and improved techniques (deep guide catheter engagement, advancing the balloon dilatation catheter to the totally occluded arterial segment to splint the guidewire) have increased the likelihood of crossing and dilatation of the occluded segment. Few cases involved the use of specially designed catheters (Hamm et al, 1990) or the Magnum-Meier system (Meier et al, 1989). Thus the impact of these specially designed angioplasty equipment is difficult to assess in the presented study cohort.

However, even with specially designed catheters, the reported overall success rate for coronary angioplasty of total occlusions was no higher than 73% and may not be superior to conventional systems (Haerer et al, 1991). Preliminary results, comparing the Magnum-Meier system with the conventional technique, have shown contradictory results (Haerer, et al, 1991; Meier et al, 1990a; Pande et al, 1992), and other new technology, such as excimer laser angioplasty (Bowes et al, 1989) and low-speed rotational angioplasty (Kaltenbach et al, 1991), will need further clinical evaluation, although preliminary data are encouraging.

Determinants of Procedural Outcome

Given the increasing use of coronary angioplasty to re-canalise chronic total occlusions, and the lower primary success rates, the ability to predict accurately the likelihood of procedural success will have important implications in selecting cases for coronary angioplasty. In the present study, multiple logistic regression analysis identified the presence of bridging collaterals, absence of a tapered entry configuration, a longer duration of occlusion, and a smaller vessel diameter as independent predictors of procedural failure. The influence of vessel size has not been previously reported but the other parameters have been shown to predict procedural failure in some studies.

Of all the occlusion characteristics shown to affect procedural outcome adversely in the present study, none have greater impact than the presence of bridging collaterals. Bridging collaterals, which represent dilated vasa-vasorum (Barger et al, 1984) and neovascular channels, might divert the guidewire during coronary angioplasty. As a result of their fragility, they perforate easily if instrumented with a guidewire during crossing attempts. The presence of bridging collaterals as a

predictor of procedural outcome has been shown by some (Stone et al, 1990) but not all previous studies (Bell et al, 1992; LaVeau et al, 1989).

A tapered entry configuration assists in guidewire placement thus providing guidewire stability, increases the chance of finding the correct channel, and allows axial force to be transmitted directly to the distal lumen. Its influence on procedural outcome is confirmed by some (Stone et al, 1990; Ivanhoe et al, 1992) but not other studies (Kereiakes et al, 1985; Bell et al, 1992; LaVeau et al, 1989).

The duration of occlusion may determine the histological components of the occluded segment and thus influence the ability of a guidewire to cross the lesion. The longer the duration, the more the lesion is organised with fibrous tissue and the likelihood of re-canalisation becomes less. In some (Kereiakes et al, 1985; Melchior et al, 1987a; Serruys et al, 1985), but again not all previous studies (Bell et al, 1992; LaVeau et al, 1989; Stone et al, 1990), the estimated duration of occlusion was related to procedural outcome. This inconsistent finding may be partly explained by the difficulty and inherent limitation of estimating the duration of occlusion from clinical information.

A larger vessel diameter may allow a greater margin of error during the passage of the guidewire across the occluded segment into the distal intraluminal course, if the guidewire deviates from the major vessel axis. Hence the likelihood of the guidewire creating subintimal pathways by getting underneath a plaque is reduced in a larger vessel as opposed to a small diameter vessel where a minor deviation from its major axis could cause the guidewire to leave its intraluminal course, create a subintimal pathway, and thereby pursue an intramural course.

There were also more unsuccessful dilatations in patients who had multivessel disease, and in lesions with side branches at the point of occlusion, although these factors did not reach statistical independence in the multivariate model. The presence of distal vessel opacification did not emerge as an important determinant of procedural success in the present study, as was shown by some investigators (LaVeau et al, 1989; Stone et al, 1990). Others however have reported conflicting results (Kereiakes et al, 1985; Serruys et al, 1985). The differences may be accounted for by the different underlying mechanisms that have caused the distal vessel opacification seen in the various study populations. These mechanisms include spontaneous recanalisation of the occlusion, subtotal occlusions, intra-coronary collaterals, and a combination of these (Meier, 1990b).

However, apart from the presence of bridging collaterals which reduces the overall probability of procedural success to 20%, the presence of the other variables in isolation should not deter attempts to re-canalise chronic occlusion. In the presence of favourable angiographic variables, even occlusions of over a year old can be dilated with a procedural success rate approaching 50%, with an acceptable complication rate. In this study, a model for predicting the probability of procedural success was developed using stepwise logistic regression analysis combining these clinical and angiographic variables. This model identified 56% of the lesions as having a procedural success rate that differed considerably from the data base mean of 61.2%; 95 lesions were classified as having a high chance of procedural success and had an actual success rate of 91%, whereas 36 were classified as having a low chance of procedural success and had an actual success rate of 19%. The remaining 105 lesions, which were classified as having an intermediate predicted probability of procedural success, had an actual success rate of 53%. Thus, the described model may assist in the selection of chronic total occlusions for potential angioplasty with

those of low likelihood of success treated by an alternative mode of revascularisation.

Long-term Results

Although angioplasty for chronic total occlusion is technically feasible, the procedure must be associated with short- and long-term symptomatic improvement to be judged clinically successful. The efficacy of any revascularisation procedure is defined by the clinical events and the patient's functional status.

The present study has shown that most patients with chronic total occlusion can be managed safely and effectively with angioplasty. The long-term results are encouraging with a 5 year cumulative survival of 97.4%, and freedom from death, myocardial infarction, and coronary artery bypass surgery of 77.4%. Successful re-canalisation of a chronic total occlusion appeared to have no impact on the major long-term cardiac events of death and myocardial infarction, consistent with the findings of other investigators (Bell et al, 1992; Finci et al, 1990). Possible explanations include the disparate use of bypass surgery in patients with successful and those with unsuccessful angioplasty, or the fact that a non-recanalised vessel cannot directly contribute to these 2 events, and recanalisation would therefore also be unable to impact on these. However, the need of subsequent elective coronary artery bypass graft surgery in these patients was significantly reduced after successful dilation compared with unsuccessful dilation. The difference was evident after attempted angioplasty and remained unchanged during follow-up. Therefore, coronary surgery may be avoided in most patients whose totally occluded vessel is successfully dilated. This is consistent with recently published data (Finci et al, 1990; Warren et al, 1990; Ivanhoe et al, 1992; Bell et al, 1992).

Among patients undergoing successful re-canalisation of total occlusions, the majority are asymptomatic at 2 to 5-year follow-up. In the 3 largest reports, 76% (Bell et al, 1992) and 69% (Ruocco et al, 1992) of patients were asymptomatic at 2 years, and 66% (Ivanhoe et al, 1992) at 4 years after coronary angioplasty. In addition, improvements in exercise capacity and ischaemic threshold have been documented during stress testing (Finci et al, 1990). In the present study, although the majority of patients were either asymptomatic, or had only mild angina during follow-up, no significant differences in the incidence of severe angina was found between patients with successful versus those with unsuccessful angioplasty procedures. The higher incidence of surgery undoubtedly contributed to the improved symptomatic status among those patients with failed angioplasty, thus explaining the lack of discernible difference in the severity of angina among patients with successful angioplasty and those with unsuccessful angioplasty during follow-up.

Restenosis

Restenosis rates after successful dilation of total coronary artery occlusions have been reported to range from 30% to 77% (Table 3.8) (Warren et al, 1990; Jost et al, 1991; Ivanhoe et al, 1992). The angiographic restenosis rate of 54% in the present study is consistent with these rates. These rates are higher than those generally reported after balloon angioplasty of subtotal occlusions. The mechanisms responsible remain speculative, and may include the presence of residual thrombus, the presence of persistent collateral flow, and the greater trauma inflicted on the arterial wall during re-canalisation of occlusions compared with dilatations of subtotal occlusions. However, direct comparison between studies may be misleading since the discrepancy may be accounted for by the differences in the rate of angiographic follow-up, and by differences in the definition of restenosis. In the

present study, only 40% of patients returned for coronary angiography, usually for recurrent symptoms. The frequency of restenosis may have been lower had all patients returned for repeat coronary angiography, irrespective of their symptomatic status. On the other hand, in some patients not restudied, restenosis may have been silent if pre-existing collateral vessels were recruited. The clinical restenosis rate, defined as the recurrence of anginal symptoms or reversible ischaemia associated with angiographic evidence of restenosis, was 21%. The true angiographic restenosis rate probably lies between 21% and 54%.

Study Limitations

This study is a retrospective analysis of data and is subject to the limitations inherent in any retrospective study. The frequency of occurrence of some of the angiographic parameters analysed was low. Thrombus was present in only 17 and calcium in only 47 of the 264 coronary angiograms included in the analysis. These parameters may have been significant determinants of procedural success had a greater number of patients been available in the study. In addition, although the model was developed from a large database and validated on the database from which it was derived using the jacknife method, it needs to be tested prospectively and against other populations. I am currently collecting new data for this purpose. Furthermore, the rate of repeat coronary angiography was low (40%) since this was performed only in patients that were symptomatic or had evidence of reversible ischaemia. Therefore the exact restenosis rate cannot be determined.

3.5 SUMMARY AND CONCLUSIONS

The present study confirms previous reports that coronary angioplasty of chronic total occlusions is associated with a low risk of acute complication. It has also shown that procedural success is adversely influenced by easily identifiable clinical and angiographic features. Although further prospective validation is necessary, the multiple logistic regression model described may help clinicians assess the suitability of coronary angioplasty in individual patients with chronic total occlusions. Furthermore, successful recanalisation of total occlusions is associated with favourable clinical outcome and reduces the use of subsequent coronary artery bypass graft surgery when compared with patients with a failed procedure. However, no significant benefits on either subsequent survival or incidence of myocardial infarction were found. Although preliminary data suggest that several new interventional technology may improve the procedural outcome of coronary angioplasty in patients with chronic total occlusions, further prospective, randomised evaluation will be necessary before any firm conclusions can be drawn.

Table 3.1. Patient and Angiographic Characteristics.

	Number	%
Total	312	100
Mean age (years)	55	SD 9 (range 31-79)
Male gender	267	86
Angina grade		
0/I	24	8
II	91	29
III	126	40
IV	71	23
Previous MI	205	66
Abnormal LV (EF<45%)	137	44
Previous CABG	21	7
Risk factors		
Smoking	189	61
Family history	145	46
Diabetes mellitus	22	7
Hypertension	74	24
Hypercholesterolaemia	137	44
Single vessel PTCA	185	59
Multivessel PTCA	127	41
Multilesion PTCA	134	43
Number of diseased vessel		
1	115	37
2	123	39
3	74	24
Occluded vessel attempted		
LAD	162	52
CX	43	14
RCA	100	32
SVG	7	2
Lesion location		
Proximal	125	40
Mid	150	48
Distal	37	12

CABG=coronary artery bypass grafting; CX=circumflex artery; EF=ejection fraction; LAD=left anterior descending artery; LV=left ventricular function; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty; RCA=right coronary artery; SD=standard deviation; SVG=saphenous vein graft.

Table 3.2. Primary Success and Complication Rates of all 312 Patients.

	Number	%
Procedural success	191	61.2
Any major complication	6	1.9
Procedural death	1	0.3
Non-fatal MI	1	0.3
Emergency CABG	5	1.6

Abbreviations as for Table 3.1.

Table 3.3. Clinical Factors Related to Procedural Outcome for all 312 Patients.

	Procedural success (n=191)	Procedural failure (n=121)	p Value
Mean age (SD) (years)	55 (9)	56 (10)	NS
Male gender	165 (86%)	102 (84%)	NS
Angina grade III/IV	127 (66%)	70 (58%)	NS
Previous MI	126 (66%)	79 (65%)	NS
EF<45%	84 (44%)	55 (45%)	NS
Smoking	115 (60%)	74 (61%	NS
Hypertension	41 (21%)	33 (27%)	NS
Family history	84 (44%)	61 (50%)	NS
Diabetes mellitus	15 (8%)	7 (6%)	NS
Hypercholesterolaemia	90 (47%)	47 (39%)	NS
Previous CABG	12 (6%)	9 (7%)	NS
Multivessel disease	105 (55%)	92 (76%)	p<0.001
Multivessel PTCA	80 (42%)	47 (39%)	NS
Multilesion PTCA	89 (47%)	45 (37%)	NS
Duration of occlusion >3 months*	114 (64%)	80 (78%)	p=0.02
Lesion location			
LAD	102 (53%)	60 (50%)	
CX	31 (16%)	12 (10%)	NS
RCA	52 (27%)	48 (40%)	
SVG	6 (3%)	1 (0.8%)	

Abbreviations as for Table 3.1; *Available only in 281 patients.

Table 3.4. Angiographic Data Related to Procedural Outcome for 264 Patients.

	Procedural success (n=159)	Procedural failure (n=105)	p Value
Calcium at occlusion	24 (15%)	23 (22%)	NS
Thrombus at occlusion	14 (9%)	3 (3%)	NS
Tapered entry configuration	121 (76%)	55 (52%)	$p<0.001$
Vessel tortuosity	44 (28%)	27 (26%)	NS
Side branch at occlusion	76 (48%)	67 (64%)	$p=0.01$
Diffuse disease proximal to occlusion	20 (13%)	16 (15%)	NS
Vessel diameter >3 mm	95 (60%)	36 (34%)	$p<0.001$
Presence of distal vessel opacification	44 (28%)	41 (39%)	NS
Bridging collaterals	10 (6%)	41 (39%)	$p<0.001$
Mean (SD) distance of occlusion from orifice (mm)	33 (18)	30 (SD 17)	NS
Mean (SD) lesion length (mm)*	12 (SD 11)	12 (SD 8)	NS

Abbreviations as for Table 3.1; *Available only in 246 patients.

Table 3.5. Multiple Logistic Regression Model to Predict Procedural Success.

Variable	Coefficient	Standard error	Odds ratio	95% Confidence interval for odds ratio	p Value
Bridging collaterals	−2.56	0.45	0.08	0.03 to 0.19	$p<0.001$
Tapered entry configuration	1.29	0.34	3.63	1.87 to 7.07	$p<0.001$
Duration of occlusion (>3 months)	−1.35	0.44	0.26	0.11 to 0.61	$p=0.001$
Vessel diameter (>3 mm)	1.00	0.33	2.72	1.42 to 5.19	$p=0.003$
Constant	0.82	0.48	2.27	0.89 to 5.82	$p=0.080$

Analysis was based on 236 patients with complete clinical and angiographic data.

Table 3.6. Patients Classified by Observed Success and Predicted Probability of Success.

	Predicted probability of success			
	<30%	30%-69%	≥70%	Total
Observed success	7	56	86	149
Observed failure	29	49	9	87
Number of patients	36	105	95	236

Predictive value for procedural success (probability ≥70%): 86 of 95 = 91%.

Predictive value for procedural failure (probability <30%): 29 of 36 = 81%.

Table 3.7. Total and Event-free Survival 1 and 5 Years After Coronary Angioplasty for all Patients and Patients With Procedural Success. Data are % (95% confidence interval).

	One year		Five years	
	All patients	Procedural success	All patients	Procedural success
Death; % survival	97.4 (95.6-99.6)	97.4 (95.1-99.7)	94.8 (92.0-97.6)	96.7 (94.0-99.4)
Death/MI; % freedom	96.5 (94.4-98.6)	96.9 (94.4-99.4)	92.9 (89.7-96.1)	95.3 (91.9-98.7)
Death/MI/CABG; % freedom	83.3 (79.1-87.5)	91.6 (87.6-95.6)	77.4 (72.4-82.4)	89.5 (84.9-94.1)
Death/MI/CABG/ PTCA; % freedom	74.5 (69.5-79.5)	82.6 (77.1-88.1)	66.9 (61.2-72.6)	77.9 (71.6-84.2)
CABG; % freedom	86.5 (82.6-90.4)	94.8 (91.6-98.0)	83.8 (79.5-88.1)	94.2 (90.8-97.6)
Repeat PTCA; % freedom	88.7 (85.1-92.3)	88.4 (83.8-93.0)	86.5 (82.6-90.4)	85.3 (80.0-90.6)
CABG/repeat PTCA; % freedom	76.2 (71.3-81.1)	84.5 (79.2-89.8)	71.7 (66.4-77.0)	81.3 (75.5-87.1)

Abbreviations as for Table 3.1.

Table 3.8. Other Published Results (Chronological Order).

First Author (year)	Patients (number)	Duration of occl Mean (mth)	Range (mth)	Primary success (%)	In-hosp death (%)	MI (%)	CABG (%)	Restenosis (%)
Dervan (1983)	13*	1	0.03-?	54	0	0	0	43
Serruys (1985)	49	2	0.03–10	57	0	18	2	65
Kereiakes (1985)	76	7	0.13–120	53	0	11	1	75
DiSciascio (1986a)	46*	2	0.1–17	63	0	0	4	-
Melchior (1987a)	100	4	1-48	56	0	2	0	55
Safian (1988)	169	-	-	63	0	0	1	-
Ellis (1989b)	484*	8	0.1–108	-	-	-	-	77
LaVeau (1989)	56*	2	0–>12	70	0	3.5	0	-
Meier (1989)	50	8	0.03-120	58	0	0	0	71
Stone (1990)	905*	12	-	72	1	1	1	-
Warren (1990)	44	1**	0.25–36	59	0	0	0	40
Hamm (1990)	154*	-	0.5-13	73	0	0	0.6	52
Jost (1991)	90	2	0.25–6	60	0	0	0	30
Bell (1992)	354*	2	0–>3	66	2	4	3	59
Maiello (1992a)	294*	-	-	60	0	0.7	0.3	-
Ivanhoe (1992)	480*	-	-	66	1	2	9	54
Stewart (1993)	100	5**	3–60	47	2	5	0	-

CABG= emergency coronary artery bypass grafting; hosp=hospital; MI=myocardial infarction; mth=months; occl=occlusion; *including functional occlusions; **median.

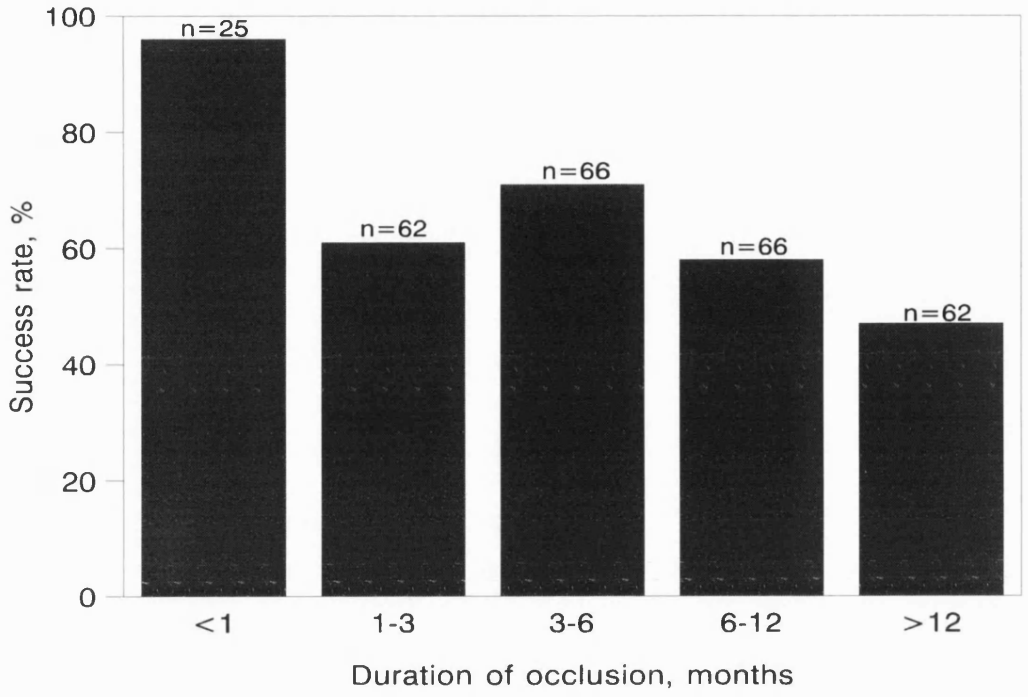


FIGURE 3.1. Bar graph of procedural success rate of attempted angioplasty of 281 occluded segments according to estimated duration of occlusion.

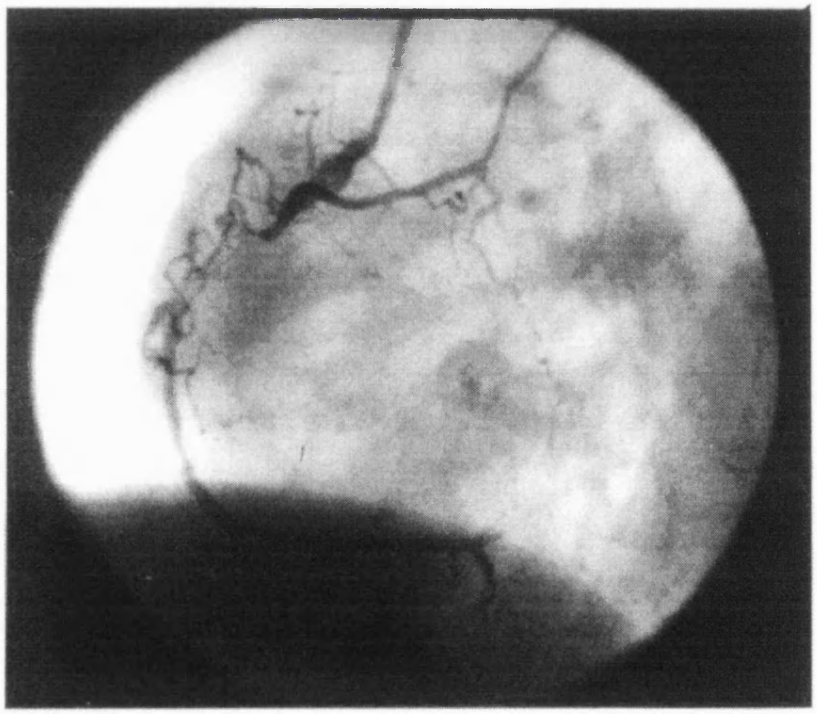


FIGURE 3.2. Chronic total occlusion of a right coronary artery with antegrade flow through bridging collaterals. The well developed bridging collaterals testify to the chronicity of the occlusion, which constitutes a contraindication to a recanalisation attempt.

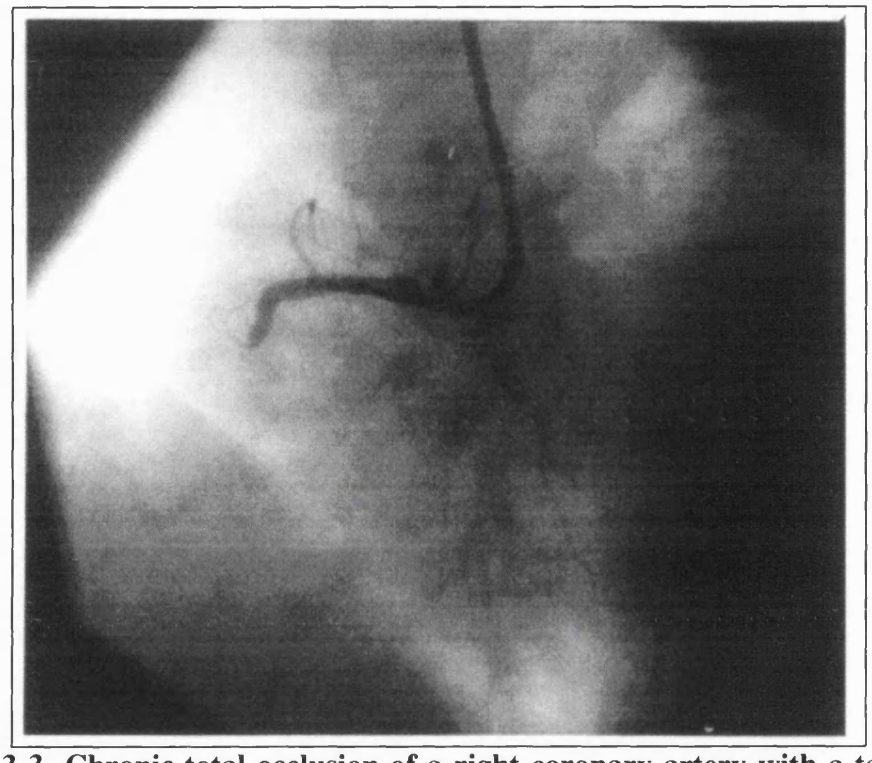


FIGURE 3.3. Chronic total occlusion of a right coronary artery with a tapered entry configuration.

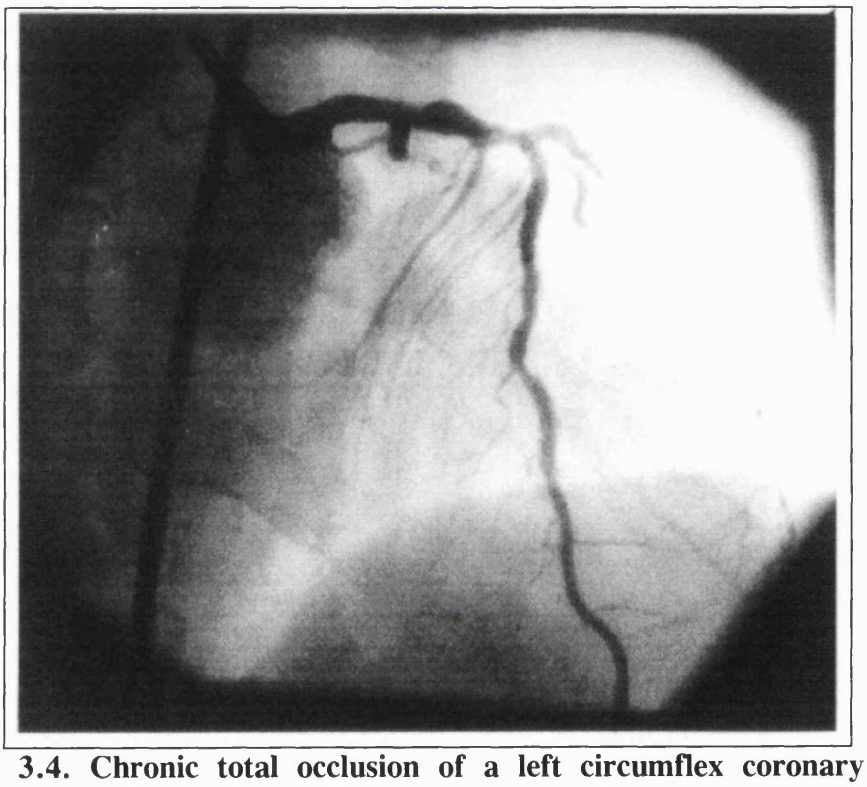


FIGURE 3.4. Chronic total occlusion of a left circumflex coronary artery without a tapered entry configuration (abrupt cut-off).

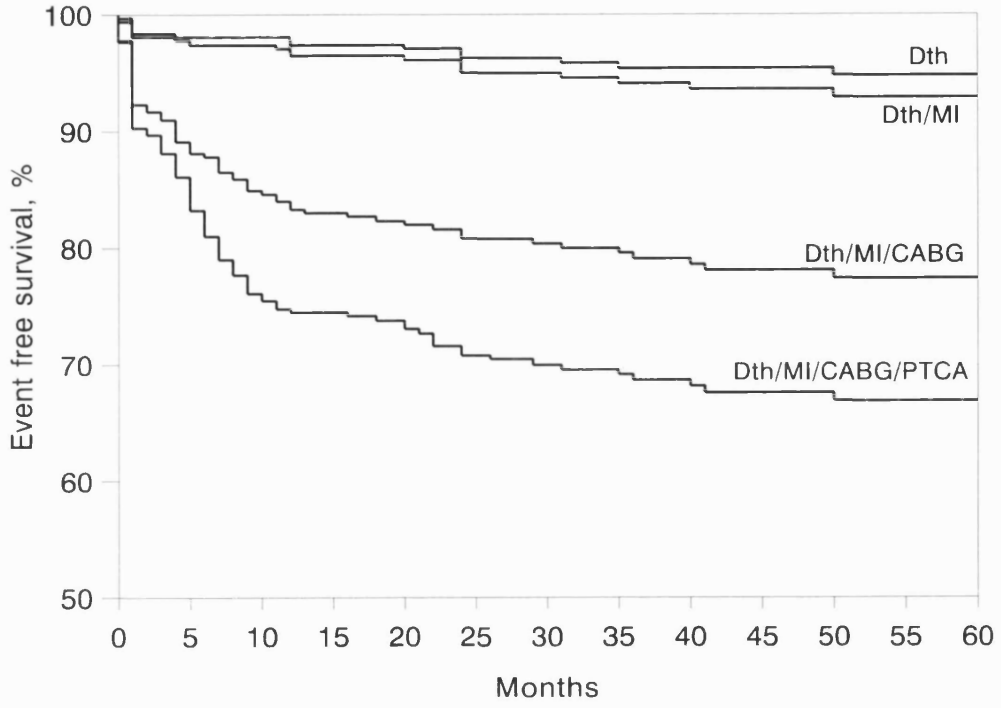


FIGURE 3.5. Plot of cumulative event free survival for all 312 patients. Dth = freedom from death; Dth/MI = freedom from death and myocardial infarction; Dth/MI/CABG = freedom from death, myocardial infarction, and coronary artery bypass grafting; Dth/MI/CABG/PTCA = freedom from death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty.

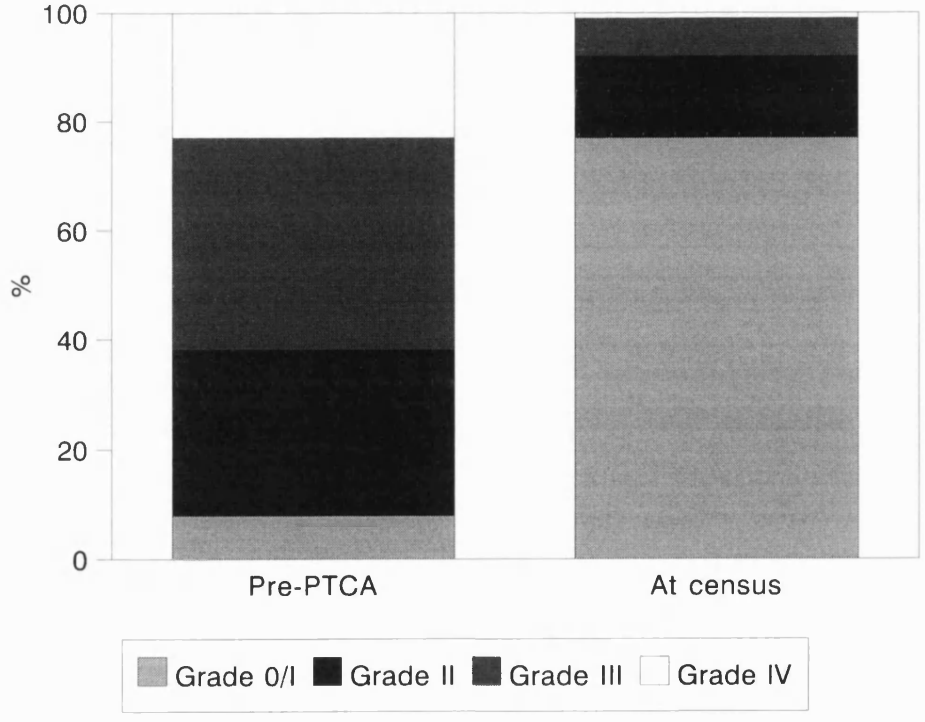


FIGURE 3.6. Angina grade before coronary angioplasty and at census in 297 survivors ($p < 0.001$).

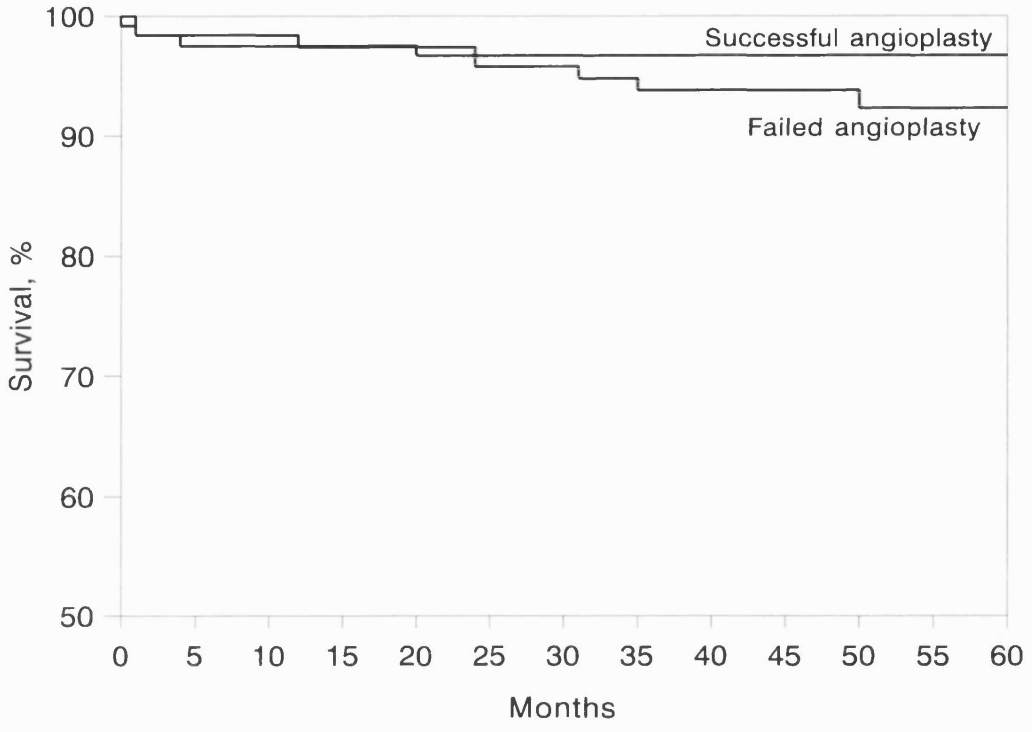


FIGURE 3.7. Plot of cumulative survival according to the outcome of initial angioplasty (p=0.13).

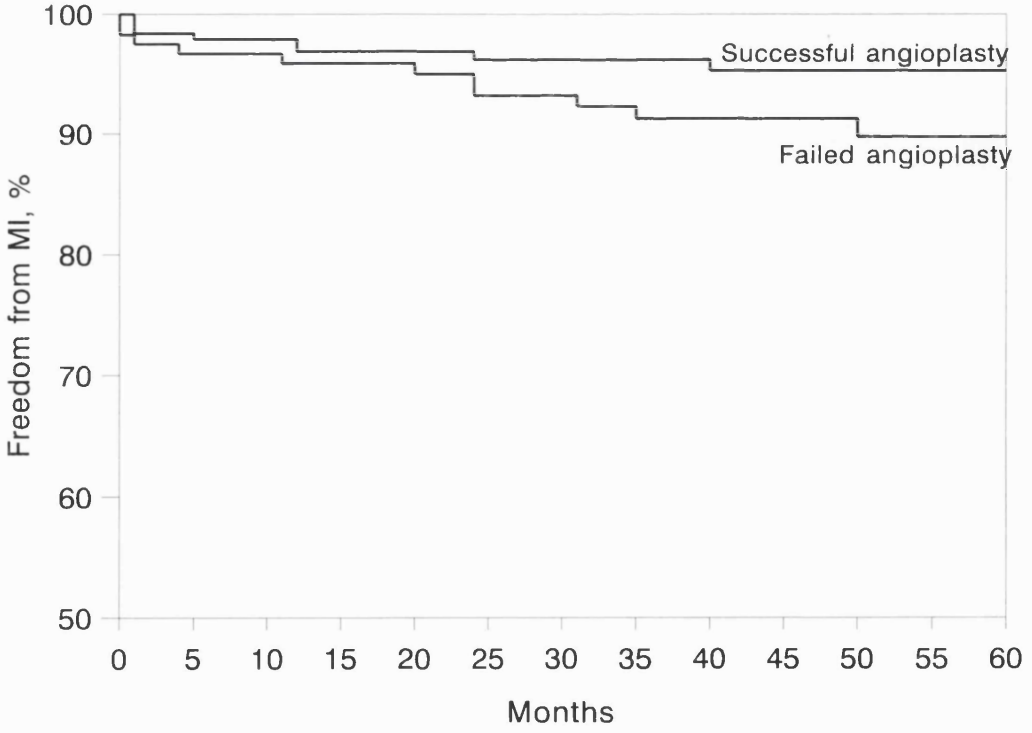


FIGURE 3.8. Plot of percentage of patients free of myocardial infarction (MI) according to the outcome of initial angioplasty (p=0.07).

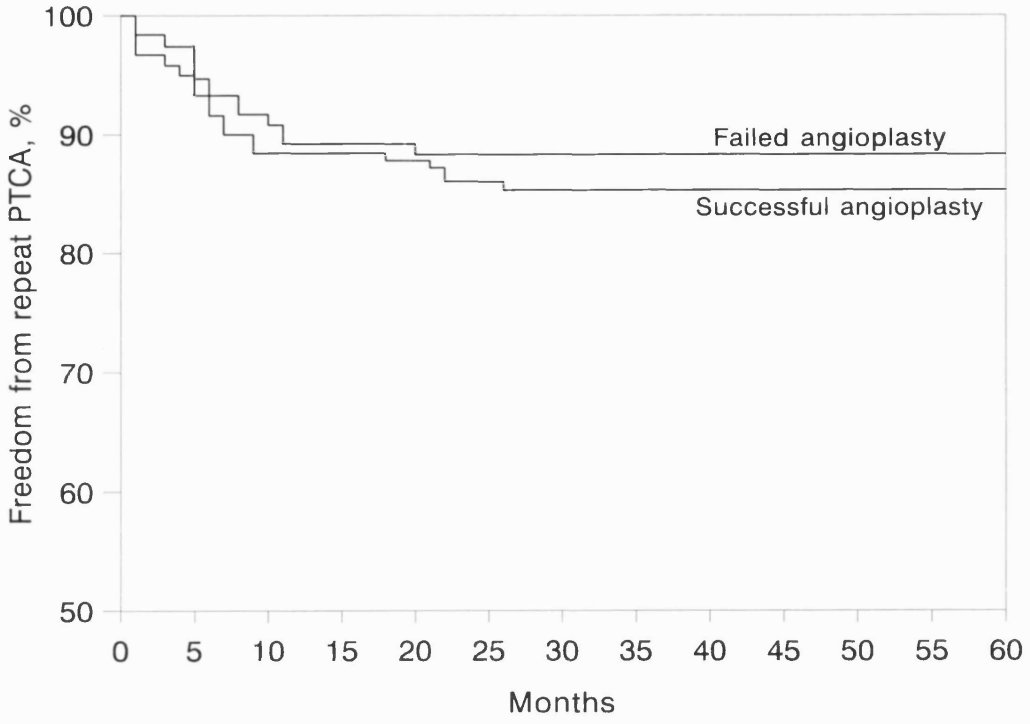


FIGURE 3.9. Plot of percentage of patients free of the need for repeat angioplasty (PTCA) according to the outcome of initial angioplasty (p=0.42).

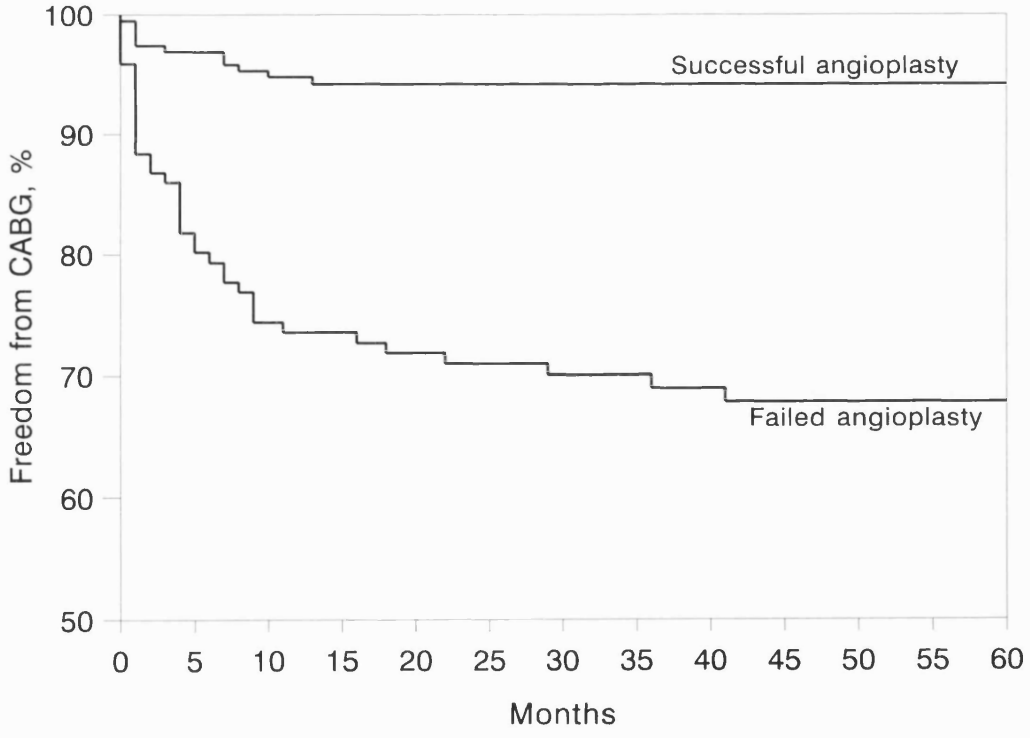


FIGURE 3.10. Plot of percentage of patients free of the need for coronary artery bypass grafting (CABG) according to the outcome of initial angioplasty (p<0.0001).

4. CORONARY ANGIOPLASTY OF AORTA OSTIAL, NON-AORTA OSTIAL, AND BRANCH OSTIAL STENOSES

4.1 INTRODUCTION

Coronary ostial stenosis is a rare manifestation of multivessel coronary artery disease, and an even rarer isolated finding. The incidence varies between 0.13% and 2.7% of patients with angiographically defined coronary artery disease (Pritchard et al, 1975; Barner et al, 1977; Salem et al, 1979; Miller at al, 1986). Aetiology of isolated coronary ostial stenosis include atherosclerosis, iatrogenic causes following coronary angioplasty or aortic valve replacement, syphilitic or Takayasu's arteritis, mediastinal radiation, and an idiopathic process that involves the coronary ostia in middle-aged women (Roberts and Morros, 1967; Rissanen, 1975; Slack and Pinkerton, 1985; Tommaso et al, 1988). On the other hand, stenosis at the ostium of a branch vessel is not an uncommon finding in patients with atheromatous coronary artery disease (Baim and Ignatius, 1988).

Although the efficacy of surgical revascularisation in patients with ostial stenosis is well recognised (Barner et al, 1989), conventional bypass grafting has resulted in some unfavourable sequelae: occlusion of the left main coronary artery, competitive flow and even the steal phenomenon when 2 bypass grafts are used, and retrograde perfusion of an extensive myocardial area which is associated with a decrease of the pressure head, known as the prizometer principle (Hitchcock et al, 1983; Hitchcock, 1985; Hutter et al, 1985; Vijayanagar et al, 1987).

Ostial lesions frequently appear well suited for coronary balloon angioplasty since they are often focal and concentric. However, ostial lesions have been identified as relatively complex and sub-optimal for balloon angioplasty by the American College of Cardiology/American Heart Association Task Force (Ryan et al, 1988). This has been attributed to the technical difficulties encountered during coronary angioplasty

of ostial stenoses, and to the unique histopathological composition of ostial lesions making them unfavourable for coronary angioplasty (Baucek et al, 1965; Rissanen, 1975; Thompson, 1986).

There is little information regarding the efficacy of coronary angioplasty in this patient subset and the limited data available has shown disparate results (Topol et al, 1987; Mathias et al, 1991; Brown et al, 1993). The study presented in this chapter reports on the acute success rate, complications, and long-term results of coronary angioplasty of aorta ostial, non-aorta ostial, and branch ostial stenoses on 198 consecutive patients. Since the technical requirements, procedural success, complication and restenosis rates differ among aorta ostial, non-aorta ostial, and branch ostial stenoses, these data are also examined separately for each of these anatomical species of ostial disease.

4.2 PATIENTS AND METHODS

(a) PATIENTS

Between 1987 and March 1993, 198 consecutive patients underwent a first coronary angioplasty procedure of an ostial stenosis. Ostial stenosis was defined as a lesion with >50% diameter stenosis involving the coronary ostium arising within 0.3 cm of the aortic orifice (aorta ostial stenosis: left main stem, right coronary artery, and saphenous vein graft), left main stem (non-aorta ostial stenosis: left anterior descending, intermediate, and circumflex coronary arteries), or the bifurcation of a large epicardial coronary artery (branch ostial stenosis) (Figures 4.1 to 4..10). None of the patients had known syphilitic or Takayasu's arteritis, and none had previous radiotherapy for mediastinal neoplasm.

The mean age was 57 years (SD 9, range 29 to 82 years) and 152 (77%) were male (Table 4.1). One hundred and four patients (53%) had a history of previous myocardial infarction and 70 (35%) had impaired left ventricular function. Forty-nine patients (25%) had previous coronary artery bypass grafting. Coronary angioplasty was performed as an emergency procedure for unstable angina in 31 patients (16%). Prior to intervention, 113 patients (57%) suffered grade III or IV angina. The majority of the patients had multivessel disease (69%). Risk factors that were present in the patients included smoking (52%), diabetes mellitus (7%), hypertension (19%), and hypercholesterolaemia (43%).

Multivessel coronary angioplasty was performed in 80 patients (40%) and multilesion coronary angioplasty in 118 patients (60%). Coronary angioplasty was attempted in 34 aorta ostial stenoses (6 protected left main stem, 22 right coronary

arteries, and 6 saphenous vein grafts), 48 non-aorta ostial stenoses (31 left anterior descending arteries, 8 intermediate arteries, and 9 circumflex arteries), and 116 branch ostial stenoses (48 diagonal, 2 septal perforator, 61 obtuse marginal, and 5 posterior descending arteries). Of the 48 non-aorta ostial stenoses, 10 involved the distal segment of the left main stem. Of the 116 branch ostial stenoses, 64 were isolated, and 52 involved the main epicardial coronary artery.

(b) ANGIOPLASTY PROCEDURE

Coronary angioplasty was performed according to the protocol described in Chapter 2. The technique used to dilate ostial stenosis differed depending on the site of the lesion.

Dilatation of aorta ostial stenoses were usually performed using guiding catheters with side holes to avoid catheter wedging and reduction in coronary flow. Frequently, guiding catheter engagement was avoided by positioning the tip just outside of the coronary ostium to mitigate catheter induced ostial trauma. The procedure involved either full inflation of the balloon with the proximal part still in the guiding catheter, or more commonly, partial withdrawal of the guiding catheter after the balloon had been partially inflated.

Coronary angioplasty of non-aorta ostial stenoses involved using protective guidewires in the non-diseased vessels and inflation with the balloon partially positioned within the left main stem. Contrast was injected after balloon inflation to ensure free flowing of contrast down the non-diseased vessel. More recently, auto-perfusion catheters have also been used.

The technique of coronary angioplasty of branch ostial stenoses differed depending on the operator and whether the ostial lesion extended across the bifurcation to involve the primary vessel. Essentially, it consisted of using either the "kissing-wire technique" using a double guidewire and a single balloon (Zack and Ischinger, 1984; Pinkerton et al, 1985), or the "kissing balloon" technique using low profile integrated balloons inflated sequentially or simultaneously in the branch vessel and the primary vessel (Meier, 1984b; Myler et al, 1989a).

(c) STUDY METHODS

The baseline clinical characteristics, angiographic details, and procedural data on all 198 patients were assessed. Lesion complexity was graded according to the guidelines published by the American College of Cardiology/American Heart Association Task Force (Table 1.1). Based on these criteria, all aorta ostial, non-aorta ostial, and bifurcation stenoses requiring double guidewires were classified as type B lesions. Forty-seven per cent of the stenoses in the present study had ≥2 adverse characteristics (type B2 lesions) and 17% were type C lesions.

Complete follow-up data were available on all 198 patients on or after the census date. Information on vital status, angina status, and the occurrence of new cardiac events was obtained up to October 31st, 1993.

Procedural success was defined as ≤50% residual diameter stenosis at the dilated sites without a major in-hospital complication (defined as the occurrence of either death, myocardial infarction, or emergency coronary artery bypass grafting). In patients who underwent multivessel or multilesion coronary angioplasty, success was judged according to the outcome of the ostial lesion. However, if a significant

in-hospital complication occurred as a result of dilating a non-ostial lesion despite an angiographic success for the ostial lesion, the procedure was judged a failure. Angiographic restenosis was defined as a recurrence of a >50% diameter stenosis at a previously successfully dilated site. Clinical restenosis was defined as the recurrence of anginal symptoms or evidence of reversible ischaemia associated with angiographic evidence of restenosis.

(d) STATISTICAL METHODS

Continuous variables are expressed as median due to their non-Normal distribution with the exception of the patients' ages which are expressed as mean (SD).

For the purpose of comparing success, complication, and restenosis rates, patients were divided into subgroups according to whether they underwent angioplasty of aorta ostial, non-aorta ostial, or branch ostial stenoses. For the analysis of survival times, patients who underwent aorta ostial and non-aorta ostial angioplasty were combined into a single subgroup (main ostial stenoses) in view of the low incidence of cardiac events. Patients were also divided into subgroups according to the extent of disease in the native vessels, and whether left ventricular function was normal or abnormal.

Comparison of success, complication, and restenosis rates were performed using the chi-square test. Procedural and angiographic data comparison between individual lesion location were performed using the Kruskal-Wallis test. Life table analyses were performed using the Kaplan-Meier method, computed from the time of coronary angioplasty, and the logrank test was used to assess differences between group outcomes.

4.3 RESULTS

(a) ACUTE RESULTS

Procedural success was achieved in 85% of aorta ostial lesions, 90% of non-aorta ostial lesions, and 87% of branch ostial lesions ($p=0.84$). A major in-hospital complication occurred in 5.9%, 6.3%, and 6.9% of patients who underwent aorta ostial, non-aorta ostial, and branch ostial stenosis angioplasty, respectively ($p=0.97$). Overall, 10 patients (5.0%) suffered a non-fatal myocardial infarction based on electrocardiographic and enzyme changes but only 6 (3.0%) had a Q-wave infarction. Three patients (1.5%) underwent emergency coronary artery bypass grafting due to intimal dissection followed by abrupt closure. No procedural deaths occurred (Table 4.2).

The angiographic and procedural data for each lesion location are shown in Table 4.3. Coronary angioplasty of left main stem and right coronary ostial stenoses leads to a less satisfactory final angiographic result when compared to other ostial sites. A greater residual stenosis remained in the left main stem and right coronary ostial sites ($p=0.005$) despite requiring a higher inflation frequency ($p<0.001$), a higher inflation pressure ($p<0.001$), a longer total inflation duration ($p<0.001$), and a balloon to artery ratio of 1.00–1.04.

Of the 198 patients, 80 (40%) underwent multivessel coronary angioplasty and 118 (60%) underwent multilesion coronary angioplasty. An additional 97 vessels (42 left anterior descending, 23 circumflex, 18 right, 5 intermediate, 2 diagonal, 3 marginal, and 4 saphenous vein grafts) and 184 non-ostial lesions were dilated. The procedural success rate was 93%. This was not significantly different from the

procedural success rate achieved with aorta ostial (p=0.2), non-aorta ostial (p=0.4), or branch ostial stenoses (p=0.2), respectively.

(b) LONG-TERM RESULTS

The median duration of follow-up was 27.5 months ranging from 1 to 71 months (SD 17 months). During the follow-up period, 8 patients (4.0%) died, 4 (2.0%) suffered a non-fatal myocardial infarction, and 13 (6.6%) underwent elective coronary artery bypass grafting. Forty-seven patients (24%) underwent a repeat angioplasty procedure for restenosis or new coronary lesions with 1 procedural death and 1 requiring emergency coronary artery bypass grafting. The cardiac event incidence (death, myocardial infarction, coronary artery bypass grafting, and repeat coronary angioplasty) during follow-up was not significantly different between patients who underwent main ostial stenosis angioplasty (aorta ostial and non-aorta ostial lesions) versus branch ostial stenosis angioplasty (37% versus 27%, p=0.14). The 8 late deaths included 6 cardiac deaths (fatal myocardial infarctions 4, revascularisation procedures 2) and 2 non-cardiac deaths (cerebral vascular accidents).

The cumulative probability of survival for all 198 patients was 99% (SE 0.7) and 93% (SE 2.9) at one and three years, respectively. The 1 and 3 year rates for freedom from death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty was 70% (SE 3.4) and 57% (SE 4.7), respectively. The 1 and 3 year cumulative event-free survival rates are shown in Table 4.4 for all patients and for the subgroups who underwent coronary angioplasty of main ostial stenoses (aorta ostial and non-aorta ostial lesions) and branch ostial stenoses (Figures 4.11). There was no significant difference in the rates for freedom from death, myocardial

infarction, coronary artery bypass grafting, and repeat angioplasty between patients who underwent angioplasty of main ostial stenoses and those who underwent angioplasty of branch ostial stenoses (Figure 4.12). Furthermore, the rates for freedom from death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty was not influenced by the extent of disease in the native coronary arteries (Figure 4.13) or by the presence or absence of left ventricular dysfunction (Figure 4.14).

At census, of the 190 survivors, 108 patients (57%) were asymptomatic, 64 (34%) had mild (grade I or II) angina, and only 18 (9%) complained of severe (grade III or IV) angina pectoris (Table 4.5, Figure 4.15).

(c) RESTENOSIS

Repeat coronary angiography was performed in 84 of the 173 patients (49%) who had initially successful procedures for recurrence of symptoms or evidence of reversible ischaemia documented on symptom-limited treadmill exercise tests. Overall, continued success was present in 46 patients and angiographic restenosis was present in 38 patients. The angiographic restenosis rate for aorta ostial stenoses, non-aorta ostial stenoses, and branch ostial stenoses was 71%, 60%, and 32%, respectively ($p=0.01$) (Table 4.6). Overall, the clinical restenosis rate was 22% (38/173).

4.4 DISCUSSION

The presence of an ostial stenosis poses a special management problem for the interventional cardiologist. By virtue of its proximity, a coronary ostial stenosis places an extensive area of myocardium in jeopardy in the event of an abrupt closure. This, in conjunction with the technical difficulties encountered during coronary angioplasty, and the unfavourable clinical outcome reported by some investigators (Topol et al, 1987), has led to surgical revascularisation being accepted as the treatment of choice (Barner et al, 1988; Barner et al, 1989). However, conventional coronary artery bypass grafting is not without problems (Hitchcock et al, 1983; Hitchcock, 1985; Hutter et al, 1985; Vijayanagar et al, 1987) and recently, coronary angioplasty has been applied with encouraging results in patients with ostial stenoses (Brown et al, 1993; Bedotto et al, 1991a).

Acute Success

Aorta and Non-aorta Ostial Lesions: The procedural success rates achieved for aorta and non-aorta ostial lesions in this study are comparable with previous studies (Table 4.7). In a multicentre study of coronary angioplasty for right coronary artery ostial stenosis, Topol et al reported a procedural success rate of 79% (Topol et al, 1987). Bedotto et al (1991) reported a procedural success rate of 85% for coronary angioplasty of aorta ostial lesions (right coronary artery and saphenous vein graft). Simon et al (1986) reported a procedural success rate of 92% for coronary angioplasty of non-aorta ostial lesions (left anterior descending and circumflex coronary artery). Procedural success rates of 83% to 91% have been reported for coronary angioplasty of a combination of both aorta and non-aorta ostial lesions (Valbracht et al, 1993; Nakhjavan et al, 1987). More recently, using a technique of progressive dilation on ostial stenosis of the left anterior descending artery, Brown

et al (1993) achieved a procedural success rate of 100%. The disparate success rates between the various studies may have resulted from the different dilatation techniques used (Brown et al, 1993) or it may have reflected the differences in location of the ostial lesions being studied. However, in the present study, lesion location was not found to be a predictor of procedural outcome. It may be the unique properties of ostial lesions, regardless of their location in the vascular system, that make them resistant to coronary angioplasty (Baucek et al, 1965; Rissanen, 1975; Thompson, 1986).

Branch Ostial Lesions: The only notable report on coronary angioplasty of branch ostial stenosis was by Mathias et al (1991). They reported an angiographic success rate of 74% on 106 patients who underwent an angioplasty of stenosis at the ostium of a branch vessel, as opposed to 87% achieved in the presented study. However, a higher proportion of their patients presented with unstable angina (46% versus 16%), which may account for the less favourable success rate.

Ostial Versus Non-ostial Lesions: Previous investigators also reported a lower primary success rate for ostial lesions compared to non-ostial lesions (Topol et al, 1987; Mathias et al, 1991). In contrast, the present series did not show a significant difference in the procedural success rate for aorta ostial, non-aorta ostial, and branch ostial stenoses when compared to the non-ostial lesions dilated at the same time, consistent with the findings of Brown et al (1993) and Vallbracht et al (1993). Furthermore, compared with angioplasty in 729 consecutive patients performed at our institution over the last three years, the procedural success rate of angioplasty of ostial stenoses did not differ significantly (87% versus 90%, $p=0.26$).

Acute Complications

Coronary angioplasty of ostial stenoses had a higher complication rate of 6.6% when compared with a complication rate of 3.3% for the 729 consecutive patients who underwent angioplasty at our institution over the last 3 years ($p=0.04$). The factors that may have contributed to the higher complication rate include: trauma to the stenosis by manipulation of the guiding catheter within the coronary ostium in the case of aorta ostial lesions; partial positioning and inflation of the balloon within the left main stem, causing vascular damage in the case of non-aorta ostial lesions; and the unique properties of ostial lesions making them unfavourable for coronary angioplasty (Baucek et al, 1965; Rissanen, 1975; Thompson, 1986).

Previous investigators have reported a widely variable incidence of procedure-related cardiac events, ranging from 0% to 9.4% (Topol et al, 1987; Brown et al, 1993; Mathias et al, 1991). Again, the differences may be the result of the varying location of the ostial lesions being dilated, or the different dilatation techniques used. However, it is more likely to have reflected the differences in baseline characteristics, especially the clinical presentation of the study patients.

Technical Considerations

Although the lesion location was not an important determinant of procedural success according to the definition that was used in this study, the final angiographic result, from angioplasty of left main stem and right coronary ostial stenoses, was less satisfactory despite a significantly greater technical requirement (median inflation pressure of 9–10 atmospheres, inflation frequency of 4.5, and total inflation duration of 360–465 seconds).

These findings may be explained by the technical difficulties in achieving guide catheter intubation and support, and balloon placement during dilatation of aorta ostial stenoses (Topol et al, 1987).

Some investigators have also suggested that the histopathological composition of aorta ostial stenoses may be different (Baucek et al, 1965; Rissanen, 1975; Thompson, 1986), and may account for the difficulty encountered during dilatation of these lesions. However, Stewart et al (1987), describing histological specimens obtained from a patient with isolated aorta ostial stenosis, have concluded that the lesion was essentially a conventional atheromatous plaque with an unusual distribution, rather than an unusual form of atheroma. In support of this, Popma et al (1991), analysing specimens obtained by directional atherectomy of coronary ostial stenoses, have shown that these lesions comprised histological components of a common hard plaque. Lastly, the possibility that aorta ostial lesions were more difficult to dilate may also be the result of lesion eccentricity or a greater tendency to elastic recoil. Aorta ostial lesions are essentially aortic wall lesions that have encroached on the ostium of the coronary arteries (Barner et al, 1988; Barner et al, 1989). The fundamentally elastic behaviour of the thick aortic wall may account for the increased tendency for elastic recoil, which may be the primary mechanism contributing to the increased residual stenosis. These mechanisms may also explain the poorer results reported by other investigators in the dilatation of aorta ostial lesions (Topol et al, 1987; Bedotto et al, 1991), when compared to non-aorta ostial lesions (Simon et al, 1986; Brown et al, 1993).

Although Mathias et al (1991) have shown a higher residual stenosis in branch ostial lesions despite adequate balloon sizing, the present study did not confirm their finding.

Long-term Results

Although angioplasty for ostial stenosis is technically feasible, the procedure must be associated with short- and long-term symptomatic improvement to be judged clinically successful. The efficacy of any revascularisation procedure is defined by the clinical events and the patient's functional status. It was not possible to determine the specific physiological and prognostic implication of coronary angioplasty of aorta ostial, non-aorta ostial, or branch ostial stenoses since other vessels were also dilated at the same time to achieve complete revascularisation.

The long-term clinical outcome of coronary angioplasty in patients with coronary artery disease is influenced by the extent of disease in the native vessel, the completeness of revascularisation, the extent of left ventricular dysfunction, and the restenosis rate. However, the present study has shown favourable long-term outcome with no significant influence from lesion location, the extent of native vessel disease, and the presence of left ventricular dysfunction. These findings may appear inconsistent but may have reflected the completeness of revascularisation that was achieved, and the relatively well preserved left ventricular function in those patients that were classified as being abnormal on a dichotomous definition. The 3 year total and event-free survival rate for all patients were 93% and 57%, respectively. The reintervention rate (coronary angioplasty or coronary artery bypass grafting) of 32% for main ostial stenoses (aorta ostial and non-aorta ostial) in the present study is comparable with the reintervention rate of 31% and 26% reported by Bedotto et al (1991) and Topol et al (1987), respectively. Although the reintervention rate of 24% for branch ostial stenoses in the present study is greater than the 13.2% reported by Mathias et al (1991), the follow-up period is shorter in their study (mean 7.8 months, SD=5.9 months).

There was marked improvement in angina status after coronary angioplasty in the present series, bearing in mind other vessels were concurrently dilated during the same time to achieve complete revascularisation, and a reintervention rate of 27% during follow-up. At census, 57% of the survivors were asymptomatic and only 9% complained of severe angina.

Restenosis

Of the 173 successfully treated patients in the present series, only 49% returned for follow-up coronary angiography, with an overall angiographic restenosis documented in 45% of these patients. The restenosis rates for both aorta ostial (71%) and non-aorta ostial stenoses (60%) in the present study are higher than the restenosis rate of previously reported studies; 38% for right coronary ostial stenoses reported by Topol et al (1987), 18.2% for left anterior descending and saphenous vein ostial stenoses reported by Nakhjavan et al (1987), 38% for left anterior descending ostial stenoses reported by Brown et al (1993), and 31% for right coronary and saphenous vein graft ostial stenoses reported by Bedotto et al (1991).

However, the finding of a higher restenosis rate in the present series is misleading, since the denominator included only the 49% who returned for repeat coronary angiography, usually for recurrent symptoms. Topol et al (1987) included all 42 patients with initial success in the denominator despite only 16 (38%) of these patients returned for repeat angiography. Nakhjavan et al (1987) included all 11 patients in their study in the denominator despite only 2 (18%) returned for repeat angiography. Sixty per cent of the patients in the study by Brown et al (1993) returned for repeat angiography but it was not clear which patients were included in the denominator. The proportion of patients that returned for repeat angiography was not reported by Bedotto et al (1991). An angiographic restenosis rate of 68%

for branch ostial stenosis has been previously reported by Mathias et al but only 22% of their patients who had initial successful dilatation returned for repeat angiography. In the present series, if the denominator included all patients with initial success, the restenosis rate for aorta ostial and non-aorta ostial lesions would be 34% and 28%, respectively. The true angiographic restenosis rate probably lies between 34% and 71% for aorta ostial lesions, and between 28% and 60% for non-aorta ostial lesions. Only 22% of patients, who had initially successful dilatation of branch ostial stenoses, returned for repeat angiography in the report by Mathias et al (1991) and angiographic restenosis was documented in 68% of these patients.

With the caveat that the repeat angiographic restudy was incomplete, the present series has shown that the restenosis rate for aorta ostial stenoses was higher when compared to non-aorta and branch ostial stenoses. Possible explanations include a less satisfactory final angiographic result attained with aorta ostial lesions (Table 4.3), increased intimal trauma caused by the multiple inflations necessary at the aorta ostial sites resulting in a greater cellular proliferative response (Table 4.3) (Hearn et al, 1991; Glazier et al, 1989a), and an intrinsic propensity for aorta ostial lesions to develop restenosis (Health and Public Policy Committee, American College of Physician, 1983; Whitworth et al, 1985; Miller et al, 1986).

New Angioplasty Technology

New angioplasty technologies, such as laser angioplasty (Lawson et al, 1993; Eigler et al, 1991; Tcheng et al, 1992), rotational coronary ablation (Popma et al, 1993, Kent et al, 1992), directional atherectomy (Popma et al, 1991; Garratt et al, 1991; Robertson et al, 1991), and coronary stenting (Teirstein et al, 1991a) have recently been introduced as alternatives to balloon angioplasty for coronary ostial lesions.

The application of some of these techniques in coronary ostial lesions has shown favourable results, although others have shown conflicting results.

Teirstein et al (1991a) reported a procedural success rate of 89% in 28 patients who underwent Palmaz-Schatz stent implantation of aorta-ostial and non-aorta ostial stenoses. Procedural success rates of 92% to 100% have been reported for directional atherectomy of non-aorta ostial stenoses, although the success rates achieved for aorta ostial stenoses were less favourable, and ranged from 71% to 78% (Hinihara et al, 1991; Robertson et al, 1991). Encouraging results have also been reported for excimer laser angioplasty of aorta ostial disease (Tcheng et al, 1992; Lawson et al, 1993). However, to date, no randomised trials comparing these new devices with balloon angioplasty have been reported and any direct comparison between studies could be misleading since the baseline characteristics may differ considerably. In addition, reduction of restenosis rate has not been observed with any of these new techniques (Popma et al, 1993; Garratt et al, 1991; Teirstein et al, 1991a). Although results from randomised studies of *de novo* stent implantation using the Palmaz-Schatz device have demonstrated reduction in restenosis rates when compared to balloon angioplasty, coronary ostial lesions were excluded from these trials (Serruys et al, 1993; Fischman et al, 1994).

The introduction of intravascular ultrasound has also provided a new opportunity for assessing the adequacy of dilatation in patients with coronary ostial stenoses. Using intravascular ultrasound imaging performed after conventional angioplasty of a right coronary ostial stenosis, Popma et al (1991) have demonstrated the presence of significant residual atheroma despite a good angiographic result. Furthermore, this device can also provide real-time monitoring and catheter guidance during

percutaneous intravascular interventions, thus increasing procedure efficacy and safety.

Study Limitations

This study is a retrospective analysis of data and is subject to all the limitations inherent in such a study. The frequency of occurrence of ostial stenosis at some locations was low, therefore analysis of clinical outcome by individual lesion locations was not possible. Repeat coronary angiography was incomplete (49%) since this was performed only in patients who were symptomatic or had evidence of reversible ischaemia. Therefore the exact restenosis rate cannot be determined.

4.5 SUMMARY AND CONCLUSIONS

Coronary angioplasty of aorta ostial, non-aorta ostial, and branch ostial stenoses carries with it an acceptable success and complication rate, and provides good symptomatic relief and favourable long-term outcome. With current techniques and appropriate case selection, 80% to 90% of aorta ostial, non-aorta ostial, and branch ostial lesions can be successfully dilated by balloon angioplasty. However, balloon angioplasty of ostial stenoses results in higher complication rates when compared to angioplasty of non-ostial lesions. Distinctive procedural features include the frequent need for higher inflation pressures and higher inflation frequency for aorta ostial lesions. Although some new angioplasty devices introduced for the dilatation of ostial lesions have resulted in success rates which compare favourably with those achieved with balloon angioplasty, reduction in restenosis rate has not been shown. Further clinical evaluation with a prospective, randomised trial will be needed to select the best device therapy for ostial lesions.

Table 4.1. Patient and Angiographic Characteristics.

	Number	%
Total	198	100
Mean age (years)	57	SD 9 (range 29-82)
Male gender	152	77
Angina grade		
I	26	13
II	59	30
III	52	26
IV	61	31
Previous MI	104	53
Abnormal LV (EF < 45%)	70	35
Previous CABG	49	25
Risk factors		
Smoking	103	52
Family history	70	35
Diabetes mellitus	13	7
Hypertension	38	19
Hypercholesterolaemia	85	43
Emergency procedure	31	16
Multivessel disease	136	69
Single vessel PTCA	118	60
Multivessel PTCA	80	40
Multilesion PTCA	118	60

CABG=coronary artery bypass grafting; EF=ejection fraction; LV=left ventricular function; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty; SD=standard deviation.

Table 4.2. Primary Success and Complication Rates of all 198 Patients. Data are Number (%).

	Number	Success	MI	Emergency CABG
LMS	6	6 (100)	0 (0)	0 (0)
RCA	22	19 (86)	1 (4.5)	1 (4.5)
SVG	6	4 (67)	0 (0)	0 (0)
LAD	31	27 (87)	1 (3.2)	1 (3.2)
INT	8	7 (88)	1 (12.5)	0 (0)
CX	9	9 (100)	0 (0)	0 (0)
DIAG	48	42 (88)	3 (6.3)	0 (0)
SEPTAL	2	1 (50)	0 (0)	1 (50)
CXOM	61	53 (87)	4 (6.6)	0 (0)
PDA	5	5 (100)	0 (0)	0 (0)
Aorta ostial stenoses	34	29 (85)	1 (2.9)	1 (2.9)
Non-aorta ostial stenoses	48	43 (90)	2 (4.2)	1 (2.1)
Branch ostial stenoses	116	101 (87)	7 (6.0)	1 (0.9)
p Value		NS	NS	NS

CABG=coronary artery bypass grafting; CX=circumflex; CXOM=circumflex obtuse marginal; DIAG=diagonal; INT=intermediate; LAD=left anterior descending; LMS=left main stem; MI=myocardial infarction; NS=not significant; PDA=posterior descending; RCA=right coronary; SEPTAL=septal perforator; SVG=saphenous vein graft.

Aorta ostial stenoses = LMS, RCA, and SVG.
Non-aorta ostial stenoses = LAD, INT, and CX.
Branch ostial stenoses = DIAG, SEPTAL, CXOM, and PDA.

Table 4.3. Angiographic and Procedural Details According to Lesion Location. Data are Median Values.

Vessel	Pre-PTCA stenosis (%)	Post-PTCA stenosis (%)	Inflation frequency	Maximum inflation pressure (atmospheres)	Total inflation duration (seconds)	Balloon/artery ratio
LMS	88	35	4.5	9	360	1.04
RCA	84	29	4.5	10	465	1.03
SVG	93	17	4.0	8	360	1.04
LAD	83	19	4.0	8	270	1.05
INT	85	18	2.0	8	180	1.09
CX	83	18	3.0	7	270	1.02
DIAG	87	19	2.0	6	180	1.03
SEPTAL	81	22	2.5	6	210	1.19
CXOM	85	14	2.0	6	180	1.03
PDA	87	26	2.0	8	180	0.95
p Value	NS	0.005	<0.001	<0.001	<0.001	NS

Abbreviations as for Tables 4.1 and 4.2.

Table 4.4. Total and Event-free Survival 1 and 3 Years After PTCA for All Patients and the Subgroups who Underwent Coronary Angioplasty of Main Ostial Stenoses (Aorta Ostial and Non-aorta Ostial Stenoses) and Branch Ostial Stenoses. Data are % (95% Confidence Interval).

	One year			Three years		
	All patients	Main ostial	Branch ostial	All patients	Main ostial	Branch ostial
Death; % survival	99 (98-100)	97 (94-100)	100 (NA)	93 (87-99)	92 (84-100)	93 (85-100)
Death/MI; % freedom	92 (88-96)	94 (89-99)	91 (86-96)	85 (78-92)	88 (79-97)	83 (73-93)
Death/MI/CABG; % freedom	88 (83-93)	88 (81-95)	88 (82-94)	78 (70-86)	80 (69-91)	76 (65-87)
Death/MI/CABG/ PTCA; % freedom	70 (63-77)	65 (54-76)	73 (64-82)	57 (48-66)	55 (42-68)	58 (45-71)
CABG; % freedom	93 (89-97)	90 (83-97)	95 (91-99)	90 (85-95)	87 (79-95)	92 (86-98)
Repeat PTCA; % freedom	78 (72-84)	76 (66-86)	80 (72-88)	73 (65-81)	72 (61-83)	72 (61-83)
CABG/repeat PTCA; % freedom	73 (66-80)	67 (56-78)	77 (69-85)	67 (59-75)	63 (52-74)	70 (59-81)

Abbreviations as for Table 4.1. NA = not applicable.

Table 4.5. Angina Grade Before Coronary Angioplasty and at Census in 190 Survivors.

Angina class	Coronary ostial stenosis (n=77)		Branch ostial stenosis (n=113)	
	Pre-PTCA	At census	Pre-PTCA	At census
0	0	39	0	69
I	13	18	13	31
II	17	10	40	5
III	20	10	28	8
IV	27	0	32	0
p Value	<0.001		<0.001	

Abbreviations as for Table 4.1.

Table 4.6. Restenosis Data on the 173 Patients who had an Initially Successful Angioplasty Procedure.

	Number	Repeat angiography	Angiographic restenosis	%
LMS	6	2	2	100
RCA	19	10	6	60
SVG	4	2	2	100
LAD	27	12	8	67
INT	7	3	2	67
CX	9	5	2	40
DIAG	42	21	4	19
SEPTAL	1	1	0	0
CXOM	53	25	11	44
PDA	5	3	1	33
Aorta ostial stenoses	29	14	10	71
Non aorta ostial stenoses	43	20	12	60
Branch ostial stenoses	101	50	16	32
p value				0.01

Abbreviations as for Table 4.2.

Table 4.7. Other Published Results (Chronological Order).

First author (year)	Patients (number)	Lesion location	Procedural success (%)	Cardiac event (%)	Death (%)	MI (%)	Emergency CABG (%)
Simon (1986)	38	LAD, CX	92	7.9	0	5.3	2.6
Nakhjavan (1987)	11	LAD, SVG	91	0	0	0	0
Topol (1987)	53	RCA	79	9.4	0	5.7	9.4
Bedotto (1991)	55	RCA, SVG	85	0	0	0	0
Mathias (1991)	106	Branch ostium	74	5.7	0	1.8	4
Brown ((1993)	40	LAD	100	0	0	0	0

Abbreviations as for Tables 4.1 and 4.2.

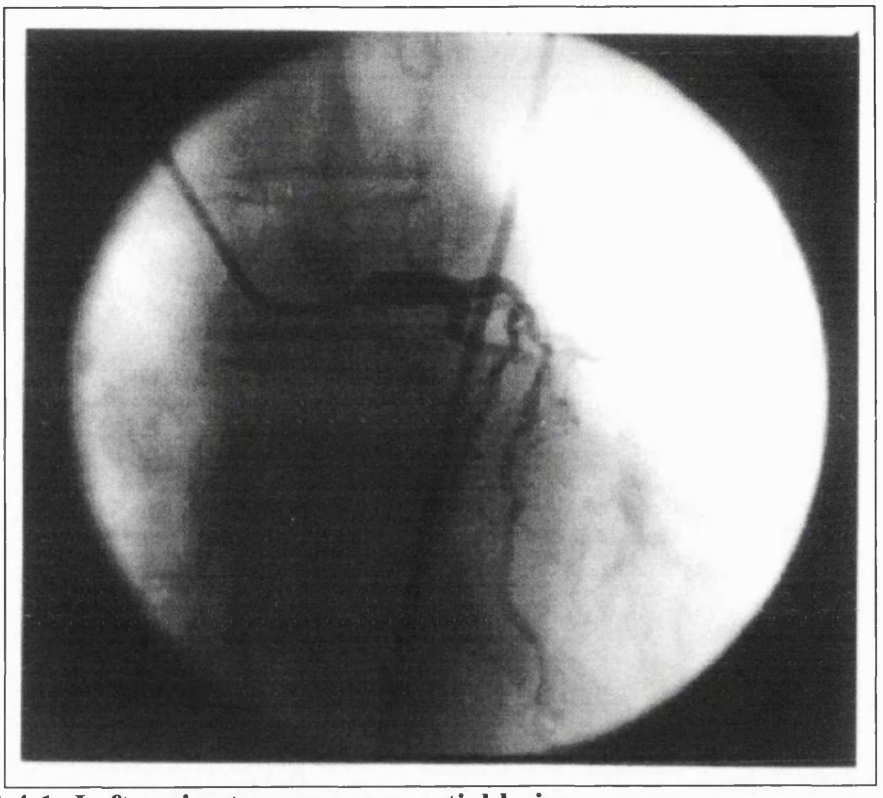


FIGURE 4.1. Left main stem coronary ostial lesion.

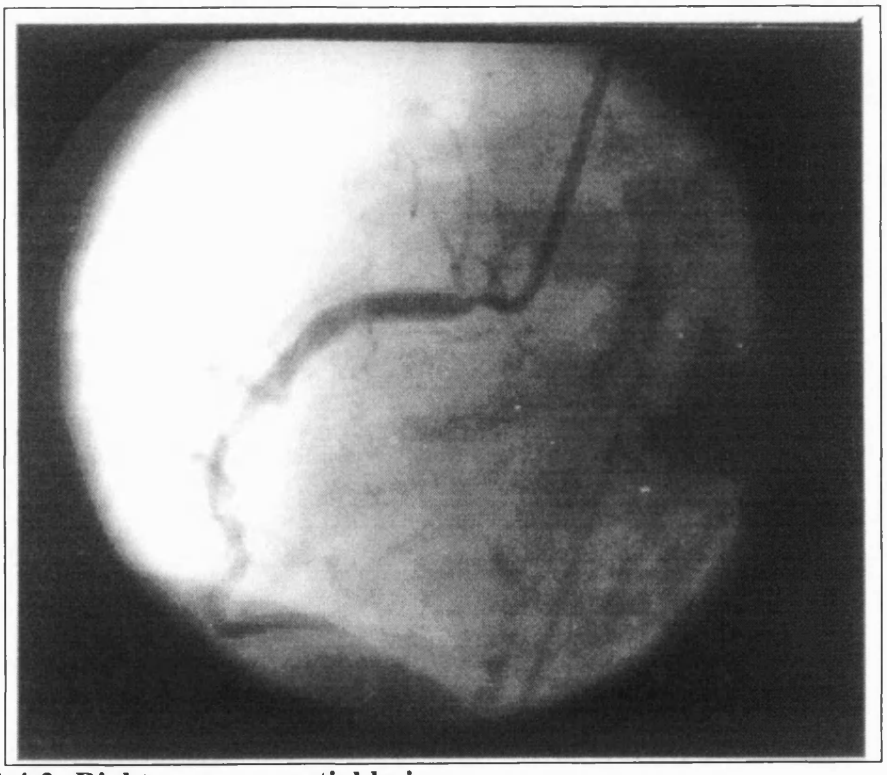
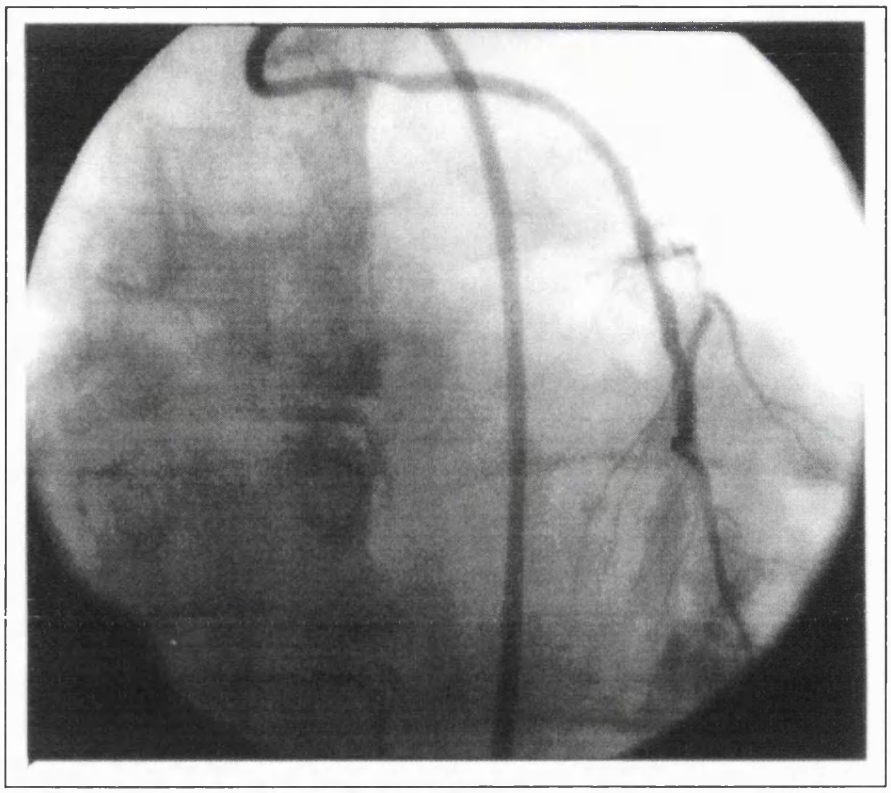


FIGURE 4.2. Right coronary ostial lesion.



FIFURE 4.3. Saphenous vein graft ostial lesion.

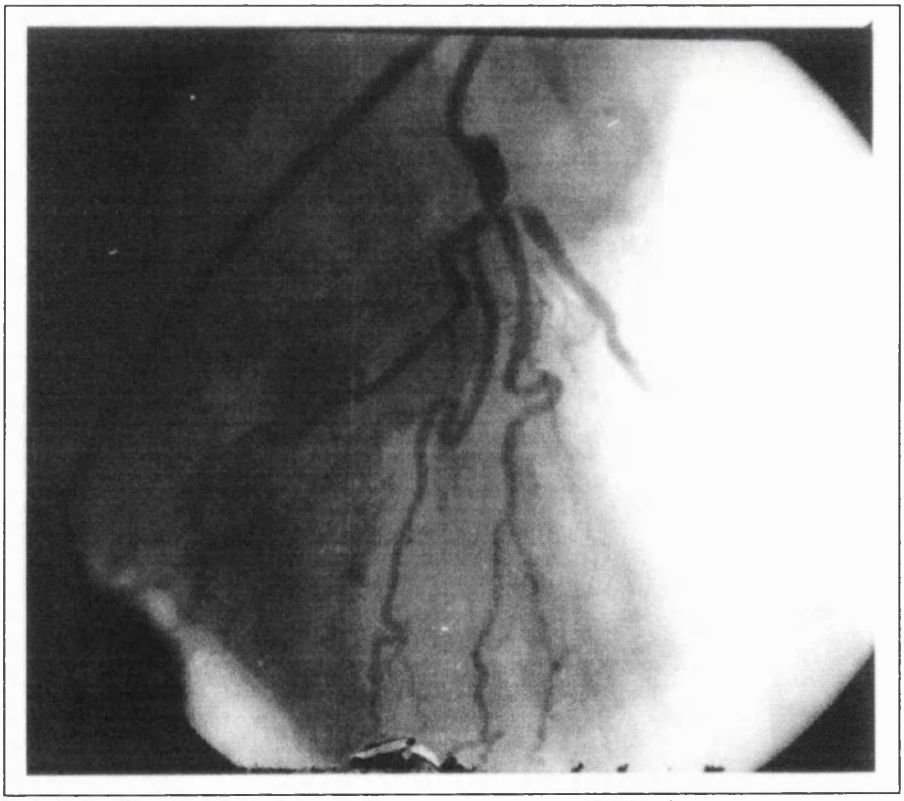


FIGURE 4.4. Left anterior descending coronary ostial lesion.

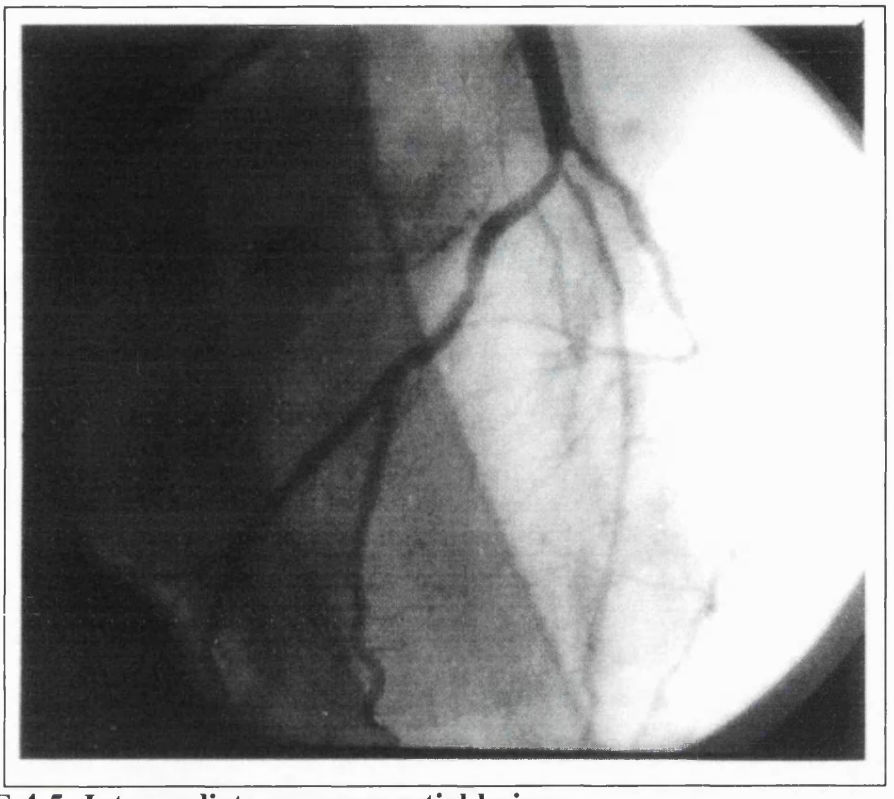


FIGURE 4.5. Intermediate coronary ostial lesion.

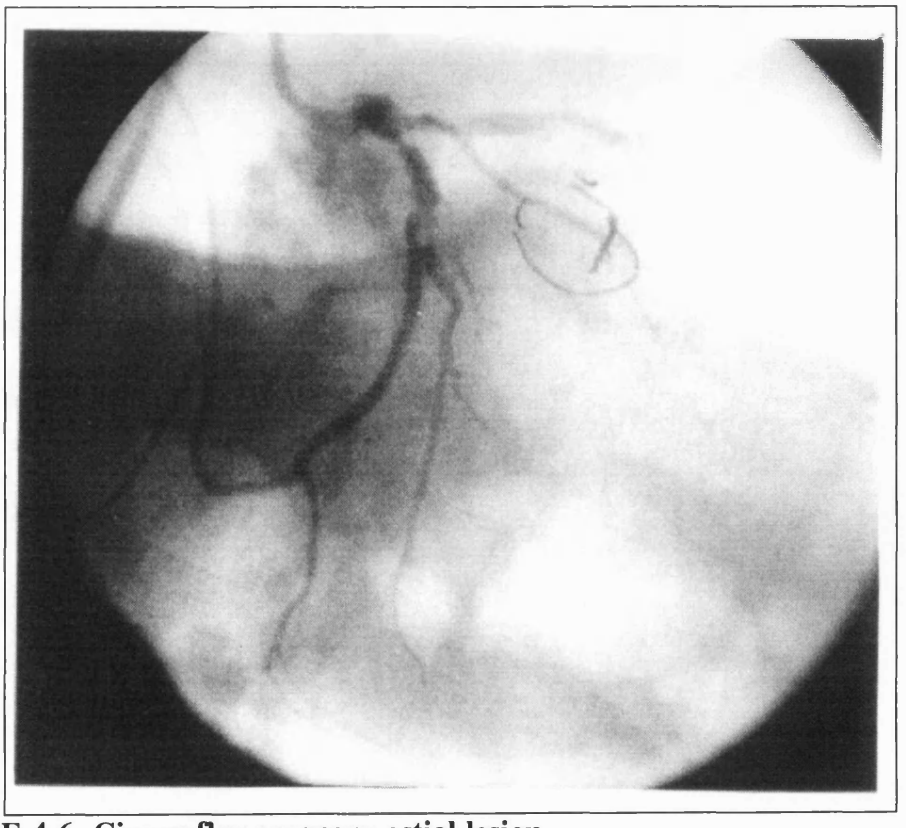


FIGURE 4.6. Circumflex coronary ostial lesion.

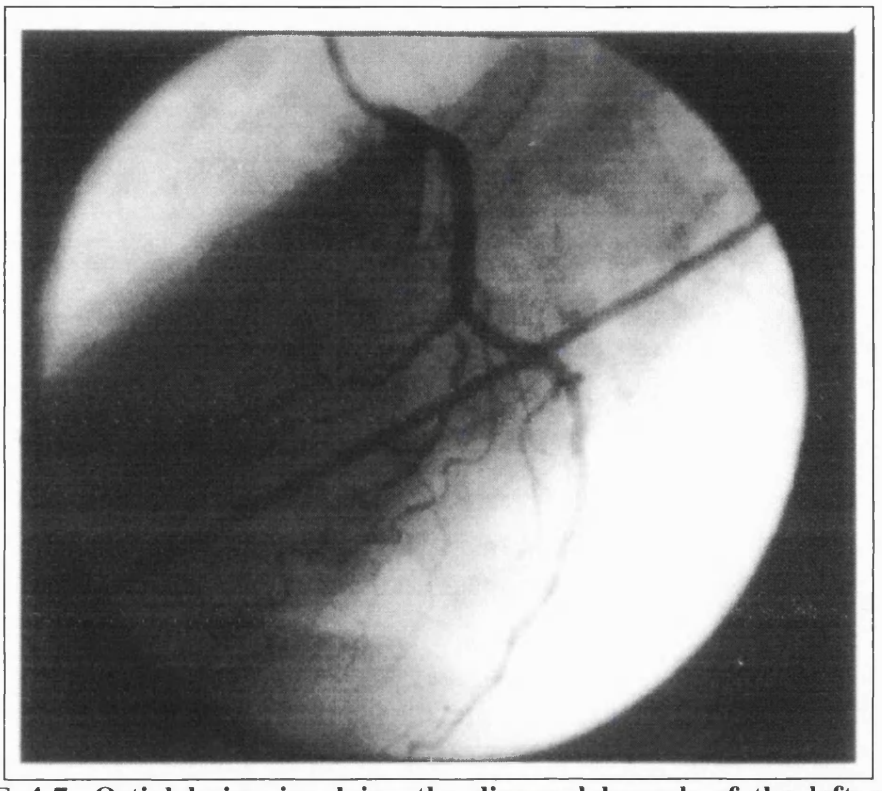


FIGURE 4.7. Ostial lesion involving the diagonal branch of the left anterior descending coronary artery.

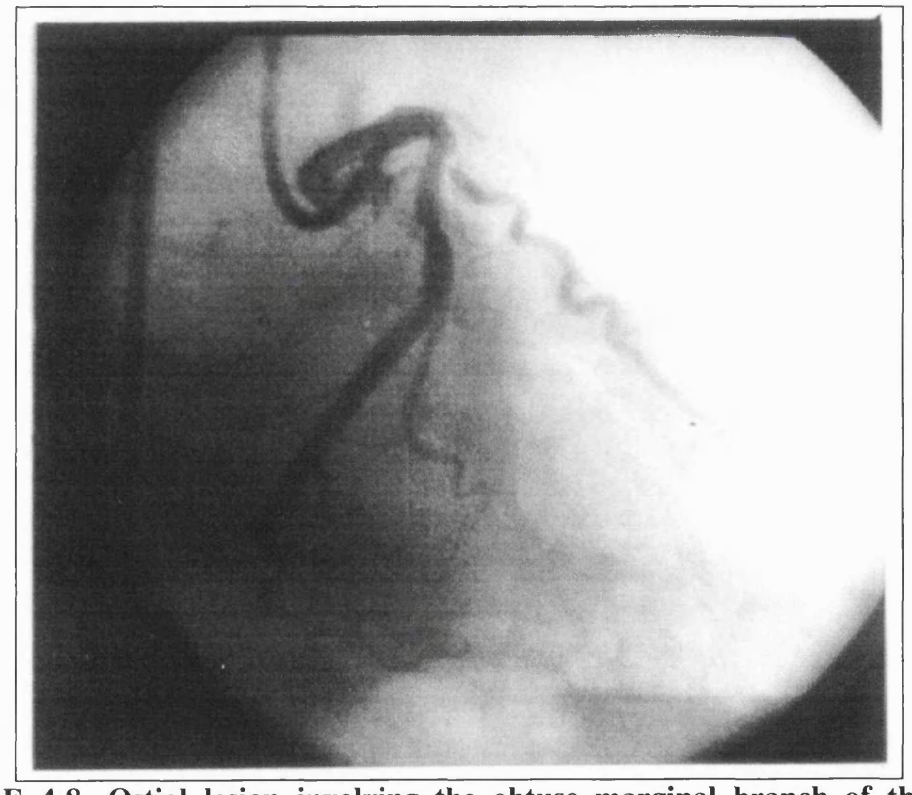


FIGURE 4.8. Ostial lesion involving the obtuse marginal branch of the left circumflex coronary artery.

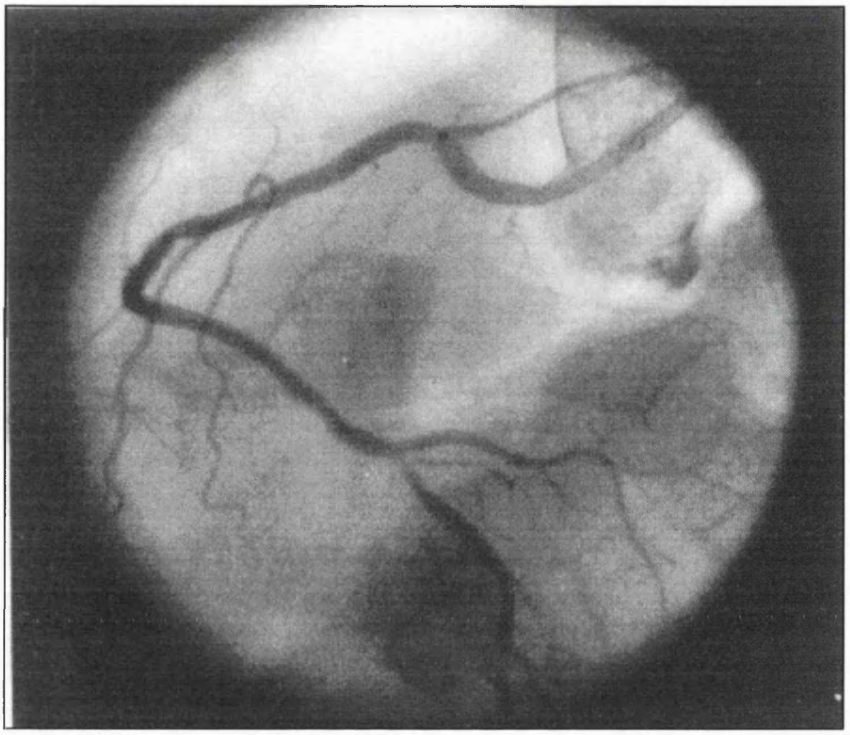


FIGURE 4.9. Ostial lesion involving the posterior descending branch of the right coronary artery.

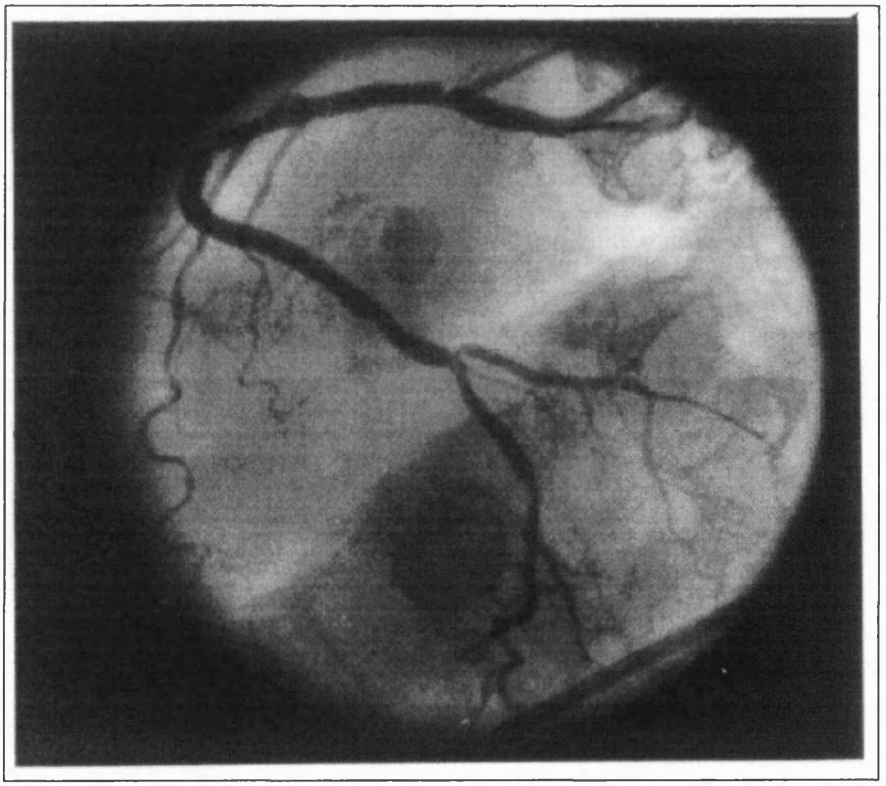


FIGURE 4.10. Ostial lesion involving the left ventricular branch of the right coronary artery.

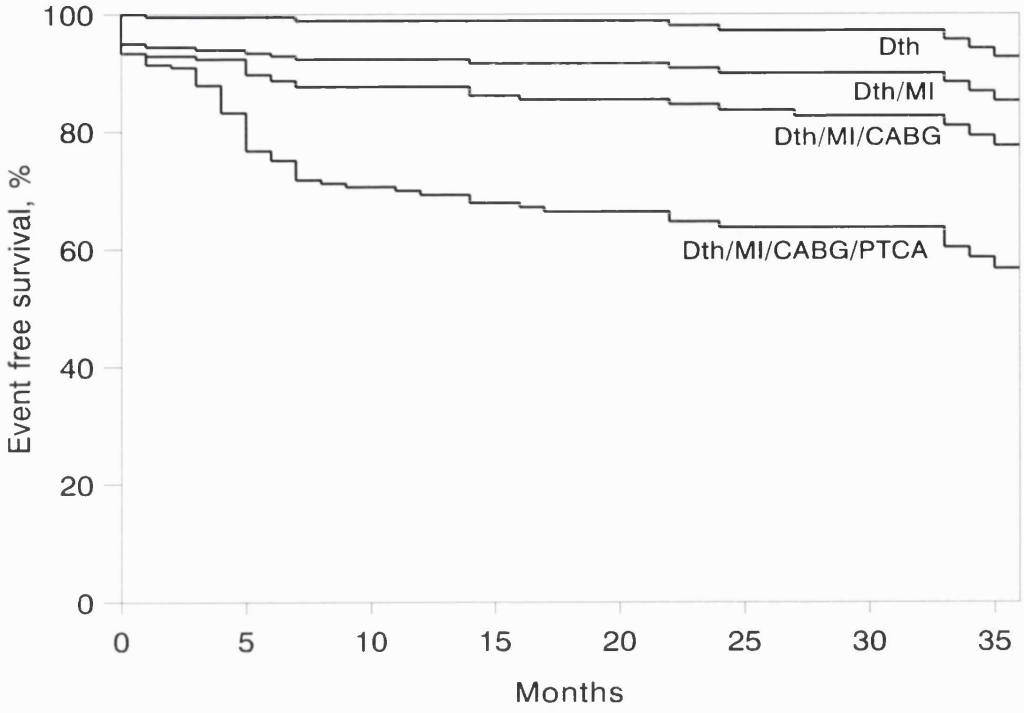


FIGURE 4.11. Plot of cumulative event free survival for all 198 patients. Dth=freedom from death; Dth/MI=freedom from death and myocardial infarction; Dth/MI/CABG=freedom from death, myocardial infarction, and coronary artery bypass grafting; Dth/MI/CABG/PTCA=freedom from death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty.

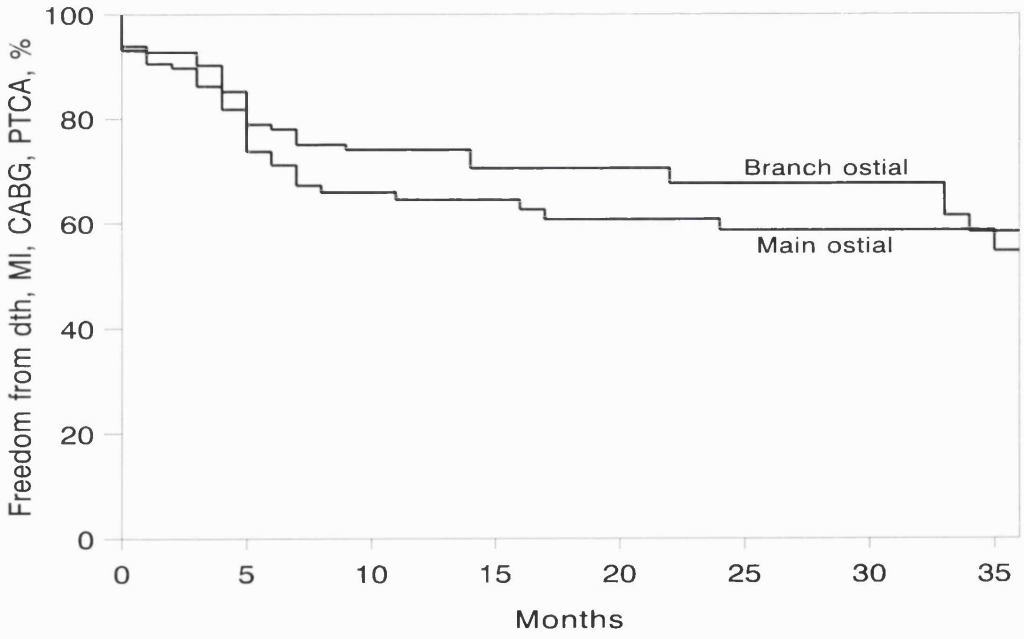


FIGURE 4.12. Plot of percentage of patients free of death (dth), myocardial infarction (MI), coronary artery bypass grafting (CABG), and repeat angioplasty (PTCA) according to the location of ostial stenoses (p=0.46).

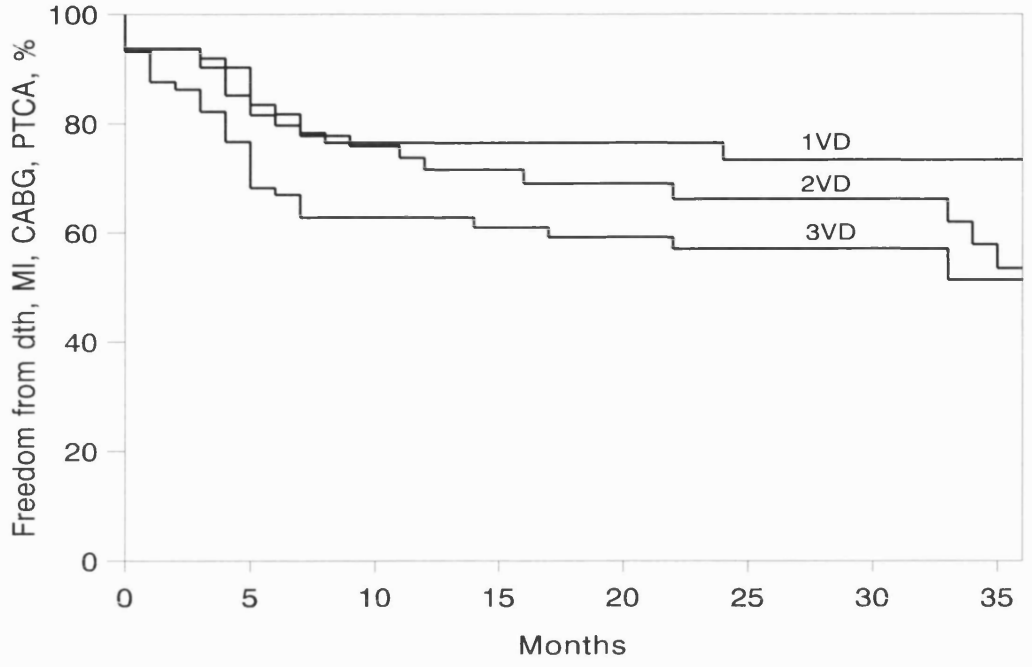


FIGURE 4.13. Plot of percentage of patients free of death (dth), myocardial infarction (MI), coronary artery bypass grafting (CABG), and repeat angioplasty (PTCA) according to number of diseased vessels (p=0.09). 1VD=single vessel disease; 2VD=double vessel disease; 3VD=triple vessel disease.

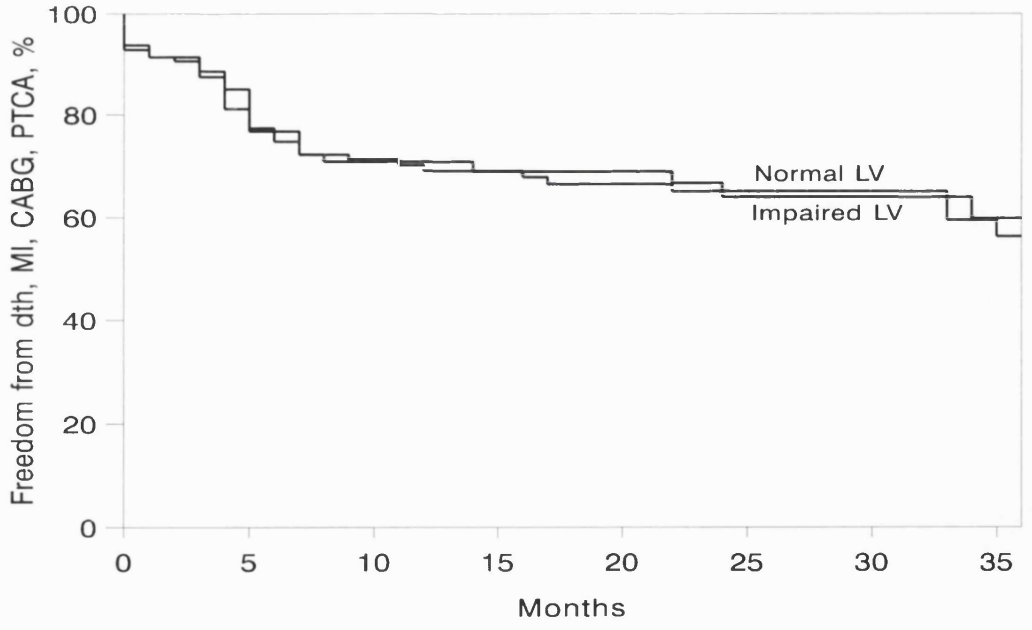


FIGURE 4.14. Plot of percentage of patients free of death (dth), myocardial infarction (MI), coronary artery bypass grafting (CABG), and repeat angioplasty (PTCA) according to left ventricular function (p=0.9).

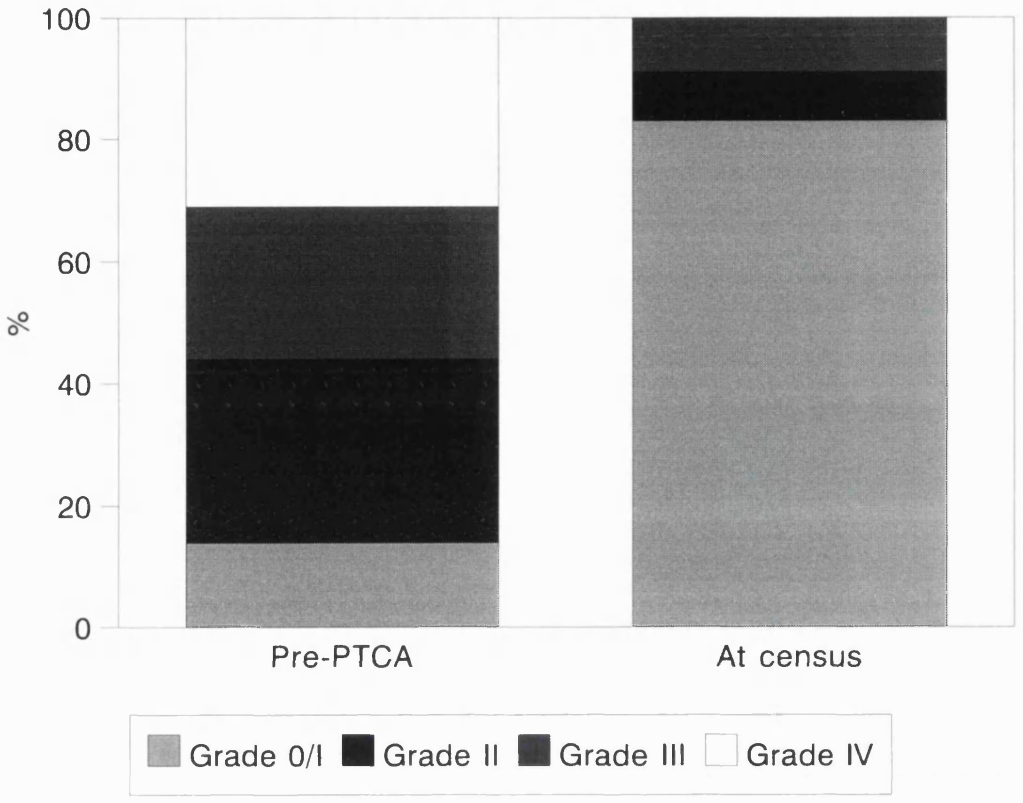


FIGURE 4.15. Angina grade before coronary angioplasty and at census in 190 survivors ($p < 0.001$).

5. *EFFICACY OF A THIRD CORONARY ANGIOPLASTY PROCEDURE FOR A SECOND RESTENOSIS*

5.1 INTRODUCTION

Despite continuing improvement in primary success rate, restenosis remains the major limitation of percutaneous transluminal coronary angioplasty. The reported incidence ranges from 16% to 47% depending on the population studied (Kaltenbach et al, 1985; Leimgruber et al, 1986; Serruys et al, 1988b). The efficacy of a second coronary angioplasty for a first restenosis has been well documented, and earlier studies have reported higher acute success and lower complication rates than those usually reported for a first angioplasty procedure (Meier et al, 1984d; Williams et al, 1984; Surgue et al, 1987; Galzier et al, 1989b; Deligonul et al, 1989b; Quigley et al, 1989b). Hence, treatment of restenosis with a repeat angioplasty has become routine clinical practice, and is currently accepted as an integral part of the overall coronary angioplasty revascularisation strategy.

Although long-term follow-up suggests that a second recurrence is no more likely than a first, restenosis after a second angioplasty is nevertheless associated with an incidence ranging from 26% to 34% in previously reported series (Meier et al, 1984d; Williams et al, 1984; Joly et al, 1988; Black et al, 1988; Quigley et al, 1989b; Dimas et al, 1992). With continuing growth in the volume of angioplasty procedures, patients with restenosis after a second angioplasty will become an increasing clinical problem. Although a third angioplasty procedure for a second restenosis has been shown to be technically feasible and safe, the long-term efficacy is less well defined (Joly et al, 1988; Glazier et al, 1989b; Teirstein et al, 1989; Dimas et al, 1992; Bauters et al, 1993). There still remains a paucity of data that address long-term clinical outcomes once a second restenosis has been documented, and to date, no randomised trials exist comparing different management strategies of these patients. Whether these patients should be subjected to a third angioplasty

procedure, or whether coronary artery bypass grafting is the preferred mode of revascularisation at this stage remains unanswered. In addition, the ability to identify those patients at higher risk of a subsequent restenosis will have important implications in planning and optimising individual therapeutic strategy.

To resolve some of these issues, the study presented in this chapter reports on the acute success and long-term follow-up of 62 patients who underwent a third coronary balloon angioplasty procedure for a second restenosis. The correlates of clinical restenosis after a third angioplasty procedure are also examined.

5.2 PATIENTS AND METHODS

(a) PATIENTS

Between January 1986 and December 1992, 62 consecutive patients underwent a third percutaneous transluminal coronary balloon angioplasty of a single coronary arterial segment at which restenosis had occurred after 2 previous angioplasty procedures. Patients who had their third angioplasty procedure within 2 weeks of the preceding procedure were not included in the study to exclude patients who had repeat dilation because of peri-procedural complication. The median time interval between the second and the third angioplasty was 6 months ranging from 1 to 22 months.

The mean age was 53 years (SD 9, range 31 to 72 years) and 52 (84%) were male (Table 5.1). Thirty patients (48%) had a history of previous myocardial infarction and 22 (35%) had impaired left ventricular function. Twelve patients (19%) had previous coronary artery bypass grafting. Coronary angioplasty was performed as an emergency for unstable angina in 10 patients (16%). Before intervention, 47 patients (76%) suffered grade III or IV angina. Thirty-seven patients (60%) had multivessel disease. Risk factors present in the patients included hypertension (23%), diabetes mellitus (10%), hypercholesterolaemia (47%), and current smoking (60%).

Eleven patients (18%) underwent multivessel coronary angioplasty, and 16 (26%) underwent multilesion coronary angioplasty during the same procedure. A mean of 1.2 vessels and 1.4 stenoses per patient were attempted.

A total of 74 vessels and 85 stenoses were attempted during the same procedure. Of the 62 coronary artery segments that were dilated for the third time for a second restenosis, 33 (53%) were located in the left anterior descending artery and its diagonal branches, 9 (15%) in the circumflex artery and its obtuse marginal branches, 15 (24%) in the right coronary artery, and 5 (8%) in saphenous vein graft. Three procedures were undertaken for totally occluded vessels. Of the remaining 23 stenoses that were dilated in those patients who underwent multilesion angioplasty, 18 were dilated for the first time, and 5 were dilated for the second time.

(b) ANGIOPLASTY PROCEDURE

Coronary angioplasty was performed according to the protocol described in Chapter 2. The femoral approach was used in all cases. The technique used to dilate coronary artery segments at which restenosis had occurred after 2 previous angioplasty procedures was no different from that of the primary procedure.

(c) STUDY METHODS

The baseline clinical, angiographic, and procedural data on all 62 patients were assessed. Lesion complexity was graded according to the guidelines published by the American College of Cardiology/American Heart Association Task Force (Table 1.1). Based on these criteria, of the 62 lesions that had a third angioplasty procedure performed, 16 (26%) were classified as type A, 17 (27%) as type B1, 13 (21%) as type B2, 15 (24%) as type C1, and 1 (2%) as type C2.

Complete follow-up data were available on all 62 patients on or after the census date. Information on vital status, angina status, and the occurrence of new cardiac events was obtained up to October 31st, 1993.

The patient-related variables analysed as possible determinants of restenosis included age, sex, angina grade, presentation with unstable angina, extent of coronary artery disease, left ventricular function, and the time interval between second and third angioplasty. Other variables considered were a history of smoking, hypertension, diabetes mellitus, hypercholesterolaemia, previous myocardial infarction, previous coronary artery bypass surgery, and the presence of a family history.

The lesion-related variables analysed as possible determinants of restenosis included lesion length, eccentricity, angulation, contour, calcification, and location (ostial, proximal, mid, or distal). Other variables considered were vessel diameter, vessel location, pre-angioplasty percentage stenosis, post-angioplasty percentage stenosis, presence of distal ectasia, presence of thrombus, and presence of post-angioplasty dissection. The procedure-related variables analysed as possible determinants of restenosis included number of inflations, maximum inflation pressure, maximum inflation duration, total inflation duration, and balloon to artery ratio.

Procedural success was defined as $\leq 50\%$ residual diameter stenosis at the dilated sites without a major in-hospital complication (defined as the occurrence of either death, myocardial infarction, or emergency coronary artery bypass grafting). In patients who underwent multivessel or multilesion coronary angioplasty, success was judged according to the outcome of the coronary artery segment that was dilated for the third time for a second restenosis. However, if a significant in-

hospital complication occurred as a result of dilating another lesion, despite an angiographic success for the coronary artery segment which had recurrent restenosis, the procedure was judged a failure. Angiographic restenosis was defined as a recurrence of a >50% diameter stenosis at a previously successfully dilated site. Clinical restenosis was defined as the recurrence of anginal symptoms or evidence of reversible ischaemia associated with angiographic evidence of restenosis. Patients who had a cardiac death or a non-fatal myocardial infarction during the follow-up period were also considered as having had a clinical restenosis.

(d) STATISTICAL METHODS

Continuous variables are expressed as mean (SD). For the purpose of assessing determinants of a third restenosis, the unit of analysis used is the stenotic lesion, not the patient. Restenosis was analysed as a dichotomous variable for each lesion. The recurrence rates were assessed for all variables analysed as possible correlates of restenosis.

The relation of categorical variables to the restenosis rate was examined using the chi-square analysis or Fisher's exact test. Continuous variables were grouped into 2 approximately equally sized subgroups according to the values of each variable. The relationship between restenosis rate and these subgroups was also analysed using the chi-square analysis or Fisher's exact test. All variables found to be significantly related to restenosis by univariate analysis were included in a multiple logistic regression analysis. The backward stepwise selection procedure was used to identify independent predictors of procedural outcome significant at the 1% level. Survival functions were estimated using the Kaplan-Meier method, computed from the time of coronary angioplasty.

5.3 RESULTS

(a) ACUTE RESULTS

Procedural success was achieved in 56 patients (90.3%). The mean stenosis was reduced from 83% (SD 13%) to 12% (SD 9%). A major in-hospital complication occurred in 2 patients (3.2%). One patient (1.6%) suffered a non-fatal Q-wave myocardial infarction and 1 (1.6%) underwent emergency coronary artery bypass grafting due to intimal dissection followed by abrupt closure. No procedural deaths occurred (Table 5.2).

(b) LONG-TERM RESULTS

The median duration of follow-up was 48 months ranging from 12 to 94 months. During the follow-up period, 4 patients (6.5%) died, 2 (3.2%) suffered non-fatal myocardial infarction, and 5 (8.1%) underwent elective coronary artery bypass grafting. Nine patients (14.5%) underwent a fourth angioplasty procedure for a third restenosis and 3 (4.8%) had a fourth angioplasty procedure for new coronary lesions. Overall, a second revascularisation procedure was necessary in 17 patients (27.4%). The 4 late deaths included 2 cardiac deaths (1 sudden death and 1 fatal myocardial infarctions), 1 from elective coronary artery bypass grafting for restenosis, and 1 from repeat angioplasty procedure for new coronary lesions.

The cumulative probability of survival for all 62 patients was 96.8% (SE 2.2) and 95.0% (SE 2.8) at 1 and 5 years, respectively. Both the 1 and 5 year cumulative survival rates for patients with an initially successful angioplasty procedure were 96.2% (SE 2.7). The 1 and 5 year rates for freedom from death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty was 82.3% (SE 4.9) and 66.6% (SE 6.4), respectively. The 1 and 5 year cumulative event-free

survival rates are shown in Table 5.3 for all patients and patients with an initially successful angioplasty procedure (Figures 5.1 and 5.2).

At census, of the 58 survivors, 31 (53%) were asymptomatic, 19 (33%) had mild (grade I or II) angina, and only 8 (14%) complained of severe (grade III or IV) angina ($p<0.001$) (Figure 5.3). Forty-four patients (76%) improved by at least 2 angina grades.

(c) INCIDENCE OF A THIRD RESTENOSIS

Repeat coronary angiography was performed in 26 of the 56 patients (46%) who had initially successful procedures for recurrence of symptoms, or reversible ischaemia documented on symptom-limited treadmill exercise tests. Continued success was present in 8 patients (8/26=31%) and angiographic restenosis was present in 18 patients (18/26=69%) (including the patient who died from coronary artery bypass surgery for restenosis). Of the remaining 30 patients who did not undergo repeat angiography, 2 suffered cardiac death and 2 had a non-fatal myocardial infarction. The remainder were asymptomatic and had a negative exercise test at follow-up except for 1 patient who had 1 mm ST segment depression at peak exercise. Hence, the total number of patients with a clinical restenosis was 22 (22/56=39%).

(d) DETERMINANTS OF A THIRD CLINICAL RESTENOSIS

Univariate analysis of 32 patient-, lesion-, and procedure-related variables showed that restenosis was more common in patients who presented with unstable angina (70% versus 33%, $p=0.03$), and in those where the time interval from the second

to the third angioplasty procedure was ≤5 months (59% versus 19%, p=0.002) (Tables 5.4, 5.5, and 5.6). The mean time interval from the second to the third angioplasty procedure was 4.8 months (SD 2.9) in patients who subsequently developed a third restenosis, and 7.7 months (SD 4.7) in those who did not (p=0.03). Multiple stepwise logistic regression analysis identified the time interval between the second and the third angioplasty as the only independent predictor of restenosis (p=0.004). None of the other variables analysed contributed significantly to this regression model.

(e) ANGIOPLASTY FOR A THIRD RESTENOSIS

Of the 9 patients who underwent a fourth coronary angioplasty procedure for a third restenosis, procedural success was achieved in 8 patients (88.9%). One patient needed emergency coronary bypass surgery. There were no procedural deaths or myocardial infarctions. The 8 patients who had a successful fourth angioplasty procedure were followed-up for a median of 33 months (range 8 to 68 months). There were no late deaths, myocardial infarctions, or coronary artery bypass graftings. At census, 4 patients were asymptomatic and 4 complained of only grade I angina pectoris. Of the 3 patients who underwent repeat angioplasty for new coronary lesions, 2 had a successful procedure and 1 patient died as a result of the procedure.

5.4 DISCUSSION

The long-term efficacy of percutaneous transluminal coronary angioplasty has been hampered by the problem of restenosis (Kaltenbach et al, 1985; Leimgruber et al, 1986; Serruys et al, 1988b). With the expansion of the indication for coronary angioplasty, the management of patients with recurrent restenosis has become a common but difficult clinical problem. Because its efficacy has been well documented, performance of a second angioplasty after the first restenosis has become routine clinical practice (Meier et al, 1984d; Williams et al, 1984). Whether further restenosis should be treated with angioplasty or coronary artery bypass surgery is less certain.

Acute Results

The success and complication rates in this study were encouraging, and did not differ from the rates usually reported for first angioplasties (Dangoisse et al, 1982; Holmes et al, 1984; Bertrand et al, 1986a). Other studies of coronary angioplasty for a second restenosis have reported procedural success rates of 92% to 97%, consistent with the 90% in our study (Abi-Mansour et al, 1985; Joly et al, 1988; Glazier et al, 1989b; Teirstein et al, 1989; Dimas et al, 1992; Bauters et al, 1993). Procedural mortality rates ranging from 0% to 2.7%, myocardial infarction rates ranging from 0 to 2.8%, and emergency bypass surgery rates ranging from 0 to 4.9% have also been reported (Table 5.7). In the present study, the corresponding mortality, myocardial infarction, and emergency bypass surgery rates were 0%, 1.6% and 1.6%, respectively. The favourable results may reflect the highly selected population in these studies, in that these patients have already had 2 previous successful procedures at the target site, or it may be the result of differences in the

physical properties of restenotic lesions compared to primary ones (Bauters et al, 1993).

Long-term Results

Although angioplasty for recurrent restenosis is technically feasible, the procedure must be associated with short- and long-term symptomatic improvement to be judged clinically successful. The efficacy of any revascularisation procedure is defined by the clinical events and the patient's functional status. It was not possible to determine the specific physiologic and prognostic implication of coronary angioplasty of the coronary segment where recurrent restenosis has occurred, since other vessels were also dilated at the same time for complete revascularisation. In addition, the long-term outcome is likely to be influenced by the extent of native coronary artery disease, the extent of left ventricular dysfunction, and the restenosis rate. Furthermore, comparison between studies may be difficult because it is not possible to take account of differences in these baseline and procedural variations. Nevertheless, this study has shown that most patients with recurrent restenosis can be managed safely and effectively with repeat angioplasty.

The long-term results were encouraging with a 5 year survival rate of 95%, and freedom from death and myocardial infarction of 91%. Furthermore, angioplasty was associated with a marked improvement in angina status: prior to angioplasty 76% of patients had severe angina, but at census 53% were asymptomatic and 76% were improved by at least 2 angina grades. Although this favourable long-term outcome was in part contributed to by the need for a subsequent revascularisation procedure in 27% of patients, only 8% needed elective coronary artery bypass surgery. Freedom from death, myocardial infarction, and coronary artery bypass surgery was 83% at 5 years. In addition, the fourth angioplasty for a third restenosis

was performed with an acceptable success rate of 88.9%. Similar favourable long-term results have also been reported by earlier studies (Glazier et al, 1989b; Teirstein et al, 1989).

Incidence And Predictors Of Recurrent Restenosis

The incidence of angiographic restenosis after a third angioplasty for a second restenosis remains high, and was 69% in the present series. However, only 46% of patients returned for coronary angiography, usually for recurrent symptoms. The frequency of restenosis might have been lower had all patients returned for repeat angiography, irrespective of their symptomatic status. The clinical restenosis rate, defined as the recurrence of anginal symptoms or reversible ischaemia associated with angiographic evidence of restenosis, and included late cardiac deaths and myocardial infarctions occurring during follow-up, was 39%. The true angiographic restenosis rate probably lies between 39% and 69%.

Some studies have reported that the restenosis rate after a third angioplasty for a second restenosis, is similar to those reported for a first and second angioplasty procedure (Bauters et al, 1993). Others have suggested that patients with multiple restenoses in the past are more likely than patients without this history to have restenosis in the future (Glazier et al, 1989b; Teirstein et al, 1989; Dimas et al, 1992). The reported incidence of restenosis after a third angioplasty ranges from 24% to 48% (Table 5.7) (Abi-Mansour et al, 1985; Joly et al, 1988; Glazier et al, 1989b; Teirstein et al, 1989; Dimas et al, 1992; Bauters et al, 1993). The discrepancy may be accounted for by the differences in the rate of angiographic follow-up, especially low in patients who were asymptomatic, and by differences in the definition of restenosis.

Although multiple variables have been associated with an increased first restenosis rate, the only variable that was found to be independently predictive of a third clinical restenosis in the present study, was the time interval between the second and the third procedure. The finding that a short time interval between previous restenoses is predictive of future restenoses has been consistently reported by other investigators, although he reason remains unclear. Teirstein et al (1989) have shown that the mean time interval between the second and the third angioplasty procedure was 4.9 months in patients who subsequently developed a third restenosis, and 6.4 months in those who did not. In the present study, the corresponding mean time interval was 4.8 months and 7.7 months, respectively. Dimas et al (1992) have shown that the mean time interval between the first and the second angioplasty procedure was 3.6 months in patients who subsequently developed a second restenosis, and 6.1 months in those who did not. In the study by Quigley et al (1989), the corresponding mean time interval was 4.5 months and 7.1 months, respectively. Black et al (1988) have shown that a time interval of <5 months between the first and the second angioplasty procedure was predictive of a second restenosis. Bauters et al (1993) have shown that a time interval of ≤ 3 months between the second and the third angioplasty procedure was associated with recurrent restenosis. The disparate time intervals between the studies probably reflect differences in the delay between symptom recurrence as a result of restenosis, and admission of patients for a repeat angioplasty.

One possible explanation is that the short time interval between angioplasty reflects the increased tendency of the patient to develop intense smooth muscle cell proliferation. Another possibility is that the short time interval between the successive angioplasty procedures enhances the degree of neointimal hyperplasia in

response to the injury caused by the balloon inflation, resulting in the development of early restenosis (Schneider et al, 1992).

New revascularisation technology, such as stents (de Jaegere et al, 1992a) and atherectomy (Hinohara et al, 1992), are currently under investigation. These new devices for percutaneous coronary recanalisation were introduced in an attempt to reduce the amount of intimal hyperplasia compared with balloon angioplasty, by producing a less reactive luminal surface and providing a larger post treatment lumen diameter. Randomised trials comparing directional atherectomy with balloon angioplasty have not shown any conclusive reduction in the rate of restenosis, or improvement in clinical outcome (Topol et al, 1993; Adelman et al, 1993). Although results from randomised studies of de novo stent implantation using the Palmaz-Schatz device have demonstrated reduction in restenosis rates when compared with balloon angioplasty, the risks associated with stenting are substantial (Serruys et al, 1994; Fischman et al, 1994). The need for intensive anticoagulant therapy requires prolonged hospitalisation, and results in bleeding problems, manifesting as a need for transfusions or major peripheral vascular complications. Furthermore, stent implantation is expensive, and the long-term results are not known. Further results should be awaited before drawing final conclusions on the merits of primary stenting. Until results of more randomised trials are made available, the study presented in this chapter provides useful information in helping clinicians and patients decide on the most appropriate therapeutic course after recurrent restenosis has occurred.

Study Limitations

Although the study population consisted of a consecutive group that underwent coronary angioplasty for a second restenosis, the study is a retrospective analysis of

data and is subject to all the limitations inherent in such a study. The rate of repeat coronary angiography was low (46%) since this was performed only in patients that were symptomatic or had evidence of reversible ischaemia documented using non-invasive investigations. Therefore the exact angiographic restenosis rate cannot be determined.

5.5 SUMMARY AND CONCLUSION

The decision in choosing the mode of revascularisation in patients with recurrent restenosis depends on many factors, including the feasibility and safety of the procedure, the long-term efficacy, and patient or clinician preference. The study presented in this chapter has shown that a third coronary angioplasty for a second restenosis can be performed safely and effectively in selected patients, and provides good symptomatic relief and favourable long-term outcome. This suggests that multiple repeated angioplasty for recurrent restenosis can be accepted as an integral part of the overall coronary angioplasty revascularisation strategy, and provides an attractive alternative to coronary bypass surgery in this group of patients.

However, the incidence of restenosis remains high, although the majority are relieved of symptoms by subsequent angioplasty procedures. A high risk of subsequent clinical restenosis can be predicted from the time interval between the previous procedures hence allowing an alternative mode of revascularisation to be considered in these patients.

Table 5.1. Patient and Angiographic characteristics.

	Number	%
Total	62	100
Male gender	52	84
Mean age (years)	53	SD 9 (range 31-72)
Previous MI	30	48
Angina grade		
0/I	2	3
II	13	21
III	23	37
IV	24	39
Unstable angina	10	16
Abnormal LV (EF<45%)	22	36
Number of diseased vessels		
1	25	40
2	26	42
3	11	18
Previous CABG	12	19
Multivessel PTCA	11	18
Multilesion PTCA	16	26
Dilation site		
LAD	28	45
CX	6	10
RCA	12	19
SVG	5	8
LAD + CX	5	8
LAD + RCA	5	8
LAD + CX + RCA	1	2
Risk factors		
Hypertension	14	23
Diabetes mellitus	6	10
Current smoking	37	60
Hypercholesterolaemia	29	47
Family history of CAD	23	37

CABG=coronary artery bypass surgery; CAD=coronary artery disease; CX=circumflex artery; EF=ejection fraction, LAD=left anterior descending artery; LV=left ventricular function, MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty, RCA=right coronary artery; SD=standard deviation; SVG=saphenous vein graft.

Table 5.2. Primary Success and Complication Rates of all 62 Patients.

	Number	%
Procedural success	56	90.3
Any major complication	2	3.2
Procedural death	0	0
Non-fatal MI	1	1.6
Emergency CABG	1	1.6

Abbreviations as for Table 5.1.

Table 5.3. Total and Event-free Survival 1 and 5 Years After PTCA for all Patients and Patients With an Initially Successful Angioplasty Procedure. Data are % (95% Confidence Interval).

	One year		Five years	
	All patients	Procedural success	All patients	Procedural success
Death; % survival	96.8 (92.3-100)	96.2 (90.9-100)	95.0 (89.4-100)	96.2 (90.9-100)
Death/MI; % freedom	95.2 (89.7-100)	96.2 (90.9-100)	90.9 (82.9-98.9)	93.2 (85.5-100)
Death/MI/CABG; % freedom	93.6 (87.4-99.8)	94.2 (87.7-100)	83.1 (72.6-93.6)	84.0 (72.6-95.4)
Death/MI/CABG/ PTCA; % freedom	82.3 (72.6-92)	86.5 (77.0-96.0)	66.6 (53.7-79.5)	72.1 (58.6-85.6)
CABG; % freedom	98.4 (95.2-100)	98.1 (94.3-100)	92.2 (84.6-99.8)	90.8 (81.9-99.7)
Repeat PTCA; % freedom	87.1 (78.6-95.6)	90.4 (82.2-98.6)	79.8 (69.3-90.3)	83.8 (73.2-94.4)
CABG/repeat PTCA; % freedom	85.8 (76.6-94.4)	88.5 (79.6-97.4)	73.7 (61.8-85.6)	76.8 (64.3-89.3)

Abbreviations as for Table 5.1.

Table 5.4. Patient-related Variables as Predictors of Clinical Restenosis.

Variable	Restenosis rates		p Value
	Number	%	
Age (years)			
≤55	11/28	39	1.00
>55	11/28	39	
Gender			
Male	18/49	37	0.41
Female	4/7	57	
Angina class			
I/II	3/13	23	0.17
III/IV	19/43	44	
Previous MI			
No	11/26	42	0.67
Yes	11/30	37	
Family history			
No	13/36	36	0.51
Yes	9/20	45	
Ever smoked			
No	9/23	39	1.00
Yes	13/33	39	
Diabetes mellitus			
No	20/51	39	1.00
Yes	2/5	40	
Hypertension			
No	15/42	36	0.34
Yes	7/14	50	
Unstable angina			
No	15/46	33	0.03
Yes	7/10	70	
Impaired LV			
No	14/34	41	0.72
Yes	8/22	36	
Hypercholesterolaemia			
No	15/31	48	0.12
Yes	7/25	28	
Multivessel disease			
No	11/20	55	0.07
Yes	11/36	31	
Time interval between second and third PTCA			
≤5 months	17/29	59	0.002
>5 months	5/27	19	

Abbreviations as for Table 5.1.

Table 5.5. Lesion-related Variables as Predictors of Clinical Restenosis.

Variable	Restenosis rates		p Value
	Number	%	
Lesion length			
≤10 millimetre	19/49	39	1.00
> 10 millimetre	3/7	43	
Eccentricity			
No	11/28	39	1.00
Yes	11/28	39	
Angulation			
<45°	18/47	38	0.73
≥45°	4/9	44	
Contour			
Smooth	16/45	36	0.24
Irregular	6/11	55	
Calcified lesion			
No	20/49	41	0.69
Yes	2/7	29	
Ostial			
No	20/51	39	1.00
Yes	2/5	40	
Thrombus			
No	21/55	38	0.39
Yes	1/1	100	
Distal ectasia			
No	20/54	37	0.15
Yes	2/2	100	
PrePTCA % stenosis			
≤83%	13/29	45	0.38
> 83%	9/27	33	
PostPTCA % stenosis			
≤12%	12/31	39	0.92
> 12%	10/25	40	
Vessel diameter			
≤2.76 millimetre	10/29	34	0.45
> 2.76 millimetre	12/27	44	
PostPTCA dissection			
No	11/28	39	1.00
Yes	11/28	39	
Lesion location			
Proximal	14/32	44	0.64
Mid	7/22	32	
Distal	1/2	50	
Vessel dilated			
LAD	14/29	48	0.33
CX	1/8	13	
RCA	5/14	36	
SVG	2/5	40	

Abbreviations as for Table 5.1.

Table 5.6. Procedure-related Variables as Predictors of Clinical Restenosis.

Variable	Restenosis rates		p Value
	Number	%	
No. of inflations			
≤2	9/24	38	0.81
>2	13/32	41	
Maximum inflation pressure (atmosphere)			
≤6	14/31	45	0.32
>6	8/25	32	
Maximum inflation duration (seconds)			
≤60	12/35	34	0.32
>60	10/21	48	
Total inflation duration (seconds)			
≤180	12/35	34	0.32
>180	10/21	48	
Balloon to artery ratio			
≤1.05	12/29	41	0.74
>1.05	10/27	37	

Table 5.7. Other Published Results (Chronological Order).

First author (year)	Patients (number)	Procedural success (%)	Death (%)	MI (%)	CABG (%)	Angiographic restenosis (%)	Follow-up angiography (%)
Abi-Mansour (1985)	17	-	0	-	0	24	-
Joly (1988)	36	92	0	2.8	2.8	37	91
Teirstein (1989)	74	93	2.7	0	4.0	39	53
Glazier (1989)	41	93	2.4	0	4.9	34	-
Dimas (1992)	49	94	0	2.0	0	57	61
Bauters (1993)	99	97	0	0	0	39	86

CABG=emergency coronary artery bypass surgery; MI=myocardial infarction.

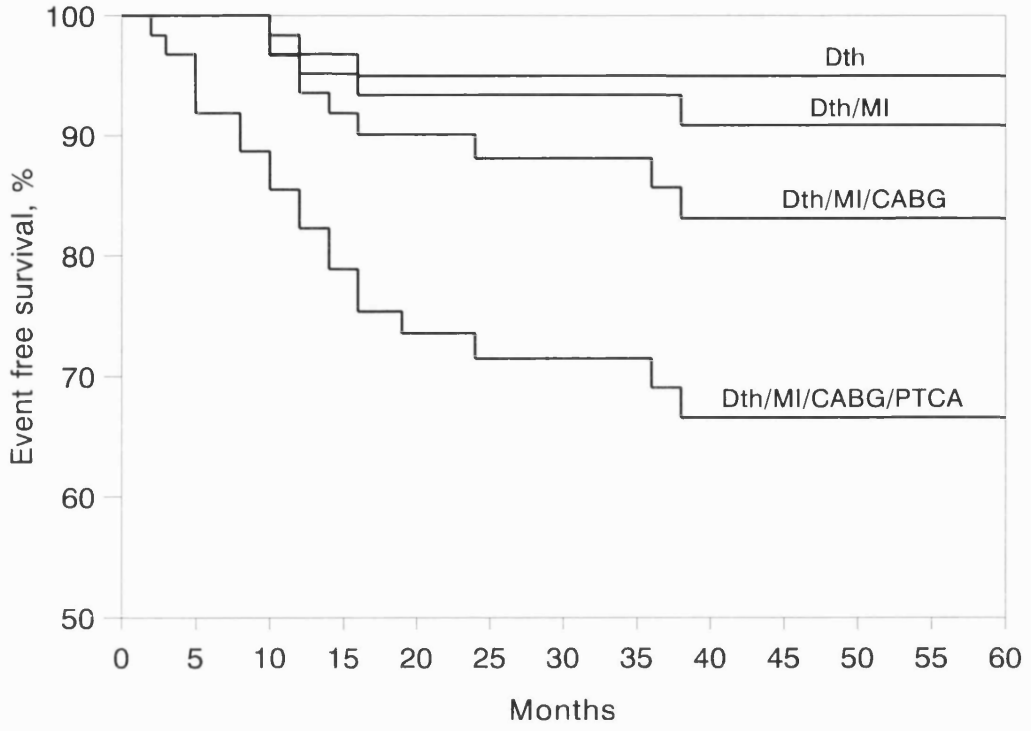


FIGURE 5.1. Plot of cumulative event free survival for all 62 patients. Dth = freedom from death; Dth/MI = freedom from death and myocardial infarction; Dth/MI/CABG = freedom from death, myocardial infarction, and coronary artery bypass grafting; Dth/MI/CABG/PTCA = freedom from death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty.

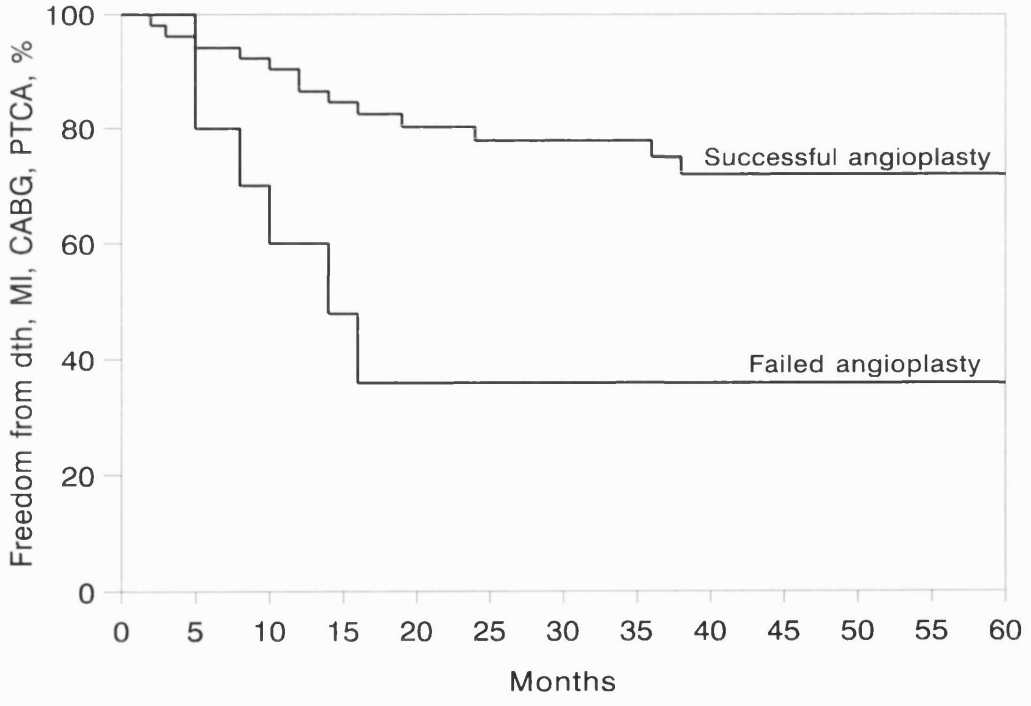


FIGURE 5.2. Plot of percentage of patients free of death (dth), myocardial infarction (MI), coronary artery bypass grafting (CABG), and repeat angioplasty (PTCA) according to the outcome of initial angioplasty (p = 0.07).

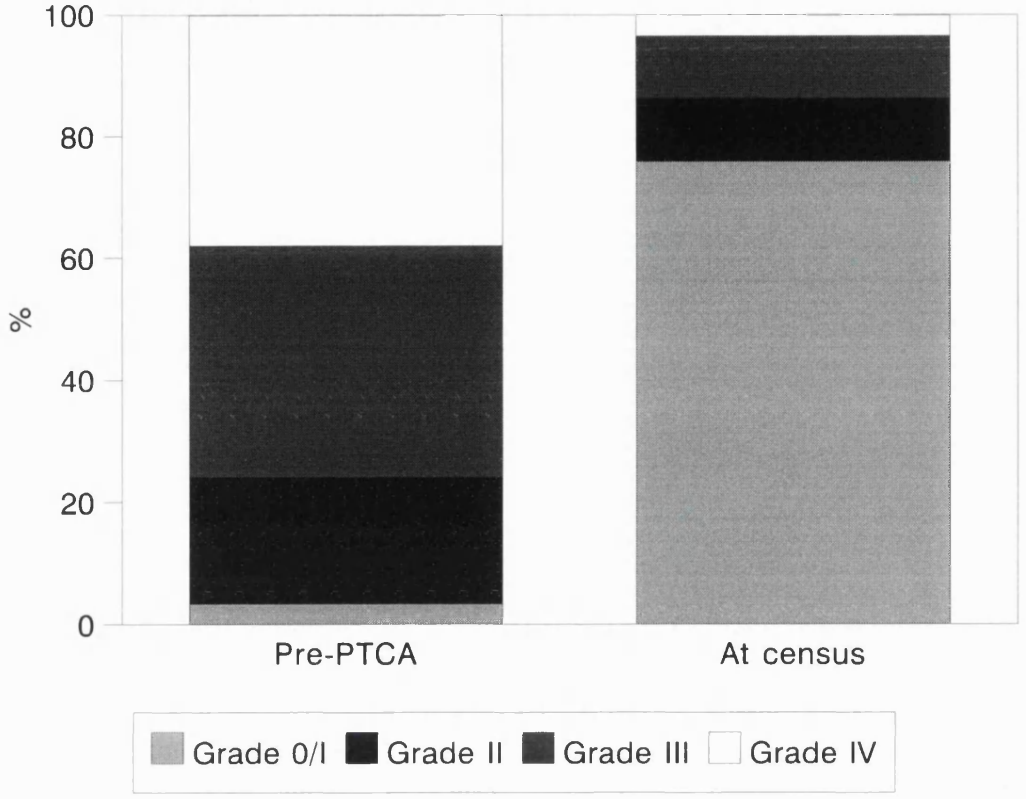


FIGURE 5.3. Angina grade before coronary angioplasty and at census in 58 survivors ($p < 0.001$).

6. *CORONARY ANGIOPLASTY IN PATIENTS WITH PRIOR CORONARY ARTERY BYPASS GRAFTING*

6.1 INTRODUCTION

Since the introduction of saphenous vein coronary artery bypass grafting by Favaloro (1968), these conduits have been widely used in the treatment of ischaemic heart disease. This procedure relieves angina, and in selected patient groups can improve prognosis, although the survival benefit diminishes with time (The Veterans Administrative Coronary Artery Bypass Surgery Cooperative Study Group, 1984; Varnauskas et al, 1988; Alderman et al, 1990). However, symptoms may recur after surgery as a result of incomplete initial revascularisation, progression of coronary atherosclerosis in the native coronary artery, or graft failure. The 3 mechanisms that play a role in graft occlusion are thrombosis, intimal hyperplasia, and atherosclerosis (Israel et al, 1991). Up to 20% of grafts occlude within the first year and there is an annual graft attrition rate of 1-5% thereafter (Kouchoukos et al, 1978; Campeau et al, 1983). With this occlusion rate, only 30% to 40% of saphenous vein grafts are without significant atherosclerotic narrowing 12 years after the surgery (Frey et al, 1984; Fitzgibbon et al, 1991).

There are no comparative longitudinal studies of survival comparing different management options in symptomatic patients with previous bypass surgery. Despite improvements in myocardial protection and increased surgical experience, repeat coronary artery bypass surgery is associated with higher mortality and morbidity, and provides less satisfactory symptom relief than is achieved with the primary operation (Laird-Meeter et al, 1987; Lytle et al, 1987). Earlier reports indicated that in-hospital mortality and morbidity of percutaneous transluminal coronary angioplasty were increased in patients with previous coronary artery bypass surgery (Kent et al, 1982; Aueron et al, 1984; Dorros et al, 1984b). However, this extended use of coronary angioplasty has been applied with encouraging acute results in recent years (Pinkerton et al, 1988; Kolettis et al, 1990), although information

about late outcome is limited. New angioplasty technologies have also recently been introduced as alternatives to balloon angioplasty for saphenous vein graft lesions (Urban et al, 1989; Serruys et al, 1991b; de Scheerder et al, 1992; Kaufmann et al, 1990; Selmon et al, 1991; Untereker et al, 1991) but the long-term results of these methods are uncertain.

The study presented in this chapter reports on the acute and long-term results of coronary angioplasty in patients with prior coronary artery bypass grafting, who were treated over a 10-year period.

6.2 PATIENTS AND METHODS

(a) PATIENTS

Between 1981 and 1991, 140 patients with previous coronary artery bypass surgery underwent a first coronary angioplasty procedure. The majority had recurrence of angina refractory to medical therapy, and for which a second revascularisation was considered necessary. In all cases, coronary angiography demonstrated at least 1 native coronary or graft stenosis considered suitable for coronary angioplasty.

The mean age was 58 years (SD 8, range 41 to 80 years) and 132 were male (94%) (Table 6.1). Eighty-seven patients (62%) had a history of previous myocardial infarction, and 69 patients (49%) had impaired left ventricular function. Coronary angioplasty was performed as an emergency procedure for unstable angina in 6 patients (4.3%). Before intervention, 114 patients (81%) suffered grade III/IV angina. The majority of patients had triple vessel disease (86%) and 16% had undergone multiple previous coronary artery bypass grafting, with an average of 2.8 grafts per patient. The most recent bypass operation and the coronary angioplasty procedure were separated by a median of 50 months (range from 1 day to 168 months) (Figure 6.1). At the time of coronary angioplasty, the mean number of patent grafts was 1.6 per patient. Significant proximal third left anterior descending artery disease was present in 112 patients (80%). Risk factors that were present in the patients included smoking (49%), diabetes mellitus (6%), hypertension (18%), and hypercholesterolaemia (36%).

Coronary angioplasty was attempted in 136 native coronary arteries (of which 14 were totally occluded) and in 50 saphenous vein grafts (Table 6.2). Of the

saphenous grafts attempted, the left anterior descending artery was the insertion site for 22 grafts (44%), the right coronary artery for 14 grafts (28%), the circumflex for 13 grafts (26%) and the diagonal for 1 graft (2%). The graft stenoses were at the proximal anastomotic site in 8 patients (16%), at the distal anastomotic site in 23 (46%), and at the graft body in 19 (38%) (Figures 6.2 to 6.4). One-hundred and four patients (74%) had single vessel coronary angioplasty and 36 (26%) underwent multivessel coronary angioplasty.

(b) ANGIOPLASTY PROCEDURE

Coronary angioplasty was performed according to the protocol described in Chapter 2. Although surgical standby is routinely available during angioplasty procedures, emergency surgery was not considered an option for most patients in this series because of the difficulties in gaining rapid access to ischaemic myocardium in patients with previous median sternotomy.

(c) STUDY METHODS

The baseline clinical, procedural, and angiographic data on all 140 patients were assessed. Complete follow-up data were available on all 140 patients on or after the census date. Clinical status, employment status, medication and the occurrence of new cardiac events were recorded up to January 31st, 1991.

Angiographic success was defined as ≤50% residual diameter stenosis at the dilated sites. Procedural success occurred when a patient had angiographic success in at least 1 vessel without any major in-hospital complication (defined as the occurrence of death, myocardial infarction, or emergency coronary artery bypass grafting).

Angiographic restenosis was defined as a recurrence of a >50% diameter stenosis at a previously successfully dilated site.

(d) STATISTICAL METHODS

Continuous variables are expressed as mean (SD). Survival functions were estimated using the Kaplan-Meier method. Comparison of success rate, restenosis rate, and angina grade were performed using the chi-square test.

6.3 RESULTS

(a) ACUTE RESULTS

Angiographic success was achieved in 153 vessels (82%) (Table 6.2). The angiographic success rate was 85% for non-occluded native vessels, 43% for occluded native vessels, and 86% for bypass grafts (96% for distal anastomotic stenoses, 90% for graft body stenoses and 50% for proximal anastomotic stenoses). Angiographic success rates improved with time (Table 6.3): in the first 70 cases, the angiographic success rate was 75% for non-occluded native vessels and 85% for bypass grafts. In the second 70 cases, the angiographic success rate was 93% for non-occluded native vessels and 87% for bypass grafts. The angiographic success rate for all vessels improved from 75% to 89% ($p=0.009$).

Overall, procedural success occurred in 115 patients (82%) (77% in the first 70, 87% in the second 70). Twenty patients (14%) had an unsuccessful but uncomplicated angioplasty. A significant complication occurred in 5 patients (3.6%). Two patients (1.4%) had a non-fatal Q-wave myocardial infarction, and there were 4 in-hospital deaths, of which 3 (2.1%) were procedure-related (Table 6.4). All 3 patients presented with unstable angina and had severe coronary artery disease with impaired left ventricular function. They were refused repeat bypass grafting because of a high surgical risk or for technical reasons, and coronary angioplasty was performed with increased risk involving either an unprotected left main stem or the last remaining patent vessel (Table 6.5). Although 64% of the saphenous vein grafts had been in place for more than 3 years, distal embolisation of bypass graft atheroma was not observed.

(b) LONG-TERM RESULTS

The median duration of follow-up was 24.5 months ranging up to 108 months. During the study period 23 patients (16%) died, 11 (8%) had non-fatal myocardial infarction, and 21 (15%) underwent elective repeat coronary artery bypass grafting. A second coronary angioplasty procedure was performed in 31 patients (22%) with procedural success achieved in 27 patients. A third angioplasty was successful in 6 patients and 2 had a successful fourth procedure. The 20 late deaths included 4 non-cardiac deaths (malignant melanoma, carcinoma of the colon, acute leukaemia and cerebral vascular accident) and 16 cardiac deaths due to sudden death (3), fatal myocardial infarction (6), heart failure (3), additional revascularisation procedures (3), and heart transplant operation (1).

The cumulative probability of survival for all 140 patients was 91.5% (SE 2.6%) and 74.5% (SE 7.5%) at 1 and 5 years, respectively (Table 6.6, Figure 6.5). Patients with an initially successful angioplasty procedure had cumulative 1 and 5 year survival rates of 95% (SE 2.3%) and 77.5% (SE 8.2%), respectively (Figure 6.5). The 1 and 5 year rates for freedom from cardiac death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty was 65.1% (SE 4.5) and 38.2% (SE 7.5), respectively. The 1 and 5 year cumulative event-free survival rates are shown in Table 6.6 for all patients and patients with an initially successful angioplasty procedure (Figures 6.6 and 6.7).

At census, of the 117 survivors, 36 (31%) were asymptomatic, 42 (36%) had mild (grade I or II) angina, and only 39 (33%) complained of severe (grade III or IV) angina (Figure 6.8). Fifty-five patients (47%) had improved by at least 2 angina grades. Forty-six patients remained in gainful employment, 49 patients were

unemployed or had retired early due to coronary disease, and the remainder had retired or were not working for other reasons.

(c) RESTENOSIS

Repeat coronary angiography was performed in 44 of the 115 patients (38%) who had initially successful procedures for recurrence of symptoms or evidence of reversible ischaemia documented on symptom limited treadmill exercise tests. Of the 43 patients who had a successful saphenous vein graft coronary angioplasty, 28 (65%) underwent repeat coronary angiography after a mean of 9.5 months (SD=8.7). Continued success was present in 17 patients (61%) and angiographic restenosis was present in 11 patients (39%). Twelve patients had evidence of new disease (9 in the native vessels and 3 in the grafts). Restenosis was highest for proximal anastomotic lesions (5/6=83%) followed by shaft lesions (4/10=40%) and distal anastomotic lesions (2/12=17%) (p=0.02).

6.4 DISCUSSION

Recurrence of symptoms after coronary artery bypass grafting is reported in 5% to 10% of patients annually (Seides et al, 1978; Guthaner et al, 1979; Campeau et al, 1983), and an estimated 10% to 15% of patients require a second revascularisation procedure after 10 years (Laird-Meeter et al, 1987; Lytle et al, 1987; Cameron et al, 1988). Re-operation exposes these patients to an operative mortality up to 4-fold (Laird-Meeter et al, 1987; Lytle et al, 1987; Cameron et al, 1988) and a peri-operative infarction rate up to 10-fold that of the primary procedure (Lytle et al, 1987). These results reflect both increased technical difficulty with re-operation and less favourable patient characteristics (ie older, more extensive coronary disease, poorer left ventricular function).

In recent years, symptomatic patients with prior bypass surgery have been increasingly considered for coronary angioplasty. However, coronary angioplasty in these patients may also carry an increased risk because, in the event of acute vessel closure, emergency coronary bypass operation is technically difficult due to chest wall and pleuro-pericardial adhesions. Despite these considerations, recent reports on coronary angioplasty in patients with prior bypass surgery have been encouraging (Kolettis et al, 1990; Webb et al, 1990, Meester et al, 1991).

Acute Results

The success and complication rates reported in this study are comparable with previous studies. The improved success rate attained in the most recent 70 patients may be attributed to improved case selection, angioplasty technique and operator experience, and equipment evolution. These developments occurred in parallel and the improved success rate cannot be attributed to any single variable.

Other studies of saphenous vein graft angioplasty have reported angiographic success rates of 75% to 97% (Table 6.7), consistent with the 86% in our study. The highest success rate was seen with stenoses located at the distal anastomotic site (96%), followed by stenoses located in the graft body (90%) and proximal anastomotic site (50%). Webb et al (1990) reported angiographic success rates of 89%, 86% and 80%, and Cooper et al (1989) reported success rates of 92%, 67%, and 56%, for stenoses located at the distal, mid, and proximal sites, respectively. The lower success rates achieved for proximal stenoses may be related to the thick elastic aortic wall, or to the technical difficulties in obtaining guiding catheter engagement and support, in the presence of a lesion located at or near the graft ostium.

Other published results have reported procedural mortality rates ranging from 0% to 5.3%, myocardial infarction rates ranging from 0% to 8.3% and emergency bypass surgery rates ranging from 0% to 4.3% (Table 6.7). In the present study, the corresponding mortality, myocardial infarction and emergency bypass surgery rates were 2.1%, 1.4% and 0%, respectively. Some studies suggest that distal embolisation commonly occurs during dilation of old grafts, which may contain friable thrombotic debris susceptible to disruption and dispersion (Douglas et al, 1983; Aueron et al, 1984; Cote et al, 1987). In the present study cohort, 64% of the vein grafts dilated were over 3 years old, and no distal embolisation of atheroma was observed during angioplasty. This probably reflects careful patient selection, in particular, avoiding grafts with diffuse lesions and a large plaque volume (Liu et al, 1993).

Although there were 3 procedure-related deaths, those patients presented with unstable angina, and had been refused repeat bypass grafting by the cardiothoracic

surgeons. Coronary angioplasty was performed with increased risk, and involved either an unprotected left main stem or the remaining patent vessel perfusing markedly impaired myocardium (Table 6.5). Although unprotected left main stem coronary artery lesions are a contraindication to coronary angioplasty, if protected by a patent bypass graft, they can be dilated with a good success rate (Stertzer et al, 1985; O'Keefe et al, 1989b). In the present study, 11 patients had dilatation of a left main stem stenosis. In 10 patients, left main coronary artery dilatation was protected by a patent bypass graft, and these patients underwent successful angioplasty with no complications.

Long-term Results

The long-term outcome of coronary angioplasty in patients with prior bypass grafting is likely to be influenced by the extent of native coronary artery disease, the completeness of revascularisation, the extent of left ventricular dysfunction, and the restenosis rate. It was not possible to determine the specific physiologic and prognostic implication of coronary angioplasty of saphenous vein grafts, since native vessels were also dilated at the same time for complete revascularisation. Furthermore, comparison between studies may be difficult because it is not possible to take account of differences in these baseline and procedural variations. Nevertheless, the long-term results in the present study are comparable with previous reports.

Plokker et al (1991) reported on the Dutch experience of coronary angioplasty of saphenous vein grafts in 454 patients. The 5 year survival for the entire study cohort was 74%, freedom from death and infarction was 58%, and freedom from death, infarction and repeat bypass surgery was 34%. Douglas et al (1991) reviewed 599 patients who underwent saphenous vein graft angioplasty and reported 5 year

survival of 81% and freedom from death, infarction, and repeat revascularisation of 31%. Webb et al (1990) reported follow-up of 351 patients who underwent successful angioplasty after prior bypass grafting. The 5 year survival rate amongst these patients was 89%, freedom from death and myocardial infarction was 83%, and freedom from death, infarction and repeat bypass surgery was 71% at 5 years. However, only 37% of these patients had 3 vessel disease, compared with 86% in the present study, which might explain their more favourable long-term outcome. Meester et al (1991) reported on 84 patients who underwent coronary angioplasty of a saphenous vein bypass graft with or without native vessel angioplasty. The cumulative probability of survival was 70% at 5 years and the survival without infarction and repeat revascularisation after a median follow-up of 2.1 years was 41%. In the present study, the 5 year survival rates were 74.5% and 77.5% for the entire cohort and for those with clinically successful procedures, respectively. At 5 years, 71.8% of patients in the present study were alive and free from infarction and 53.9% were alive, free from infarction, and continued to be managed without repeat bypass surgery. Furthermore, angioplasty was associated with a marked improvement in angina status: prior to angioplasty 81% of patients had severe angina, but at census 31% were asymptomatic and 47% were improved by at least 2 angina grades (Figure 6.8). In keeping with previous reports on repeat bypass surgery (Laird-Meeter et al, 1987; Lytle et al 1987), symptomatic relief was achieved in a relatively smaller proportion of patients but this was often sufficient to avoid repeat surgery with its associated mortality and morbidity.

Restenosis

The precise incidence of restenosis after vein graft angioplasty is unknown secondary to the relatively small number of patients reported, incomplete angiographic follow-up, the varying definitions used, and the different intervals

between angioplasty and follow-up angiography. The reported restenosis rates vary from 33% to 73% of patients undergoing angiographic follow-up (Douglas et al, 1983; Block et al, 1984; Marquis et al, 1985; Corbelli et al, 1985; Reeder et al, 1986; Platko et al, 1989) (Table 6.8). The present study has shown that the location of the lesion within the vein graft may be an important determinant of restenosis after coronary angioplasty. The finding that the recurrence rate is highest in lesions located at the proximal anastomotic site and lowest at the distal anastomosis has also been confirmed by other studies (Block et al, 1984; Ernst et al, 1987b; Webb et al, 1990; Reeves et al, 1991; Douglas et al, 1991). This may reflect the different histological composition of the lesions in each site, which influence the mechanism of dilatation and the tendency to restenosis. The proximal anastomotic stenosis involves the thick elastic wall of the thoracic aorta. Distal graft anastomotic lesions may be associated with plaque in the recipient coronary artery or fibrous intimal hyperplasia, while the graft body lesions are often composed of friable atherosclerotic plaque (Culliford et al, 1979).

To date, no randomised trial of coronary angioplasty versus repeat operation in patients with prior coronary artery bypass surgery has been reported. Direct comparison between studies may be misleading since patient characteristics may differ considerably. Nevertheless, surgical centres have reported peri-operative mortality rates of 3.4–12.5%, myocardial infarction rates of 2–11.5%, and 5 year survival rates ranging from 75% to 85% after a second coronary bypass operation. In addition, under half of the patients undergoing reoperation remain asymptomatic long-term (Laird-Meeter et al, 1987; Lytle et al, 1987; Cameron et al, 1988; Culliford et al, 1979). The present study provides further evidence that coronary angioplasty in patients with prior bypass grafting can be performed with an acute mortality and morbidity comparable to those of repeat coronary artery bypass

surgery, and provides similar long-term therapeutic benefits. Judicious patient selection is important and in particular, the consequence of acute vessel closure should be considered given the limitations of emergency surgery to salvage myocardium in these patients.

6.6 SUMMARY AND CONCLUSIONS

Coronary angioplasty can be performed safely and effectively in patients with symptom recurrence after coronary artery bypass grafting, and provides good symptomatic relief and favourable long-term outcome. Angioplasty success is highest and restenosis rates are lowest with lesions at the distal anastomosis. This procedure, when feasible, provides an attractive alternative to reoperation. In an attempt to overcome the major limitations of saphenous vein graft angioplasty (ie distal embolisation, restenosis), new revascularisation technology, such as stents (Urban et al, 1989; Serruys et al, 1991b; de Scheerder et al, 1992), atherectomy (Kaufmann et al, 1990; Selmon et al, 1991) and laser angioplasty (Untereker et al, 1991) has been introduced. These new devices are currently under investigation and results of randomised trials are eagerly awaited.

Table 6.1: Patient and Angiographic Characteristics.

	Number	%
Total	140	100
Male gender	132	94
Mean age (years)	58	SD 8 (range 41-80)
Previous MI	87	62
Angina grade		
0	3	2
I	4	3
II	19	14
III	64	46
IV	50	36
Abnormal LV (EF<45%)	69	49
Femoral approach	129	92
Number of diseased vessel		
1	1	1
2	18	13
3	121	87
Proximal LAD disease	112	80
Previous CABG		
1	117	84
2	21	15
3	2	1
No. of saphenous grafts inserted	394	
No. of patent grafts	224	
0	9	6
1	51	36
2	64	46
≥3	16	11
Single vessel PTCA	104	74
Multivessel PTCA	36	26

CABG=coronary artery bypass surgery, EF=ejection fraction, LAD=left anterior descending artery, LV=left ventricular function, MI=myocardial infarction, PTCA=percutaneous transluminal coronary angioplasty, SD=standard deviation.

Table 6.2: Primary Angiographic Success of Saphenous Vein Grafts and Native Vessels

	Number	Success	%
Native Vessels, non-occluded	122	104	85
Native Vessels, occluded	14	6	43
LMS	11	10	91
LAD	34	26	76
RCA	35	26	76
CX	53	45	85
DIAG	3	3	100
Saphenous Vein Grafts	50	43	86
Proximal anastomotic site	8	4	50
Body	19	17	90
Distal anastomotic site	23	22	96
All vessels	186	153	82

CX=circumflex artery; DIAG=diagonal artery; LAD=left anterior descending artery; LMS=left main stem; RCA=right coronary artery.

Table 6.3: Primary Angiographic Success in First 70 and Second 70 Patients.

	First 70 patients			Second 70 patients		
	Number	Success	%	Number	Success	%
Native Vessels, non-occluded	52	39	75	70	65	93
Native Vessels, occluded	7	2	29	7	4	57
Saphenous Vein Grafts	27	23	85	23	20	87
Total	86	64	75	100	89	89

Table 6.4: Primary Success and Complication Rates of all 140 Patients.

	Number	%
Procedural success	115	82
Any major complication	5	3.6
Procedural deaths	3	2.1
Non-fatal Q-wave MI	2	1.4
Emergency CABG	0	0

Abbreviations as for Table 6.1.

Table 6.5: Clinical Details of the 3 Procedural Deaths.

Age (years)	Previous operation	Angina grade	Ejection fraction	Comments	Vessel status	Vessel attempted	Outcome
57	Tetralogy of Fallots correction X 3, CABG X 1	unstable	30%	During previous CABG, LCA not identified due to adhesions	LMS stenosis, occluded RCA, patent RCA graft	LMS	Acute occlusion during procedure, reopened, but death 6 hours later.
58	CABG X 2	unstable	20%	Repeat CABG due to poor LV function.	Only patent native vessel was CX with 90% stenosis. No patent grafts.	CX	Primary angiographic success. Patient died 12 hours later from VF.
72	CABG X 1	4	25%	Distal vessels too small for repeat CABG	Only patent native vessel was LAD with 90% stenosis. No patent grafts.	LAD	Acute occlusion with death occurring during procedure.

LCA=left coronary artery; VF=ventricular fibrillation; Other abbreviations as for Table 6.1 and Table 6.2.

Table 6.6. Total and Event-free Survival 1 and 5 Years After PTCA for all Patients and Patients With an Initially Successful Angioplasty Procedure. Data are % (95% Confidence Interval).

	One year		Five years	
	All patients	Procedural success	All patients	Procedural success
Death; % survival	91.5 (86.3-96.7)	95.0 (90.4-99.6)	74.5 (59.5-89.5)	77.5 (61.1-93.9)
CD; % survival	91.5 (86.3-96.7)	95.0 (90.4-99.6)	77.8 (63.2-92.4)	77.5 (61.1-93.9)
CD/MI; % freedom	88.5 (82.5-94.5)	93.0 (87.6-98.4)	71.8 (58.6-85.0)	73.5 (58.9-88.1)
CD/MI/CABG; % freedom	77.3 (69.3-85.3)	85.7 (78.3-93.1)	53.9 (38.3-69.5)	57.1 (40.3-73.9)
CD/MI/CABG/ PTCA; % freedom	65.1 (56.1-74.1)	70.7 (61.1-80.3)	38.2 (23.2-53.2)	42.8 (26-59.6)
Repeat PTCA; % freedom	82.8 (75.4-90.2)	79.6 (71.0-88.2)	70.5 (57.9-83.1)	65.8 (46.0-85.6)
CABG; % freedom	87.6 (81.0-94.2)	92.5 (86.7-98.3)	78.6 (64.0-93.2)	77.6 (60.2-95.0)
CABG/ repeat PTCA; % freedom	73.2 (64.6-81.8)	75.3 (66.1-84.5)	55.4 (38.4-72.4)	55.5 (34.9-76.1)

CD=cardiac death; other abbreviations as for Table 1.

Table 6.7. Acute Results of Coronary Angioplasty in Patients With Prior Coronary Artery Bypass Grafting: Other Published Studies (Chronological Order).

First author (year)	Patients (number)	NV		SVG		Cardiac event (%)	Death (%)	MI (%)	CABG (%)
		n	Succ (%)	n	Succ (%)				
Ford (1980)	18	7	86	11	45	5.5	0	0	5.5
Douglas (1983)	116	59	83	62	94	2.6	0	0.9	2.6
El Gammal (1984)	31	-	-	44	93	6.5	0	6.5	0
Block (1984)	40	-	-	40	78	2.5	0	0	2.5
Dorros (1984b)	61	72	75	33	79	8.2	3.3	4.9	1.6
Marquis (1985)	18	-	-	24	79	0	0	0	0
Corbelli (1985)	94	68	88	47	92	6.4	1.1	3.2	4.3
Reeder (1986)	19	-	-	19	84	10.6	5.3	5.3	0
Cote (1987)	82	-	-	101	85	3.6	0	3.6	1.2
Ernst (1987b)	83	59	86	33	97	1.2	0	1.2	0
Dorros (1988)	76	81	88	53	83	5	2.6	1.3	1.3
Pinkerton (1988)	236	300	93	100	93	3.4	0.4	3.0	3.0
Reed (1989)	55	75	87	54	91	1.8	0	0	1.8
Cooper (1989)	59	117	78	24	75	6.8	1.7	5.1	0
Platko (1989)	101	-	-	117	92	4.0	2.0	2.0	2.0
Webb (1990)	422	397	84	168	85	4.7	0.2	3.1	2.4
Kolettis (1990)	47	41	90	23	90	0	0	0	0
Meester (1991)	84	40	93	93	84	13.1	1.2	8.3	2.4
Douglas (1991)	599	-	-	672	90	7.0	1.2	2.3	3.5
Plokker (1991)	454	-	-	-	90*	4.8	0.7	2.8	1.3
Reeves (1991)	57	-	-	64	95	7.0	1.7	3.5	1.7

Cardiac event=any major cardiac event including death, myocardial infarction or emergency coronary artery bypass grafting; CABG=emergency coronary artery bypass grafting; MI=Q-wave myocardial infarction; n=number of stenoses; NV=native vessel; SVG=saphenous vein graft, Succ=angiographic success; *=clinical success.

Table 6.8. Restenosis Rates After Coronary Angioplasty of Saphenous Vein Grafts: Other Published Studies (Chronological Order).

First author (year)	Patients (number)	Angiographic follow-up (%)	Restenosis rate (%)
Douglas (1983)	62	34/58 (59)	13/34 (38)
Block (1984)	40	22/31 (71)	12/22 (55)
Marquis (1985)	18	12/14 (86)	7/12 (58)
Corbelli (1985)	35	18/31 (58)	6/18 (33)
Reeder (1986)	19	11/16 (69)	8/11 (73)
Platko (1989)	101	49/90 (54)	30/49 (61)
Present (1991) study	50	28/43 (65)	11/28 (39)

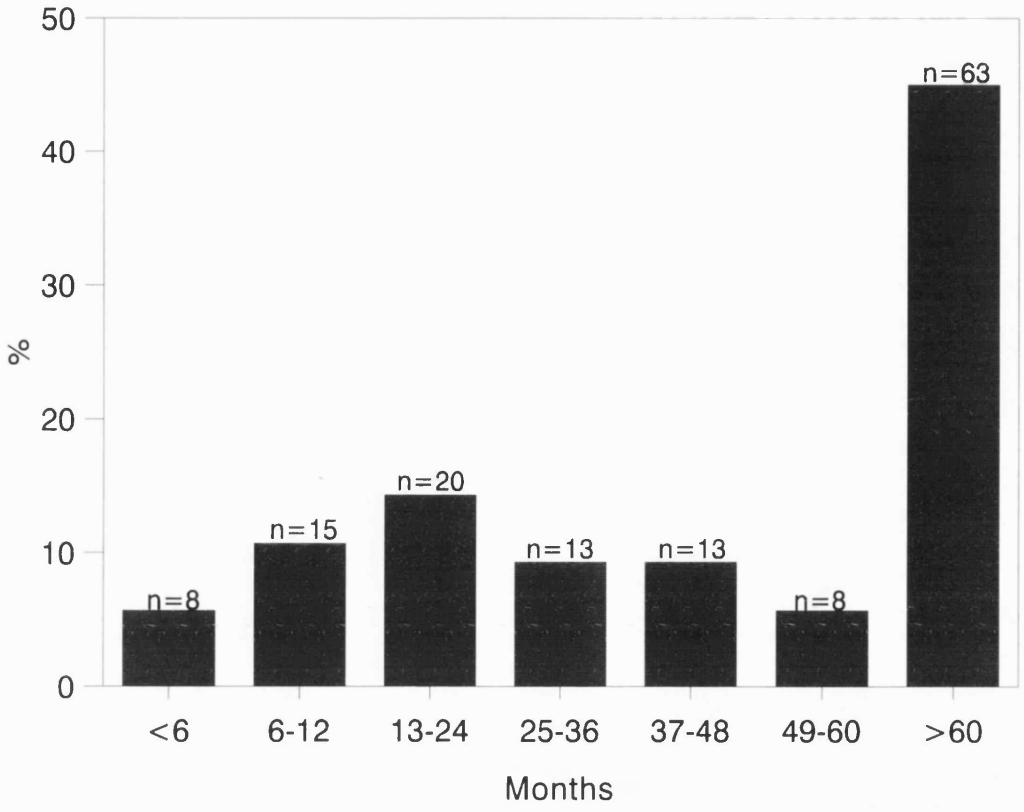


FIGURE 6.1. Interval between coronary artery bypass surgery and percutaneous transluminal coronary angioplasty.

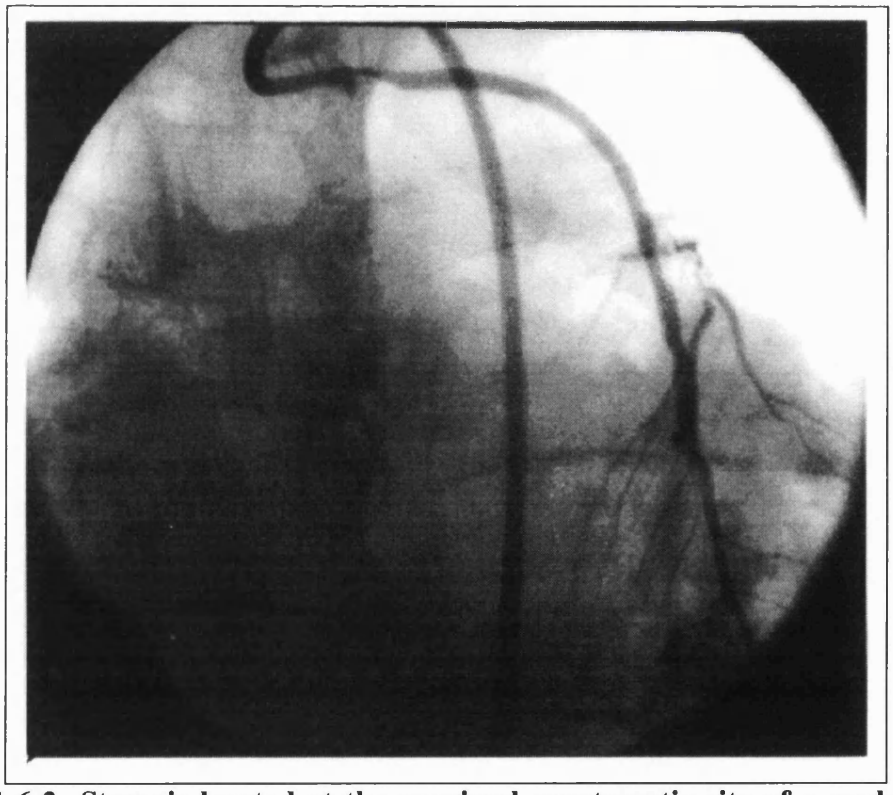


FIGURE 6.2. Stenosis located at the proximal anastomotic site of a saphenous vein graft.

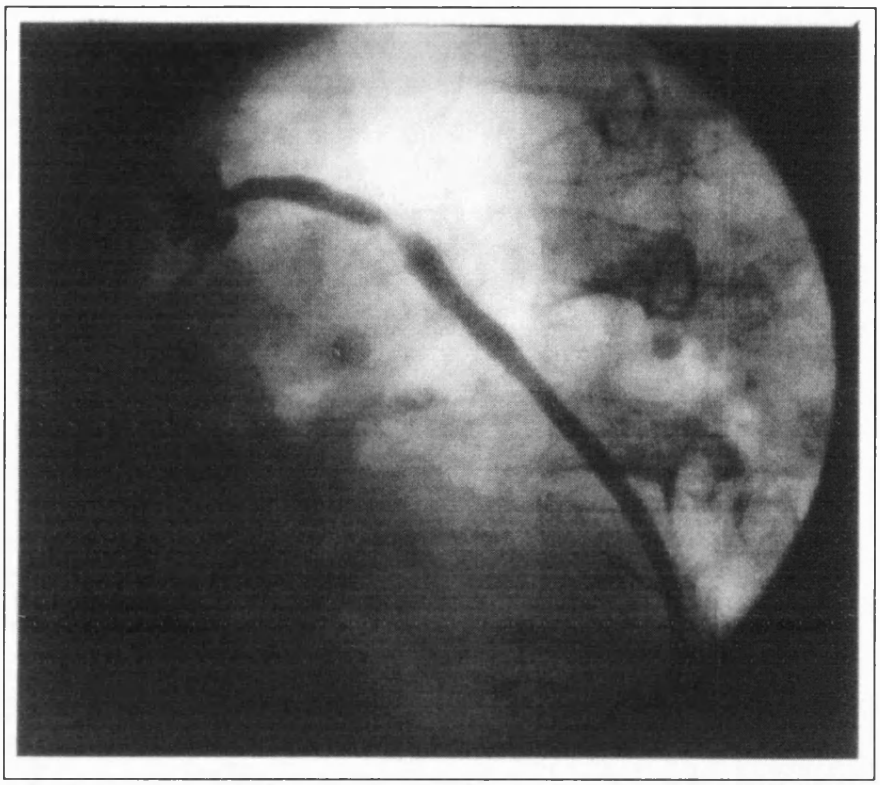


FIGURE 6.3. Stenosis located at the body of a saphenous vein graft.

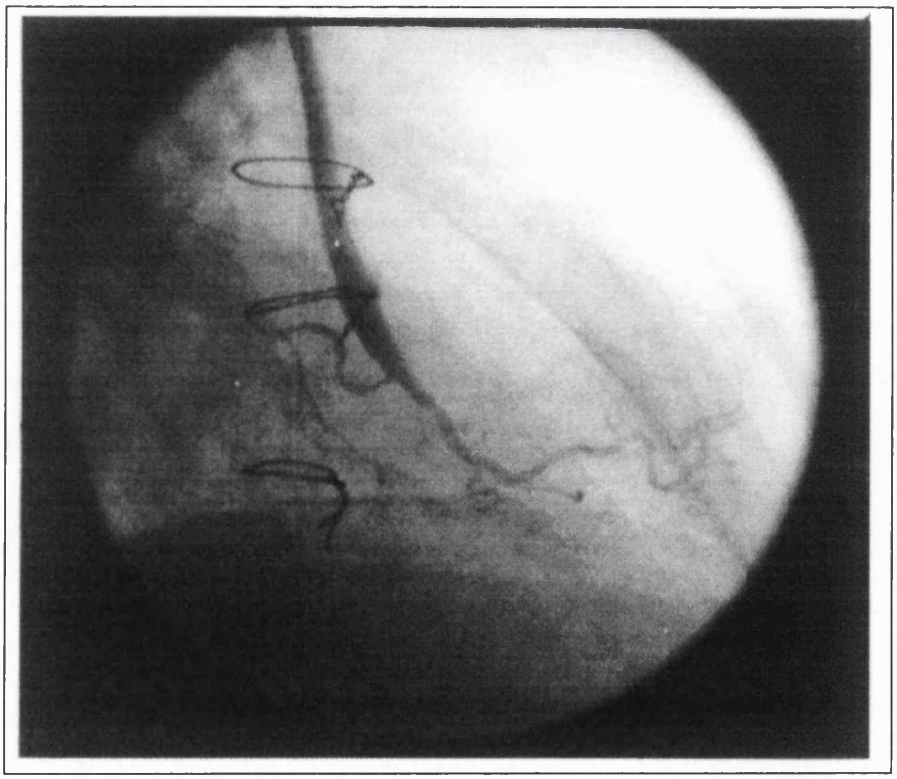


FIGURE 6.4. Stenosis located at the distal anastomotic site of a saphenous vein graft.

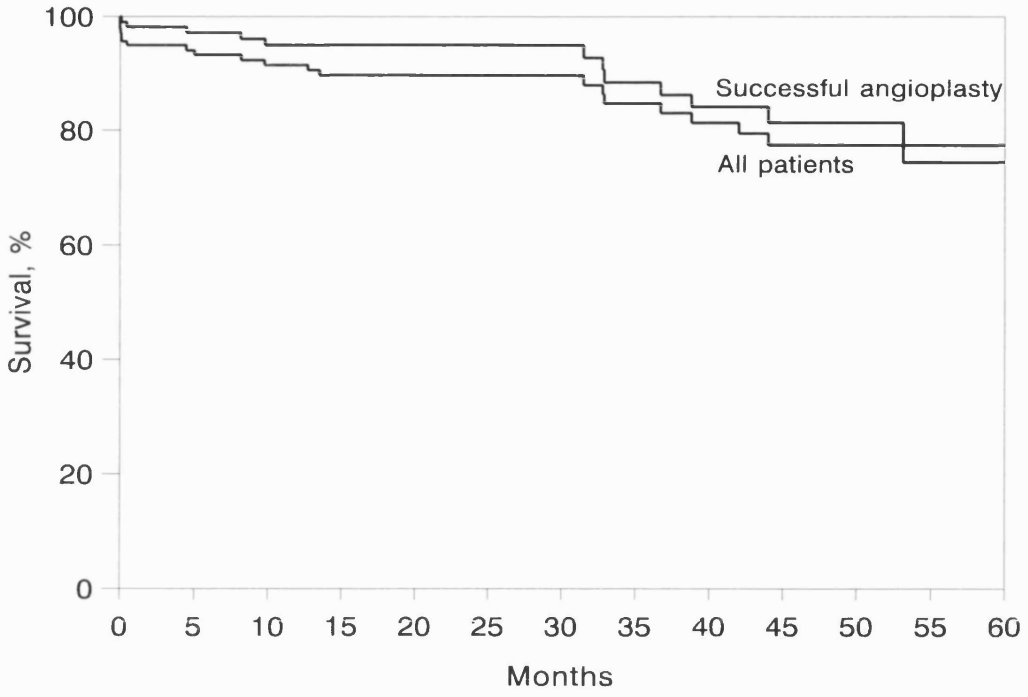


FIGURE 6.5. Plot of cumulative survival for all patients and patients with an initially successful angioplasty procedure.

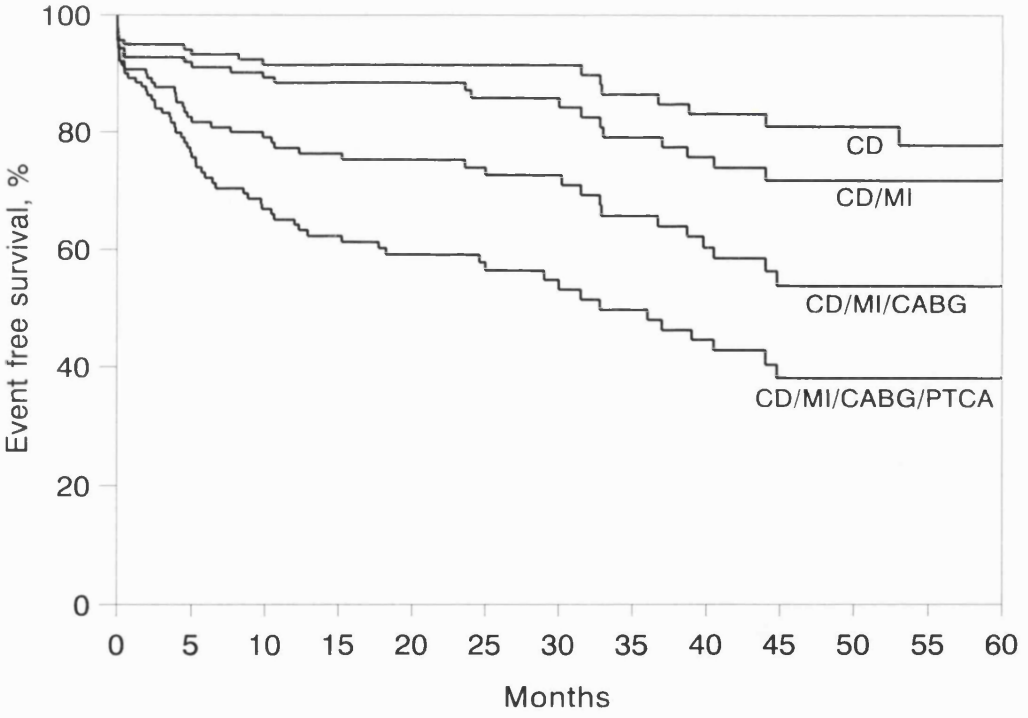


FIGURE 6.6. Plot of cumulative event free survival for all 140 patients. CD=freedom from cardiac death; CD/MI=freedom from cardiac death and myocardial infarction; CD/MI/CABG=freedom from cardiac death, myocardial infarction, and coronary artery bypass grafting; CD/MI/CABG/PTCA=freedom from cardiac death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty.

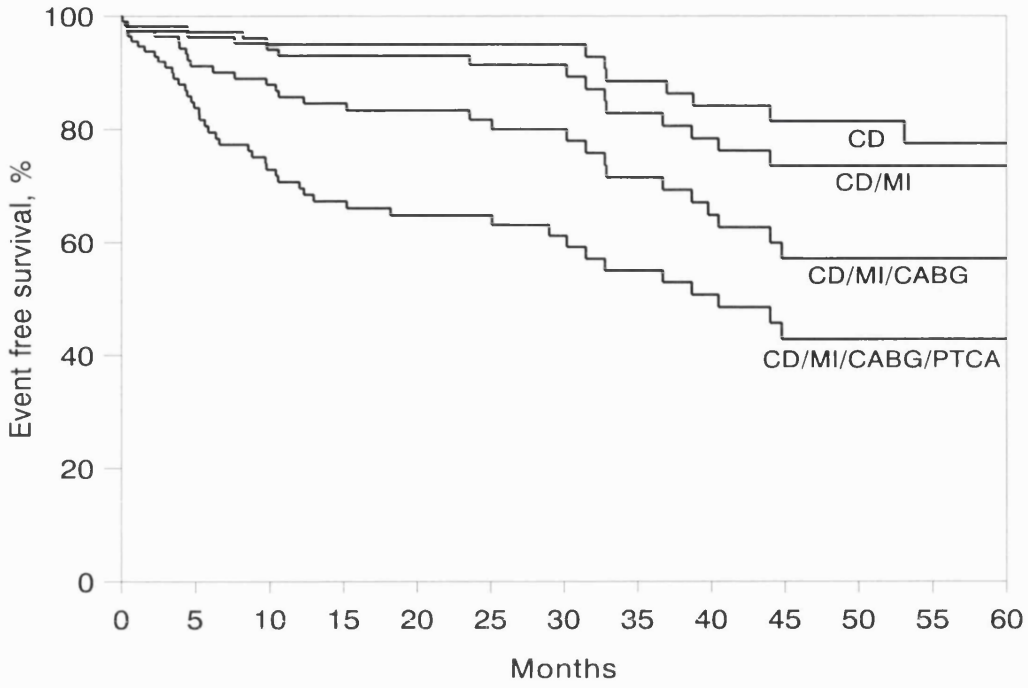


FIGURE 6.7. Plot of cumulative event free survival for patients with an initially successful angioplasty procedure. CD = freedom from cardiac death; CD/MI = freedom from cardiac death and myocardial infarction; CD/MI/CABG = freedom from cardiac death, myocardial infarction, and coronary artery bypass grafting; CD/MI/CABG/PTCA = freedom from cardiac death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty.

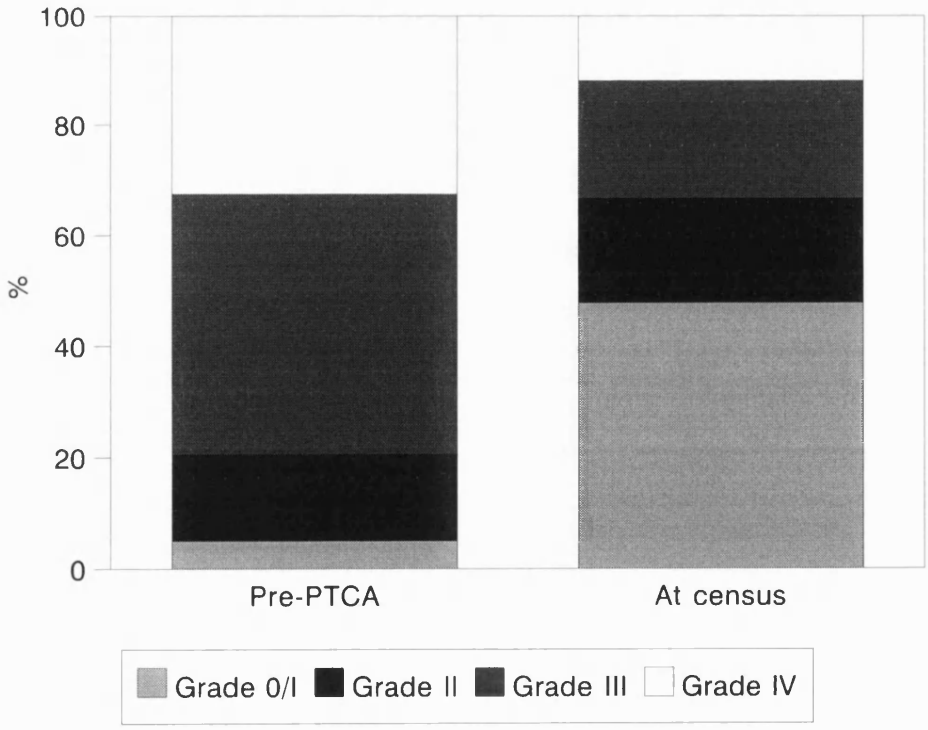


FIGURE 6.8. Angina grade before coronary angioplasty and at census in 117 survivors ($p < 0.001$).

7. *CORONARY ANGIOPLASTY IN PATIENTS AGED SEVENTY YEARS OF AGE OR OLDER*

7.1 INTRODUCTION

Since the proportion of elderly patients suffering from symptomatic coronary artery disease is increasing (Moritz and Ostfeld, 1990), the efficacy of the various treatment modalities needs to be constantly evaluated in this patient group. Although elderly patients have more extensive atherosclerotic coronary artery disease, most clinicians have adopted a conservative approach towards their management, usually with medications and modification of their activities. This is, in part, attributed to the increased peri-operative morbidity and mortality, longer duration of hospitalisation, and less favourable long-term outcome reported in most coronary surgery studies in patients with advanced age compared to younger patients with comparable disease (Hochberg et al, 1982; Gersh et al, 1983a; Gersh et al, 1983b; Elayda et al, 1984; Horneffer et al, 1987; Loop et al, 1988; Grondin et al, 1989). However, medical therapy is often ineffective and poorly tolerated in the elderly, and side effects are common (Nolan and O'Malley, 1988). The incidence of adverse drug reactions in elderly patients may be at least twice that observed in younger patients (Vestal, 1978). Furthermore, the limitation of physical activity imposed on these patients in order to provide symptomatic relief often becomes intolerable.

Percutaneous transluminal coronary balloon angioplasty, by virtue of being less invasive, offers an attractive alternative mode of myocardial revascularisation in these patients. However, elderly patients have a higher incidence of impaired left ventricular function and multivessel coronary artery disease, which increase the risk associated with balloon angioplasty (Hartzler et al, 1988; O'Keefe et al, 1990). In addition, coronary lesions in the elderly patients tend to be diffuse and calcified, and their vessels are more rigid and tortuous (Kelley et al, 1985; Dorros et al,

1986). This may increase the technical difficulties of angioplasty, and adversely affect the outcome of this procedure.

There have been no randomised trials specifically addressing angioplasty for the elderly. Previous reports on the acute and long-term results of coronary angioplasty in this subset of patients have shown conflicting results (Mock et al, 1984; Dorros and Janke, 1986; Urban et al, 1987; Hartzler et al, 1988; Imburgia et al, 1989; Bedotto et al, 1991b). The study presented in this chapter describes the acute and long-term results of coronary angioplasty in patients aged 70 years and older who were treated over a 12-year period.

7.2 PATIENTS AND METHODS

(a) PATIENTS

Between 1981 and 1993, 163 patients aged 70 years or older underwent their first percutaneous transluminal coronary balloon angioplasty. There were no other exclusion criteria.

The mean age was 73 years (SD 3, range 70 to 83 years) and 102 (63%) were male (Table 7.1). Seventy-four patients (45%) had a history of previous myocardial infarction and 66 (40%) had impaired left ventricular function. Twenty-eight (17%) had previous coronary artery bypass grafting. Coronary angioplasty was performed as an emergency for unstable angina in 27 patients (17%). Before intervention, 117 patients (72%) suffered grade III or IV angina. One hundred and sixteen (71%) had multivessel disease. Risk factors that were present in the patients included smoking (46%), diabetes mellitus (7%), hypertension (18%), and hypercholesterolaemia (46%).

Forty-four patients (27%) underwent multivessel coronary angioplasty, and 62 (38%) underwent multilesion coronary angioplasty during the same procedure. A mean of 1.3 vessels and 1.4 stenoses per patient were dilated. Coronary angioplasty was attempted in 213 vessels including 2 (1%) protected left main stems, 102 (48%) left anterior descending arteries and their diagonal branches, 8 (4%) intermediate arteries, 41 (19%) circumflex arteries and their obtuse marginal branches, 53 (25%) right coronary arteries, and 7 (3%) saphenous vein grafts. Twenty-two procedures were undertaken for totally occluded vessels. A total of 275 lesions were attempted.

(b) ANGIOPLASTY PROCEDURE

Coronary angioplasty was performed according to the protocol described in Chapter 2. Coronary angioplasty was frequently chosen as an alternative mode of revascularisation when surgery was considered too risky because of haemodynamic instability or other concurrent medical problems commonly found in this subgroup of patients. In these high risk patients, the strategy of angioplasty was not to accomplish complete revascularisation, but to achieve symptomatic improvement by dilating the 'culprit' lesion (usually, but not always, the most critical lesion).

(c) STUDY METHODS

The baseline characteristics, procedural, and angiographic data on all 163 patients were assessed. Complete follow-up data were available on all 163 patients on or after the census date. Information on vital status, current angina status, and the occurrence of new cardiac events was obtained up to July 31st, 1993.

Angiographic success was defined as ≤50% residual diameter stenosis at the dilated sites. Procedural success occurred when a patient had angiographic success in at least 1 vessel without a major in-hospital complication (defined as the occurrence of death, myocardial infarction, or emergency coronary artery bypass grafting).

(d) STATISTICAL METHODS

Continuous variables are expressed as mean (SD). Categorical variables were compared using the chi-squared test for trend or Fisher's exact test (2 sided), and continuous variables using the unpaired t test. Life table analyses were performed

using the Kaplan-Meier method, computed from the time of coronary angioplasty. The logrank test and proportional hazards regression analysis were used to identify which prognostic factors independently influenced long-term survival and the time to a cardiac event during follow-up; prognostic factors were selected using the backwards stepwise procedure.

7.3 RESULTS

(a) ACUTE RESULTS

Angiographic success was achieved in 183 vessels (86%) and 243 lesions (88%). The angiographic success rate was 92% for non-occluded lesions and 59% for totally occluded lesions. The distribution of the lesions and the success rate per lesion are shown in Table 7.2. An abrupt closure occurred in 13 lesions. Nineteen lesions could not be crossed of which 12 were chronic total occlusions. Revascularisation was complete in only 70 patients (43%) and incomplete in 93 patients (57%). Complete revascularisation was lowest in patients with triple vessel disease (14%), intermediate (36%) in those with double vessel disease, and highest (87%) in patients with single vessel disease ($p<0.001$).

Procedural success was achieved in 134 patients (82%). The procedural success rate was 85% for those patients who were aged 70 to 74 years, 73% for those aged 75 to 79 years, and 50% for those aged >80 years.

A significant complication occurred in 12 patients (7.4%), which was invariably the result of an abrupt occlusion of the vessel being dilated. Four patients died (2.4%), 3 (1.8%) suffered a non-fatal Q-wave myocardial infarction, and 5 (3.1%) underwent emergency coronary artery bypass grafting. Of the 4 patients who died, 3 had triple vessel disease and all 4 had markedly impaired left ventricular function. They were not considered candidates for bypass grafting because of a high surgical risk. Three patients died during the procedure of irreversible haemodynamic failure and the remainder died despite emergency bypass grafting. Seventeen patients

(10%) had an unsuccessful but uncomplicated angioplasty. None of the patients suffered an irreversible cerebrovascular accident.

(b) DETERMINANTS OF PROCEDURAL OUTCOME

The 11 variables that were analysed to assess their association with procedural outcome are shown in Table 7.3. Patients with impaired left ventricular function had a significantly lower procedural success rate (70% versus 91%, $p<0.001$) and a suggestion of a higher complication rate (12% versus 4%, $p=0.07$) than those with well preserved left ventricular function. None of the other variables analysed were significantly associated with procedural outcome.

(c) LONG-TERM RESULTS

The median duration of follow-up was 35 months, ranging from 2 to 146 months. During the follow-up period, 16 patients (10%) died, 2 (1%) suffered non-fatal myocardial infarction, and 12 (7%) underwent elective coronary artery bypass grafting. A second coronary angioplasty procedure was performed in 24 patients (15%) with procedural success in 22 patients. In total, a second revascularisation procedure was necessary in 36 patients (22%). The 16 late deaths included 4 non-cardiac deaths (bronchopneumonia, carcinoma of the colon, acute leukaemia, and cerebrovascular accident) and 8 cardiac deaths (2 sudden deaths and 6 fatal myocardial infarctions). Four patients died as a result of additional revascularisation procedures.

The cumulative probability of survival for all 163 patients was 90.7% (SE 2.4%) and 83.4% (SE 3.7%) at 1 and 5 years, respectively (Table 7.4). Patients with an

initially successful angioplasty procedure had cumulative 1 and 5 year survival rates of 93.9% (SE 2.3%) and 85.7% (SE 4.1%), respectively. The 1 and 5 year rates for freedom from death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty was 68.2% (SE 3.8) and 56.0% (SE 4.9), respectively. The 1 and 5 year cumulative event-free survival rates are shown in Table 7.4 for all patients and patients with an initially successful angioplasty procedure (Figures 7.1 and 7.2).

At census, of the 143 survivors, 75 (52%) were asymptomatic, 58 (41%) had mild angina and only 10 (7%) complained of grade 3 or 4 angina (Figure 7.3). One hundred and twelve patients (78%) improved by at least 2 angina grades.

(d) DETERMINANTS OF LONG-TERM SURVIVAL

To determine predictors for overall and event-free survival (freedom from death, myocardial infarction, bypass surgery, and repeat angioplasty), the variables examined were: age; impaired left ventricular function (ejection fraction $<45\%$); extent of native vessel disease (single versus multivessel disease); prior coronary artery bypass surgery; stable versus unstable angina pectoris; presence of diabetes mellitus; and completeness of revascularisation.

Individual survival analyses showed that incomplete revascularisation ($p=0.014$), impaired left ventricular function ($p=0.01$), multivessel vessel disease ($p<0.001$), and prior coronary artery bypass grafting ($p=0.01$) were negative correlates for overall survival (Figures 7.4 to 7.6). Incomplete revascularisation ($p<0.001$) and impaired left ventricular function ($p=0.01$) were also shown to be negative

correlates for survival free from death, myocardial infarction, bypass surgery, and repeat angioplasty (Figures 7.7 and 7.8).

Proportional hazards regression analyses identified incomplete revascularisation as the only independent predictor of poorer overall survival ($p=0.04$) and survival free from myocardial infarction, bypass surgery, and repeat angioplasty ($p<0.001$). The incidence of late cardiac events (death, myocardial infarction, coronary artery bypass surgery, or repeat angioplasty) was 21% versus 42% in patients with complete revascularisation and those with incomplete revascularisation, respectively.

7.4 DISCUSSION

The proportion of elderly patients with symptomatic coronary artery disease continues to expand with an increasing average life expectancy. As a result, more and more are subjected to invasive diagnostic and therapeutic interventions. One third of the cardiac catheterisations and bypass operations in the United States are performed on elderly patients (Stason et al, 1987; Kashyap, 1989). Data derived from the National Heart, Lung, and Blood Institute registry indicate that patients over age 65 accounted for 27% of percutaneous transluminal coronary angioplasty procedures during 1985 to 1986, compared with just 12% in 1977 to 1981 (Kowalchuk et al, 1990). At the Mayo Clinic, Thompson et al (1991) reported that 53.6% of patients undergoing PTCA were over age 65 by 1988.

The need for myocardial revascularisation in symptomatic elderly patients is not in dispute, but the safety and efficacy of the various therapeutic modalities need to be evaluated in these seemingly fragile patients. Although surgical studies have reported improved symptoms and survival in this subset of patients, the operative mortality and morbidity are high (Kennedy et al, 1981; Hochberg et al, 1982; Elayda et al, 1984; Gersh et al, 1985; Horneffer et al, 1987; Loop et al, 1988; Grondin et al, 1989) (Table 7.5). Percutaneous transluminal coronary angioplasty has proved a safe and effective method of myocardial revascularisation. As a result, patients who are at high risk for cardiac surgery have been increasingly treated with coronary angioplasty in recent years, including the elderly.

Acute Results

Although the overall angiographic success rate achieved in the present study was only 88% with a complication rate of 7.4%, most of the failures occurred in

occluded lesions (angiographic success of 59%). Angioplasty was technically successful in 92% of non-occluded lesions. This suggests that the procedure is technically feasible in these elderly patients, despite the higher occurrence of clinical and lesion parameters that are less ideal for angioplasty. These results are comparable to those of other centres. Previous studies on coronary angioplasty in elderly patients have reported angiographic success rates ranging from 68% to 96%, procedural success rates ranging from 53% to 93%, mortalities from 0% to 15.1%, myocardial infarction rates from 0.8% to 14%, and emergency bypass surgery rates from 0% to 8.2% (Table 7.6). The low procedural success rate of 53% and the high complication rate reported by Mock et al (1984) on behalf of the "first generation" National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry represent an early multicentre experience circa 1977-1981. Considerable advances in angioplasty technology and operator experience have occurred since that period. More recently, Simpfendorfer et al (1988) reported a high procedural success rate of 93%, with the lowest rate of major cardiac complications among previously reported studies. However, only 23% of their patients had multivessel disease as opposed to 71% in the present series, which might explain their more favourable results. The largest reported series is that of Bedotto et al (1991), who described the outcome of multivessel percutaneous transluminal coronary angioplasty in 1373 patients aged ≥65 years. An overall angiographic success rate of 96% was achieved, with a mortality rate of 1.6%, myocardial infarction rate of 1.4%, and an emergency bypass surgery rate of 0.8%.

Earlier studies have suggested that coronary balloon angioplasty in elderly patients is associated with lower success and higher complication rates, when compared to those achieved in younger patients. The initial report from the "first generation" National Heart, Lung, and Blood Institute percutaneous transluminal coronary

angioplasty registry reported procedural success rates of 53% and 62%, and mortality rates of 0.7% and 2.2%, in patients aged ≥65 years and those aged <65 years, respectively (Mock et al, 1984). However, such differences have not been confirmed in recent studies, which have reported high technical success rates in elderly patients (Jones et al, 1986; Raizner et al, 1986). Despite the higher incidence of unstable angina, multivessel disease, and attempted lesions containing calcium in the elderly population, the report from the "second generation" National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry (1985-1986) has shown similar angiographic success rates in patients aged ≥ 65 years, and those aged <65 years (Kelsey et al, 1990). This may be explained by the differences in baseline characteristics of the study population due to selection bias, or advances made in angioplasty technology and operator experience resulting in the improved primary success rates.

Despite the presence of multivessel disease in 71% of the patients, only 27% underwent multivessel coronary angioplasty in the present study. Complete revascularisation was achieved in only 43% of the patients, and was lowest in patients who had 3 vessel disease. These findings are similar to those of earlier studies (Deligonul et al, 1988a; Bell et al, 1990). Coronary angioplasty was frequently chosen as an alternative mode of revascularisation when surgery was considered too risky because of haemodynamic instability or other concurrent medical problems commonly found in elderly patients. In such high risk patients, coronary angioplasty was frequently performed on the 'culprit' lesion (usually, but not always, the most critical lesion) to achieve symptomatic improvement, without attempting to accomplish complete revascularisation. This approach towards coronary angioplasty in the elderly reduces the length of procedure and the amount of contrast utilised, hence minimising the risk of complication.

Determinants of Procedural Outcome

The presence of impaired left ventricular function was significantly associated with a lower procedural success and a trend towards a higher complication rate. Similar results have been shown by other investigators (Hartzler et al, 1988; Stevens et al, 1991; Serota et al, 1991). Coronary angioplasty in patients with left ventricular dysfunction is associated with multiple technical difficulties, resulting from poor tolerance of any reduction in coronary flow, either transiently during balloon inflation or more prolonged in the event of an abrupt closure. The recent introduction of new angioplasty technology, such as autoperfusion balloon catheters (which allow prolonged inflations without interruption of antegrade flow), intravascular stents, and directional atherectomy (both which enable re-establishment of antegrade flow in the event of dissection leading to abrupt closure), have improved the procedural outcome (Sigwart et al, 1987; Topol, 1989; Lee et al, 1990). Furthermore, the use of supported angioplasty with intra-aortic balloon pump or partial cardiopulmonary bypass, has further enhanced the procedural safety of coronary angioplasty in these patients (Kahn et al, 1990; Vogel et al, 1990).

Without randomised studies, direct comparison of these results with those achieved with coronary bypass surgery may be misleading, because of the possibility of selection bias resulting from differences in baseline and procedural variations. However, a higher risk of surgical mortality (ranging from 2.3% to 12%) and peri-operative morbidity (ranging from 14 to 65%) in the elderly has been confirmed, (Hochberg et al, 1982; Gersh et al, 1983a; Loop et al, 1988), although more recent surgical studies have shown an improved survival rate compared with earlier reports (Tsai et al, 1989; Darling et al, 1989). Coronary angioplasty, when successful, is associated with less morbidity than bypass surgery, and is therefore potentially more attractive. Of particular note is that none of the patients in the present series and

those reported previously (Dorros and Janke, 1986; Simpfendorfer et al, 1988) suffered an irreversible cerebrovascular accident as opposed to the 2.7%-7.5% reported in surgical studies (Horneffer et al, 1987; Grondin et al, 1989) (Table 7.5).

Long-term Results

Although angioplasty in the elderly is technically feasible, the procedure must be associated with short- and long-term symptomatic improvement before being judged clinically successful. The present study has shown that the long-term survival of coronary angioplasty in elderly is influenced by the completeness of revascularisation. Survival may also be influenced by the risk of restenosis, which might be increased in the elderly. However, information on restenosis rate was not available in this study due to the low incidence of follow-up angiography; angiography being repeated only when it was clinically indicated. Nevertheless, despite the presence of multivessel disease and incomplete revascularisation in the majority of patients, the overall rate of survival at 1 and 5 years was encouraging, and rivalled those reported for elderly patients undergoing coronary bypass surgery (Gersh et al, 1985; Horneffer et al, 1987).

This favourable long-term survival has also been substantiated by previous coronary angioplasty studies, which have shown a remarkable similarity in the overall and event-free survival rates (Holt et al, 1988; Simpfendorfer et al, 1988; Dorros et al, 1989; Bedotto et al, 1991b; de Jaegere et al, 1992b). de Jaegere et al (1992b) reported overall survival of 89% and event-free survival (freedom from death, myocardial infarction, bypass surgery, and repeat angioplasty) of 61% at 4 years from the primary procedure, in 166 patients aged 70 and over. Bedotto et al (1991b) showed an actuarial survival of 92% and 78% at 1 and 5 years, respectively in 1,373 patients aged 65 years and older. They also reported freedom from death,

myocardial infarction, and coronary bypass surgery of 81% and 56% at 1 and 5 years, respectively. Dorros et al (1989) reported 6-year overall survival of 92% and freedom from death, myocardial infarction, or bypass surgery of 73% in 242 patients over the age of 70 years. The present study has shown an overall survival of 91% at 1 year and 83% at 5 years. The 1 and 5 year rates for freedom from death, myocardial infarction, and coronary bypass surgery were 81% and 71%, respectively. The rates for freedom from death, myocardial infarction, coronary bypass surgery, and repeat angioplasty was 68% at 1 year and 56% at 5 years.

Determinants of Long-term Survival

Although complete revascularisation was achieved in less than half of the patients in the present series, the patients' quality of remaining life appeared good with marked improvement in angina status. This has also been substantiated by previous studies, where coronary angioplasty has been found to provide prolonged relief of angina in approximately 75% of elderly patients undergoing a successful procedure (Kelsey et al, 1990; Bedotto et al, 1991; Thompson et al, 1991). However, the incidence of late cardiac events was also significantly higher in patients who had incomplete revascularisation than in those with complete revascularisation. It appeared that dilatation of only the culprit lesion provided adequate relief of ischaemia and led to sufficient and often dramatic clinical improvement, but often at the expense of a higher incidence of late cardiac events and less favourable long-term survival. Although a subsequent revascularisation procedure was necessary in 22% of patients, only 7% needed an elective coronary artery bypass surgery. Hence, achieving complete revascularisation in the elderly population may not be necessary if the primary therapeutic goals are to provide symptomatic relief and improvement in the quality of life.

The findings in this study are consistent with previous surgical (Lawrie et al, 1982; Jones et al, 1983; Lavee et al. 1986) and angioplasty (Finci et al, 1987d; Deligonul et al, 1988a; O'Keefe et al, 1990; Bell et al, 1990) studies, which have shown that patients with multivessel disease, in whom revascularisation was incomplete, have generally shown poor symptomatic relief and survival. However, the clinical importance of the completeness of revascularisation in the elderly population on long-term outcome remains controversial. Bedotto et al (1991b) have shown that long-term survival after coronary angioplasty in elderly patients was significantly influenced by the degree of revascularisation. Maiello et al (1992b) reported a trend towards increased cardiac events in patients with partial revascularisation. On the other hand, de Jaegere et al (1992b) showed that the degree of revascularisation did not influence event-free survival. These discrepancies may be explained by variation in the baseline patient characteristics, or by differences in the functional significance of the remaining stenoses in patients with incomplete revascularisation (Faxon et al, 1992b).

Study Limitations

This study is a retrospective analysis of data which was collected prospectively and is subject to all the limitations inherent in such a study. Since it was not a randomised study, no attempt was made to compare the results with those achieved with coronary artery bypass grafting, since selection criteria may not have been identical.

7.5 SUMMARY AND CONCLUSIONS

Medical therapy is often poorly tolerated by the elderly, and side effects from drugs are common. Elderly patients whose quality of life is significantly limited by angina, and who are refractory to or intolerant of medical therapy, should be considered for revascularisation. The enthusiasm for surgical ravascularisation, although effective in relieving symptoms and improving prognosis, has been tempered by the higher mortality and morbidity in this population. The study presented in this chapter has shown that coronary angioplasty can be performed safely and effectively in selected elderly patients, and provides good symptomatic relief and favourable long-term outcome. This procedure, when feasible, provides an attractive alternative to coronary bypass surgery in this group of patients. Until results of randomised trials are made available, this study provides useful information in helping clinicians decide on the optimal method of revascularisation in elderly patients.

Table 7.1: Patient and Angiographic Characteristics.

	Number	%
Total	163	100
Mean age (years)	73	SD 3 (range 70-83)
Male gender	102	63
Angina grade		
0/I	12	7
II	34	21
III	49	30
IV	68	42
Previous MI	74	45
Abnormal LV (EF<45%)	66	40
Previous CABG	28	17
Risk factors		
Hypertension	29	18
Diabetes mellitus	12	7
Current smoking	75	46
Hypercholesterolaemia	75	46
Emergency procedure	27	17
Number of diseased vessels		
1	47	29
2	58	36
3	58	36
Single vessel PTCA	119	73
Multivessel PTCA	44	27
Multilesion PTCA	62	38

CABG=coronary artery bypass surgery; EF=ejection fraction; LV=left ventricular function; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty; SD=standard deviation.

Table 7.2. Primary Angiographic Success for all 275 lesions.

	Number	Success	%
LMS	2	2	100
LAD	128	112	88
RCA	75	66	88
CX	53	48	91
INT	9	9	100
SVG	8	6	75
Totally occluded lesions	29	17	59
Non-occluded lesions	246	226	92
Total	275	243	88

CX=circumflex artery, INT=intermediate artery, LAD=left anterior descending artery, LMS=left main stem, RCA=right coronary artery, SVG=saphenous vein graft.

Table 7.3. Variables Associated With Acute Angioplasty Success and Complications. Data are Number (%).

Variables	Number	Procedural success	p Value	Procedural complications	p Value
Gender					
Male	102	86 (84)	0.40	7 (7)	0.76
Female	61	48 (79)		5 (8)	
Angina grade					
0/I/II	46	41 (89)	0.18	1 (2)	0.18
III/IV	117	93 (79)		11 (9)	
Previous MI					
Yes	74	58 (78)	0.30	4 (5)	0.55
No	89	76 (85)		8 (9)	
Previous CABG					
Yes	28	20 (71)	0.11	1 (4)	0.48
No	135	114 (84)		11 (8)	
Current smoking					
Yes	75	61 (81)	0.84	4 (5)	0.39
No	88	73 (83)		8 (9)	
Diabetes mellitus					
Yes	12	11 (92)	0.47	0 (0)	0.60
No	151	123 (81)		12 (8)	
Hypertension					
Yes	29	27 (93)	0.11	1 (3)	0.48
No	134	107 (80)		11 (8)	
Unstable angina					
Yes	27	21 (78)	0.58	4 (15)	0.12
No	136	113 (83)		8 (6)	
Multivessel disease					
Yes	116	93 (80)	0.37	10 (9)	0.51
No	47	41 (87)		2 (4)	
Impaired LV					
Yes	66	46 (70)	<0.001	8 (12)	0.07
No	97	88 (91)		4 (4)	
Hypercholesterolaemia					
Yes	75	59 (79)	0.31	7 (9)	0.28
No	88	75 (85)		5 (6)	

Abbreviations as for Table 7.1.

Table 7.4. Total and Event-free Survival 1 and 5 Years After PTCA for all Patients and Patients With Initially Successful Angioplasty Procedures. Data are % (95% confidence interval).

	One year		Five years	
	All patients	Procedural success	All patients	Procedural success
Death; % survival	90.7 (85.9-95.5)	93.9 (89.4-98.4)	83.4 (76.1-90.7)	85.7 (77.5-93.9)
Death/MI; % freedom	88.3 (83.1-93.5)	94.0 (89.6-98.4)	79.3 (71.2-87.4)	83.8 (74.9-92.7)
Death/MI/CABG; % freedom	80.6 (74.2-87.0)	91.6 (86.5-96.7)	70.5 (61.3-79.7)	79.2 (69.3-89.1)
Death/MI/CABG/ PTCA; % freedom	68.2 (60.7-75.7)	77.1 (69.6-84.6)	56.0 (46.3-65.7)	62.3 (51.3-73.3)
CABG; % freedom	89.9 (85.0-94.7)	96.7 (93.4-100)	87.2 (81.3-93.2)	93.4 (87.8-99.0)
Repeat PTCA; % freedom	86.8 (81.4-92.2)	85.5 (79.3-91.7)	83.8 (77.6-90.0)	83.0 (76.0-90.0)
CABG/repeat PTCA; % freedom	76.0 (69.1-83.0)	82.1 (75.3-88.9)	70.5 (62.1-78.9)	75.3 (66.2-84.4)

Abbreviations as for Table 7.1.

Table 7.5. Coronary Artery Bypass Grafting in the Elderly: Mortality and Morbidity (Chronological Order).

First Author (year)	Age (years)	Patients (number)	Death (%)	MI (%)	CVA (%)
Ashor (1973)	≥70	22	9.1	-	-
McCallister (1975)	≥70	48	6.3	4.2	4.2
Meyer (1975)	≥70	95	22.1	6.3	-
Tucker (1977)	≥70	67	-	1.5	-
Gann (1977)	≥70	50	8	10	2
Stephenson (1978)	≥70	35	2.9	-	-
LaFollette (1980)	≥70	35	2.9	8.6	-
DuCailar (1980)	≥70	11	11.8	11.8	2.4
Berry (1981)	≥70	65	3.1	4.6	3.1
Knapp (1981)	≥70	121	1.7	3.3	2.5
Hochberg (1982)	≥70	75	12	5	2.7
Gersh (1983b)	≥70	283	7.1	-	-
Faro (1983)	≥70	105	10.5	-	8.6
Elayda (1984)	≥70	1275	5.8	-	-
Montague (1985)	≥70	597	2.7	1.5	2
Tsai (1986)	≥80	38	5.2	0	2
Johnson (1987)	≥70	379	16	-	-
Goldman (1987)	≥70	349	6.4	-	6.2
Dorros (1987)	≥70	674	7.4	7.1	4.2
Rich (1988)	≥75	60	3.3	5	0
Grondin (1989)	≥70	88	10.2	3	6.8
Horvath (1990)	≥75	222	10.8	4.1	2.3

CVA=cerebrovascular accident; MI=myocardial infarction.

Table 7.6. Other Published Results (Chronological Order).

First author (year)	Age (years)	Patients (number)	Angiographic success (%)	Procedural success (%)	Death (%)	MI (%)	CABG (%)
Mock (1984)	≥65	370	-	53	2.2	5.6	6.8
Jones (1986)	≥65	159	84	81	0.0	3.1	5.7
Raizner (1986)	≥65	119	81	-	0.8	2.5	4.1
Urban (1987)	≥65	51	-	71	4.6	4.6	4.6
Kelsey (1990)	≥65	394	81	76	3.0	4.6	5.3
Bedotto (1991b)	≥65	1373	96	-	1.6	1.4	0.8
Thompson (1991)	≥65	752	-	85	2.8	4.3	8.2
Dorros (1986)	≥70	109	89	83	1.8	2.8	0.9
Hartzler (1988)	≥70	1038	94	-	1.4	0.8	1.3
Holt (1988)	≥70	54*	-	80	0.0	4.0	6.0
Simpfendorfer (1988)	≥70	124**	-	90	0.0	0.8	4.0
	≥70	212*	-	93	0.9	0.9	2.8
Dorros (1989)	≥70	242	91	86	3.3	2.1	1.2
de Jaegere (1992b)	≥70	166	85	86	2.4	3.0	3.6
Maiello (1992b)	≥70	92	92	83	5.4	1.1	3.2
Present study	≥70	163	86	82	2.4	1.8	3.1
Imburgia (1989)	≥75	43	68	57	6.0	2.0	8.0
Kern (1988)	≥80	21	78	67	19	-	14
Rich (1990)	≥80	22	89	-	0.0	14.0	0.0
Rizo-Patron (1990)	≥80	53*	-	83	1.8	5.5	7.5
Jeroudi (1990)	≥80	54	93	91	4.0	4.0	0.0
Santana (1992)	≥80	53*	83	-	15.1	3.8	-

CABG=emergency coronary artery bypass surgery; MI=myocardial infarction; *Only patients with unstable angina; **Only patients with stable angina.

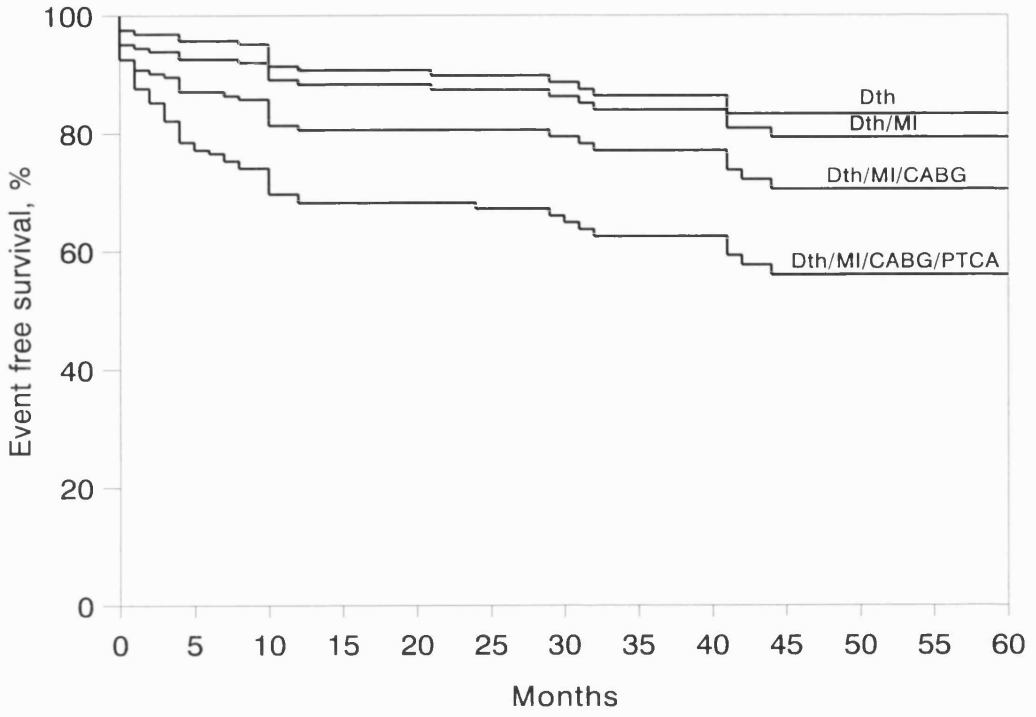


FIGURE 7.1. Plot of cumulative event free survival for all 163 patients. Dth = freedom from death; Dth/MI = freedom from death and myocardial infarction; Dth/MI/CABG = freedom from death, myocardial infarction, and coronary artery bypass grafting; Dth/MI/CABG/PTCA = freedom from death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty.

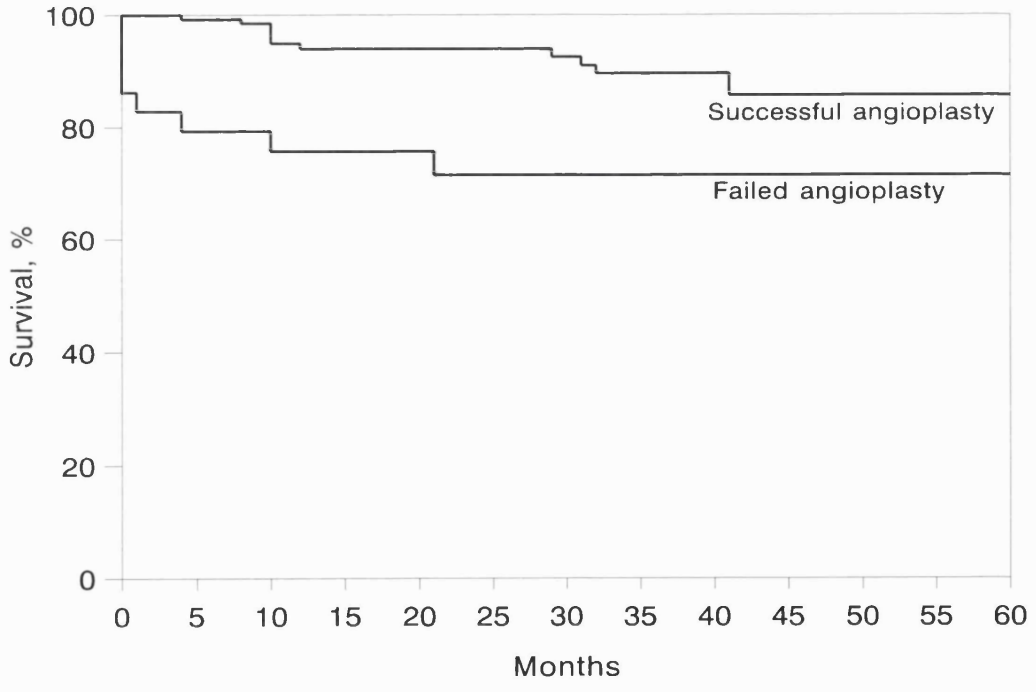


FIGURE 7.2. Plot of cumulative survival according to the outcome of initial angioplasty procedure (p = 0.007).

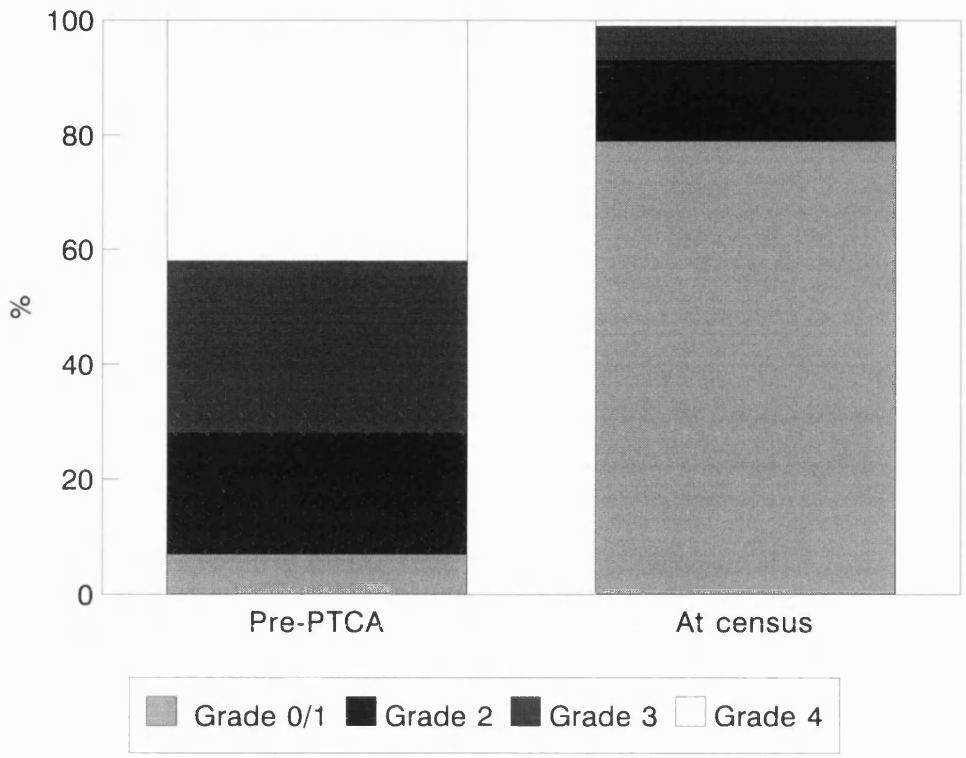


FIGURE 7.3. Angina grade before coronary angioplasty and at census in 143 survivors ($p < 0.001$).

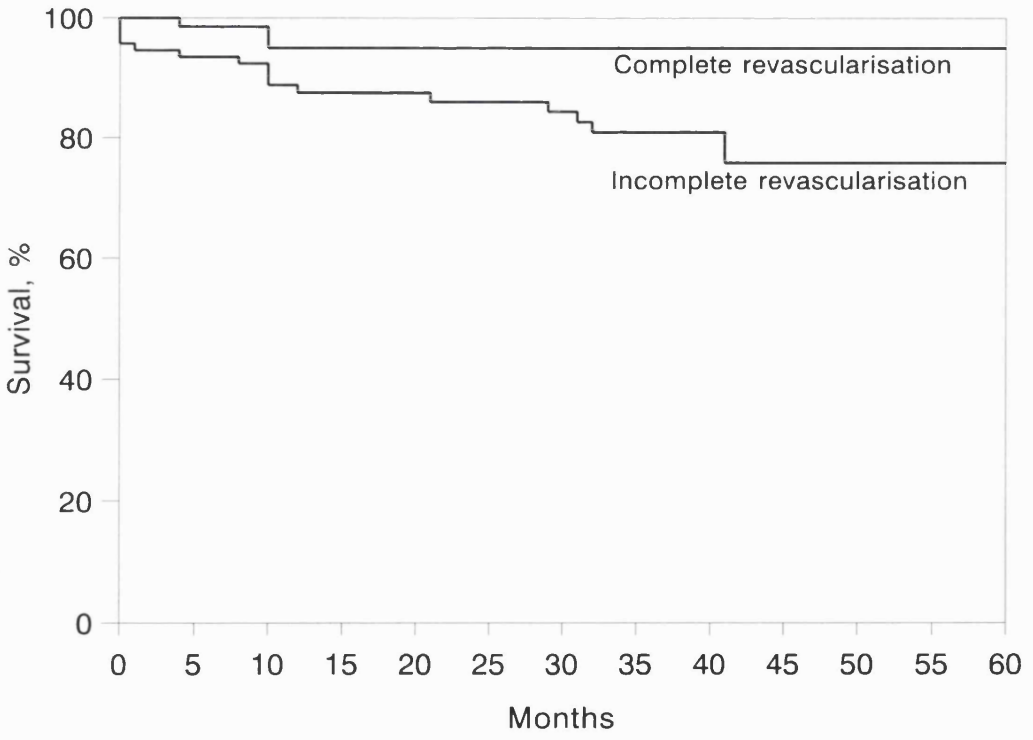


FIGURE 7.4. Plot of cumulative survival according to the completeness of revascularisation ($p = 0.01$).

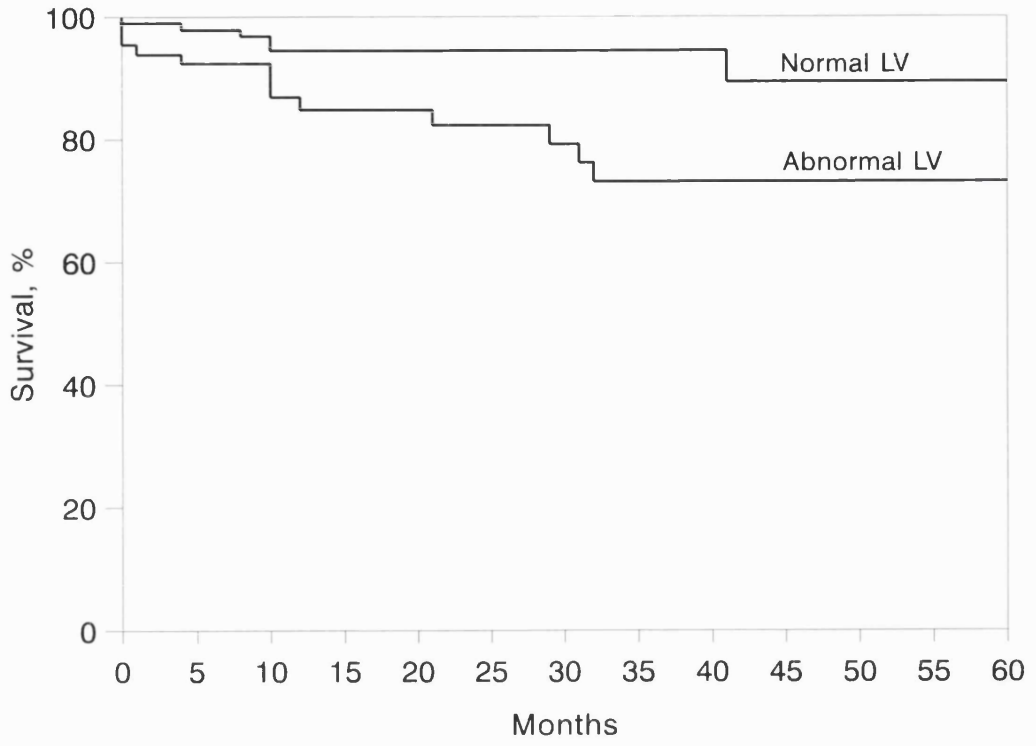


FIGURE 7.5. Plot of cumulative survival according to left ventricular function (p=0.01).

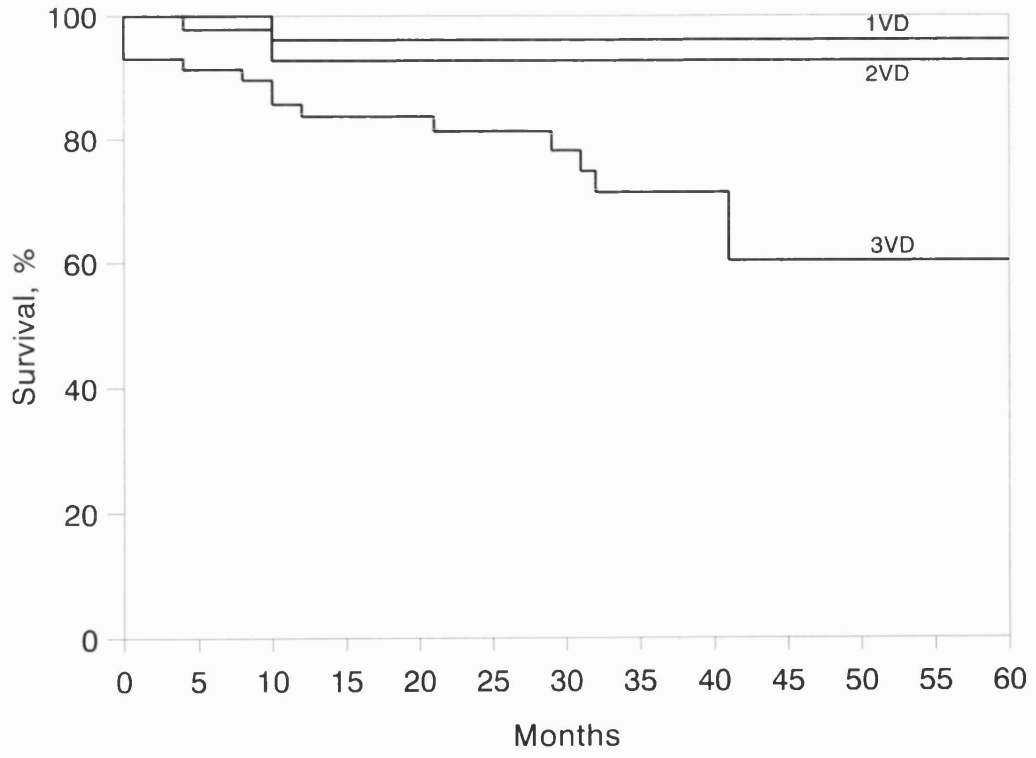


FIGURE 7.6. Plot of cumulative survival according to the number of diseased vessels (p=0.01). 1VD=single vessel disease; 2VD=double vessel disease; 3VD=triple vessel disease.

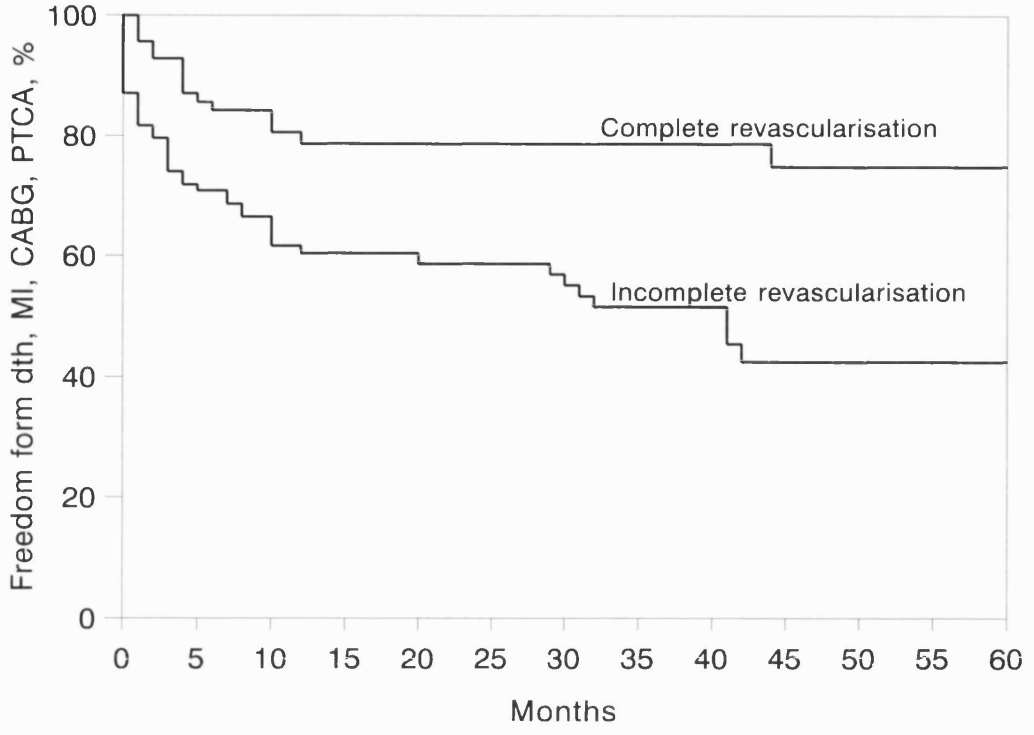


FIGURE 7.7. Plot of percentage of patients free of death (dth), myocardial infarction (MI), coronary artery bypass grafting (CABG), and repeat angioplasty (PTCA) according to the completeness of revascularisation ($p < 0.001$).

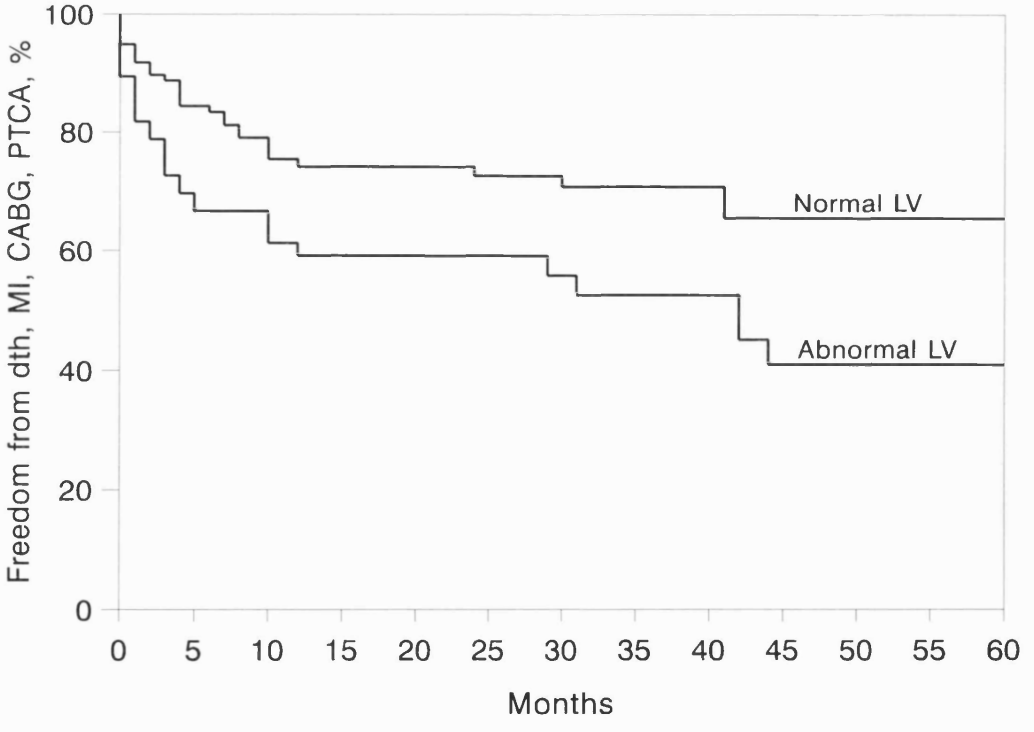


FIGURE 7.8. Plot of percentage of patients free of death (dth), myocardial infarction (MI), coronary artery bypass grafting (CABG), and repeat angioplasty (PTCA) according to left ventricular function (LV) ($p = 0.01$).

8. *'TANDEM LESION' CORONARY ANGIOPLASTY*

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8.1 INTRODUCTION

Despite being extended to more complex cases, the success rate of percutaneous transluminal coronary angioplasty remains high with acceptable complication rates (Dorros et al, 1984c; Vandormael et al, 1985; Detre et al, 1988; Tuzcu et al, 1989). Included in the definition of complex angioplasty are those angioplasties involving sequential (tandem) lesions. Little data is available regarding the acute success and complication rates of tandem lesion coronary angioplasty (Dorros et al, 1984c; Lambert et al, 1987; DiSciascio et al, 1985). In addition, the limited clinical follow-up data previously reported in this subset of patients, are of medium term only (Lambert et al, 1987). Most reports have not distinguished between multivessel disease and sequential lesions when presenting data on long-term therapeutic benefit after multilesion coronary angioplasty.

Restenosis is the major unsolved problem afflicting coronary angioplasty. The incidence is higher in patients with dilatation of multiple lesions (especially in the same artery) and ranges from 26-53% (Roubin et al, 1986; Vandormael et al, 1987; Holmes et al, 1988b). To date, no therapeutic strategy has been shown to reduce the rate of restenosis (Thornton et al, 1984; Corcos et al, 1985; Califf et al, 1991). It is therefore vital to identify factors associated with an increased rate of restenosis, so that appropriate measures can be taken to modify them. Tandem lesion coronary angioplasty provides an ideal model for studying factors which might be related to restenosis. If the underlying pathophysiology of restenosis is influenced predominantly by systemic or clinical factors which should affect all the dilated sites equally, the incidence of restenosis occurring concurrently at both sites should be high after tandem lesion coronary angioplasty. In contrast, if restenosis is independent of systemic influences and is determined mainly by local or procedure-

related factors which would be specific for each lesion, isolated restenosis would predominate.

The study presented in this chapter evaluates the acute and long-term results of coronary angioplasty in patients with left anterior descending artery tandem lesions. It extends the reported experience of coronary angioplasty involving tandem lesions, and provides longer-term follow-up results compared to those of earlier studies. The angiographic patterns of restenosis are also examined, and the factors that may predict clinical restenosis are assessed.

8.2 PATIENTS AND METHODS

(a) PATIENTS

Between 1981 to 1991, 102 patients underwent a first coronary angioplasty of 2 separate stenoses (tandem lesion) in the left anterior descending artery. "Tandem lesion" was defined as sequential lesions in different segments of the left anterior descending artery separated by an angiographically disease free segment (Figures 8.1 and 8.2). Patients treated previously with coronary artery bypass grafting, coronary angioplasty, or having disease in vessels other than the left anterior descending artery were excluded from the study.

The mean age was 54 years (SD 8, range 34-71 years) and 79 were male (77.4%) (Table 8.1). Twenty-six patients (25%) had a history of previous myocardial infarction and 19 patients (19%) had impaired left ventricular function. Coronary angioplasty was performed as an emergency procedure for unstable angina in 11 patients (11%). Prior to the procedure, 68 patients (66.7%) suffered grade III or IV angina. Two patients (2%) had no angina but had reversible myocardial ischaemia documented during exercise treadmill testing. The risk factors that were present included smoking (41%), diabetes mellitus (6%), hypertension (18%), and hypercholesterolaemia (35%).

(b) ANGIOPLASTY PROCEDURE

Coronary angioplasty was performed according to the protocol presented in Chapter 2. The more distal lesion was usually dilated first, followed by the proximal lesion.

Complete revascularisation was achieved by dilatation of both sequential lesions during a single procedure.

(c) STUDY METHODS

The baseline clinical, angiographic, and procedural data on all 102 patients were assessed. Complete follow-up data was available for all 102 patients on or after the census date. Information on vital status, angina status, and the occurrence of new cardiac events was obtained up to October 30th, 1991.

The clinical parameters analysed as possible determinants of angiographic restenosis included age, gender, angina grade, extent of coronary artery disease, left ventricular function, and whether multivessel or multilesion coronary angioplasty was performed. Other clinical factors considered were a history of smoking, hypertension, diabetes mellitus, hypercholesterolaemia, previous myocardial infarction, prior coronary artery bypass surgery, and the presence of a family history.

The angiographic parameters analysed included lesion location, vessel diameter, pre-angioplasty lesion severity, post-angioplasty lesion severity, and lesion length. The procedural parameters analysed included inflation frequency, inflation duration, inflation pressure, and balloon to artery ratio.

Angiographic success was defined as $\leq 50\%$ residual diameter stenosis at the dilated sites. Procedural success was defined as successful dilatation of both sequential lesions without a major in-hospital complication (defined as the occurrence of either death, myocardial infarction, or emergency coronary artery bypass surgery).

Angiographic restenosis was defined as a recurrence of a >50% diameter stenosis at a previously successfully dilated site. Clinical restenosis was defined as the recurrence of anginal symptoms or evidence of reversible ischaemia associated with angiographic evidence of restenosis. Patients who had a cardiac death, or a non-fatal myocardial infarction during the follow-up period, were also considered as having a clinical restenosis.

(d) STATISTICAL METHODS

Continuous variables are expressed as mean (SD). The study patients and lesions were divided into subgroups according to whether restenosis had occurred. The clinical, angiographic, and procedural variables analysed as possible correlates of restenosis were compared between these patient and lesion subgroups. Categorical variables between patient groups were compared using the Fisher's exact test and comparisons of continuous variables were performed using the Mann Whitney U test.

All variables found to be significantly related to restenosis by univariate analysis were included in multiple logistic regression analysis. The backwards stepwise selection procedure was used to identify independent predictors of restenosis significant at the 1% level. Life table analyses were performed using the Kaplan-Meier method computed from the time of coronary angioplasty.

8.3 RESULTS

(a) ACUTE RESULTS

Angiographic success was achieved for both tandem lesions in 96 patients (94%). In 3 patients (3%), the proximal lesions could not be crossed by the guidewire or dilatation catheter. In the other 3 patients (3%) the proximal stenoses were successful dilated but the distal lesions could not be crossed or were unsatisfactorily dilated. A total of 195 lesions were successful dilated (96%).

Overall, procedural success was achieved in 91 patients (89%). Five patients (4.9%) suffered a non-fatal Q-wave myocardial infarction of whom 1 also proceeded to emergency coronary artery bypass grafting 48 hours after the procedure, due to acute vessel re-occlusion after an apparently successful angioplasty. There were no procedure-related deaths (Table 8.2).

(b) LONG-TERM RESULTS

The median duration of follow-up was 46 months (range 1 to 122 months). During the follow-up period, 2 patients died as a result of fatal myocardial infarction, and 2 suffered non-fatal Q-wave myocardial infarction. The number of patients requiring a second revascularisation procedure during follow-up were 18; 6 underwent elective coronary artery bypass grafting, 7 had a repeat coronary angioplasty, and 5 underwent both coronary artery bypass grafting and repeat coronary angioplasty.

The cumulative probability of survival for all 102 patients was 98.9% (SE 1.1%) and 97.8% (SE 1.5%) at 1 and 5 years, respectively. The 1 and 5 year cumulative

survival rates for patients with initially successful procedures, were 98.8% (SE 1.2%) and 97.5% (SE 1.7%), respectively. The 1 and 5 year rates for freedom from death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty was 80.8% (SE 4.0%) and 74.9% (4.5%), respectively. The 1 and 5 year cumulative event-free survival rates are shown in Table 8.3 for all patients and patients with an initially successful angioplasty procedure (Figure 8.1).

At census, of the 100 survivors, 62 patients (62%) were asymptomatic and only 7 patients (7%) complained of grade III or IV angina ($p<0.001$) (Figure 8.2). Eighty-two patients (80%) improved by at least 2 angina grades.

(c) INCIDENCE OF RESTENOSIS

Repeat coronary angiography was performed in 30 of the 91 patients (33%) who had initially successful procedures for recurrence of symptoms or reversible ischaemia documented on symptom-limited treadmill exercise tests (mean 8.8 months, SD 7.2 months). Continued success was present in 8 patients (8/30=27%) and angiographic restenosis was present in 22 patients (22/30=73%). Of the 61 patients who did not undergo repeat angiography, 2 died of fatal myocardial infarction. The remaining patients were asymptomatic and had a negative exercise test at follow-up. Hence, the total number of patients with clinical restenosis was (24/91=26%).

(c) DETERMINANTS OF ANGIOGRAPHIC RESTENOSIS

Of the 22 patients who had angiographic restenosis, 14 had recurrence at a single dilated site (the proximal site in 11 patients and the distal site in 3), 6 had

recurrence in both dilated sites, and 2 had total occlusion of the left anterior descending artery. Excluding those patients with total occlusion, restenosis occurred in 26 of the 56 dilated sites in patients who had recurrent symptoms or evidence of reversible ischaemia. Univariate analysis of 22 patient-, lesion-, and procedure-related variables showed that restenosis was significantly associated with an increased number of inflations ($p<0.001$) and an increased total inflation duration ($p<0.01$) (Tables 8.4, 8.5, and 8.6). Multiple logistic regression analysis identified frequency of inflation ($p<0.001$) as the only independent predictor of restenosis. Total inflation duration did not have an independent relationship with the occurrence of restenosis once the effect of inflation frequency was accounted for (Table 8.7).

DISCUSSION

Percutaneous transluminal coronary angioplasty has been increasingly applied to patients with multilesion and multivessel disease. The procedural success rates achieved have been comparable with those seen in single vessel or single lesion coronary angioplasty (Dorros et al, 1984c; Vandormael et al, 1985). However, most reports on multilesion coronary angioplasty have not distinguished between multivessel angioplasty and dilatation of tandem lesions in the same vessel.

Acute Results

The primary angiographic success and complication rates achieved in this study are comparable to that reported in previous studies. Dorros et al (1984c) reported an angiographic success rate of 90.6% per patient and 91.2% per lesion in a cohort 85 patients who underwent tandem lesion coronary angioplasty. DiSciascio et al (1985) described 74 patients who had tandem lesion coronary angioplasty and reported a success rate of 89% per patient. In contrast, Lambert et al (1987) reported on 78 patients who had multilesion coronary angioplasty in the same vessel and found a primary angiographic success rate per lesion of only 73%. This was attributed to an angiographic success rate of only 62% for the distal lesions. However, inability to adequately dilate the distal lesion accounted for only 3 procedural failures in the present study. This apparent disparity may be due to differences in patient selection since only those with tandem lesion in the left anterior descending artery were included in our study. Distal lesions in the left anterior descending artery may be more amenable to the procedure compared to those in the circumflex and right coronary artery because the left anterior descending artery is less tortuous.

Long-term Results

There has been little published data on the long-term results following tandem lesion coronary angioplasty. Lambert et al (1987) followed up 78 patients for 6 months after tandem lesion coronary angioplasty. During the follow-up period, 2 patients suffered myocardial infarction, 3 had coronary artery bypass surgery and 12 had repeat coronary angioplasty. At 6 months, 56 of the 78 patients (72%) available for follow-up were in Canadian Cardiovascular Society functional class 0 or I. In the present study, the freedom from death, myocardial infarction, coronary artery bypass grafting and repeat coronary angioplasty at 1 and 5 years were 80.8% (SE 4.0%) and 74.9% (SE 4.5%), respectively. Only 18 patients required a second revascularisation procedure. Most patients were successfully managed conservatively with or without medication. The long-term symptomatic improvement achieved was excellent. Prior to coronary angioplasty, 67% of patients suffered grade III or IV angina. At census, 62% were asymptomatic and only 7 patients complained of grade III or IV angina.

The 3 patients who had incomplete revascularisation nevertheless enjoyed good symptomatic relief from the procedure. Prior to coronary angioplasty, all 3 patients had class III angina but at follow-up, 1 was symptom free and the other 2 had grade I angina. This was almost certainly due to dilatation of the 'culprit lesion' which was the physiologically important lesion. In support of this, Lambert et al (1987) found that patients who underwent multilesion coronary angioplasty in the same artery, in whom the distal stenosis could not be crossed, had a clinical outcome no worse than those in whom the distal coronary angioplasty was successful. Therefore, improved angina status can still be expected, even when incomplete revascularisation is obtained.

Determinants of Angiographic Restenosis

Factors that may influence the restenosis process include patient-, lesion- and procedure-related factors. Tandem lesion coronary angioplasty provides an ideal model for studying which of these factors is important in determining restenosis. In this study, since restenosis occurred at a single site more often than at both, this suggests that systemic factors do not play a dominant role in influencing restenosis. In support of this, the present study did not identify any clinical variables that were associated with restenosis. In contrast, procedure-related variables were found to be predictive of restenosis and, in particular, increased inflation frequency was found to be strongly associated with increased restenosis rates.

The association between inflation frequency and restenosis has also been shown by other investigators. Uebis et al (1989) carried out a prospective study to assess whether multiple versus single balloon inflation would decrease restenosis. They found a trend towards higher recurrence in the multiple inflation group. Hearn et al (1991) analysed 699 angioplasty procedures according to procedural variables, and found that repeated inflation was the only variable associated with increased restenosis rate. Similar findings have also been shown by Guiteras Val et al (1987b) and Glazier et al (1989a). The mechanism is unclear, but an explanation is provided by considering the mechanism of coronary angioplasty and its relation to restenosis. Pathological studies have shown that marked vessel damage can occur after coronary angioplasty with endothelial denudation, cracking, splitting or disruption of the atherosclerotic plaque and intima, and stretching or tearing of the media (Castaneda-Zuniga et al, 1980; Block et al, 1981; Baughman et al, 1981). According to the injury hypothesis of atherosclerosis (Ross and Glomset, 1976a; Ross and Glomset, 1976b; Ross, 1981), the above vascular injury leads to platelet adhesion, thrombus formation, monocyte infiltration and finally smooth muscle

proliferation. The degree of platelet adhesion and accumulation at the angioplasty site is directly related to the degree of vascular damage (Wilentz et al, 1987) which then leads to a greater cellular proliferative response and ultimately to restenosis. Repeated dilatation of a vessel during angioplasty could increase the extent of already considerable vascular damage. In addition, cyclical stretching of medial cells has been shown to stimulate increased synthesis of matrix components by arterial smooth muscle cells (Leung et al, 1975).

However, the association between increased inflation frequency and restenosis could simply reflect the greater complexity of the lesions dilated. If these lesions are more difficult to dilate as a result of their complexity, more frequent dilatation would be needed to achieve a satisfactory result. Since complex lesions have an intrinsic propensity to restenose after coronary angioplasty (Myler et al, 1987), this could explain why higher inflation frequencies were observed in lesions that restenosed.

Study Limitations

This study is a retrospective analysis of data and is subject to all the limitations inherent in such a study. Furthermore, a systematic repeat angiography was not undertaken, and repeat angiography was performed only when symptoms recurred or if reversible ischaemia was documented during non-invasive testing of all patients. Hence, the exact angiographic restenosis rate cannot be determined.

8.5 SUMMARY AND CONCLUSIONS

The study presented in this chapter has shown that left anterior descending artery tandem lesion coronary angioplasty can be achieved with a high primary success rate, a low incidence of complications, and good long-term outcome with comparable mortality and morbidity to single lesion coronary angioplasty. The restenosis pattern suggests that systemic or clinical factors do not play an instrumental role in the pathogenesis of restenosis. However, procedure-related variables do appear to influence the incidence of restenosis; specifically, repeated inflations may have an adverse effect.

Table 8.1. Patient and Angiographic Characteristics.

	Number	%
Total	102	100
Male gender	79	77
Mean age (years)	54	SD 8 (range 34-71)
Angina grade		
0/I	8	8
II	26	25
III	33	32
IV	35	35
Previous MI	26	26
Abnormal LV (EF<45%)	19	19
Risk factors		
Smoking	42	41
Family history	36	35
Diabetes mellitus	6	6
Hypertension	18	18
Hypercholesterolaemia	36	35
Emergency procedure	11	11

EF=ejection fraction; LV=left ventricular function; MI=myocardial infarction; SD=standard deviation.

Table 8.2. Primary Success and Complication Rates of all 102 Patients.

	Number	%
Angiographic success	96	94
Procedural success	91	89
Any major complication	5	5
Procedural deaths	0	0
Non-fatal MI	5	5
Emergency CABG	1	1

CABG=coronary artery bypass grafting; Other abbreviations as for Table 8.1.

Table 8.3. Total and Event-free Survival 1 and 5 Years After Coronary Angioplasty for all Patients and Patients With Initially Successful Angioplasty Procedures. Data are % (95% Confidence Interval).

	One year		Five years	
	All patients	Procedural success	All patients	Procedural success
Death; % survival	98.9 (96.8-100)	98.8 (96.5-100)	97.8 (94.7-100)	97.5 (94.1-100)
Death/MI; % freedom	93.1 (88.0-98.1)	97.7 (94.5-100)	90.7 (84.7-96.6)	95.0 (90.1-99.9)
Death/MI/CABG; % freedom	88.0 (81.5-94.5)	97.7 (94.5-100)	79.7 (71.3-88.1)	89.6 (82.6-96.6)
Death/MI/CABG/ PTCA; % freedom	80.8 (72.9-88.8)	90.9 (84.7-97.0)	74.9 (66.0-83.9)	84.2 (76.1-92.3)
CABG; % freedom	94.0 (89.2-98.8)	100 (NA)	86.9 (79.8-94.0)	93.2 (87.4-99.1)
Repeat PTCA; % freedom	89.8 (83.6-95.9)	90.8 (84.7-97.0)	87.3 (80.5-94.2)	88.1 (81.0-95.2)
CABG/repeat PTCA; % freedom	84.8 (77.5-92.0)	90.8 (84.7-97.0)	80.0 (71.8-88.3)	85.5 (77.7-93.3)

PTCA=percutaneous transluminal coronary angioplasty; Other abbreviations as for Tables 8.1 and 8.2.

Table 8.4. Patient-related Variables as Predictors of Angiographic Restenosis.

Variable	Restenosis rates		p Value
	Number	%	
Age (years)			
≤53	13/15	87	0.21
>53	9/15	60	
Gender			
Male	16/19	84	0.10
Female	6/11	55	
Angina class			
0/I/II	6/8	75	1.00
III/IV	16/22	73	
Previous MI			
No	16/22	73	1.00
Yes	6/8	75	
Family history			
No	8/11	73	1.00
Yes	14/19	74	
Smoking			
No	7/12	58	0.21
Yes	15/18	83	
Diabetes mellitus			
No	22/30	73	-
Yes	0/0	40	
Hypertension			
No	15/22	68	0.39
Yes	7/8	88	
Unstable angina			
No	3/4	75	1.00
Yes	19/26	73	
Impaired LV			
No	16/22	73	1.00
Yes	6/8	75	
Hypercholesterolaemia			
No	17/23	74	1.00
Yes	5/7	71	

Abbreviations as for Table 8.1.

Table 8.5. Lesion-related Variables as Predictors of Angiographic Restenosis. Values are mean (SD)

Variables	Restenosis (26 lesions)	No Restenosis (30 lesions)	p Value
Arterial size (millimetre)	3.40 (0.34)	3.27 (0.44)	NS
PrePTCA stenosis (%)	76 (6)	79 (9)	NS
PostPTCA stenosis (%)	16 (9)	16 (6)	NS
PrePTCA diameter (millimetre)	0.83 (0.26)	0.70 (0.28)	NS
PostPTCA diameter (millimetre)	2.85 (0.46)	2.71 (0.41)	NS
Lesion length (millimetre)	6.49 (2.54)	6.75 (2.00)	NS

NS=not significant; Other abbreviations as for Table 8.3.

Table 8.6. Procedure-related Variables as Predictors of Angiographic Restenosis. Value are mean (SD).

Variables	Restenosis (26 lesions)	No restenosis (30 lesions)	p Value
Number of inflations	6.6 (2.4)	4.0 (1.9)	$p<0.001$
Total inflation duration (minutes)	4.6 (1.5)	3.3 (1.9)	$p<0.01$
Longest inflation duration (seconds)	50 (14)	55 (11)	NS
Maximum inflation pressure (atmosphere)	7.2 (2.4)	8.2 (2.1)	NS
Balloon to artery ratio	0.97 (0.08)	0.96 (0.08)	NS

Abbreviations as for Table 8.5.

Table 8.7. Multiple Stepwise Logistic Regression Model to Predict Angiographic Restenosis.

Variable	Coefficient	Standard error	Odds ratio	95% Confidence interval for odds ratio	p Value
Number of inflations	0.61	0.18	1.84	1.28 to 2.63	0.001

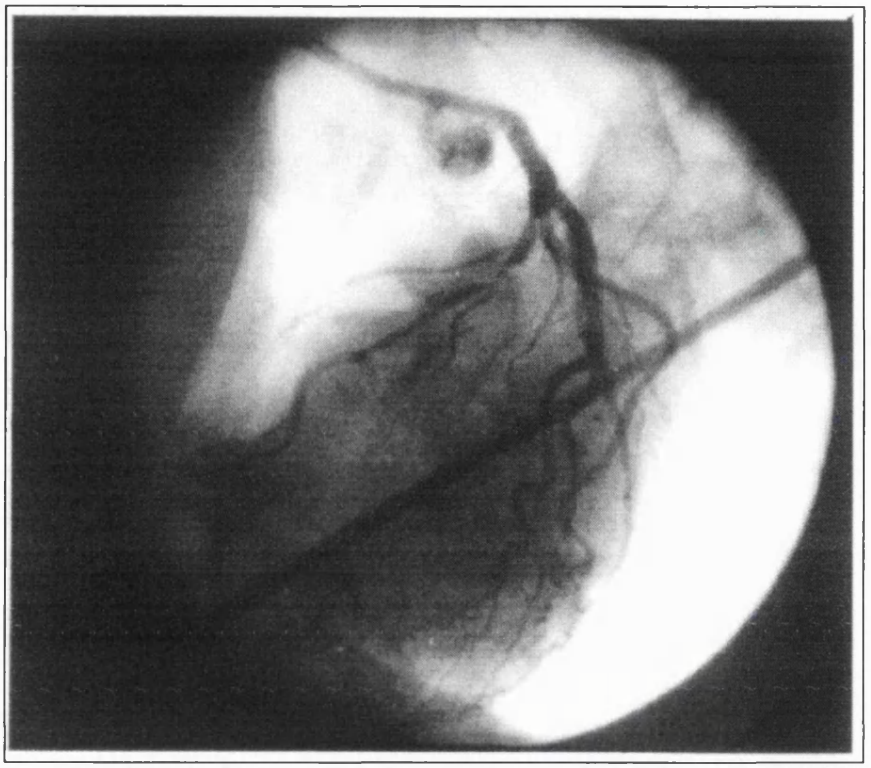

FIGURE 8.1. Sequential lesions (tandem lesion) located in the proximal and mid segments of the left anterior descending artery.

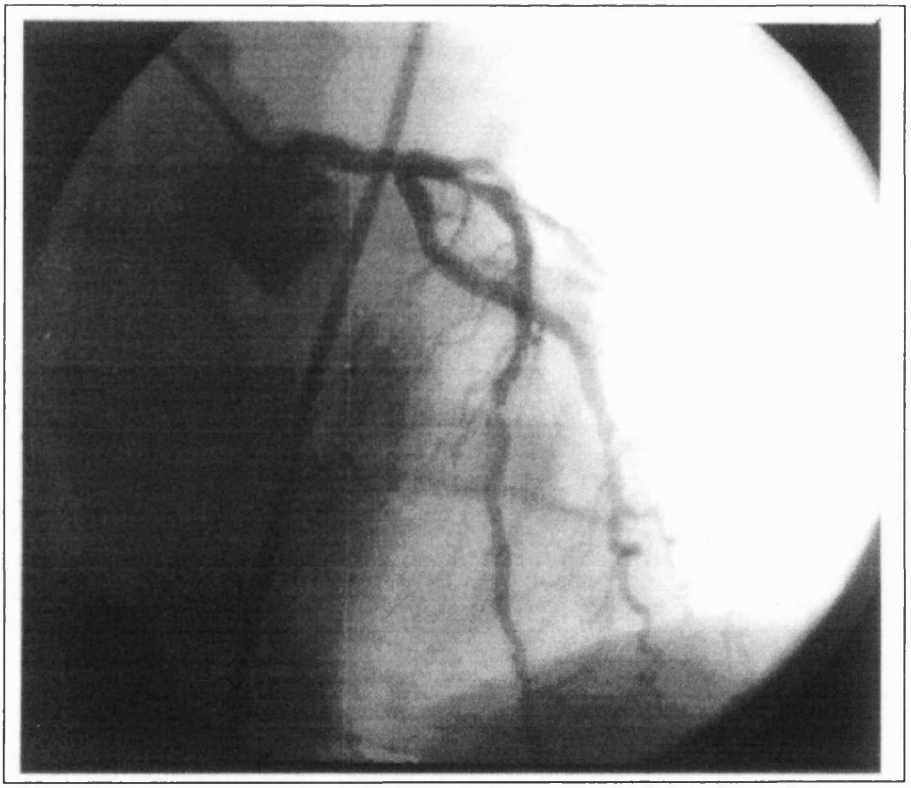

FIGURE 8.2. Sequential lesions (tandem lesion) located in the mid and distal segments of the left anterior descending artery.

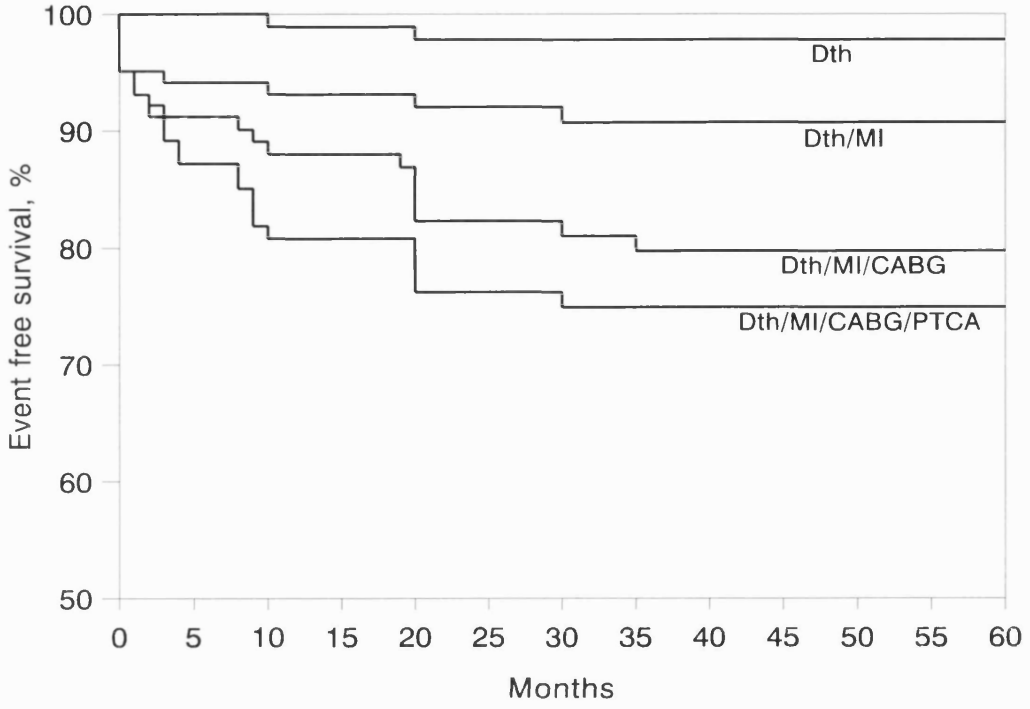

FIGURE 8.3. Plot of cumulative event free survival for all 102 patients. Dth = freedom from death; Dth/MI = freedom from death and myocardial infarction; Dth/MI/CABG = freedom from death, myocardial infarction, and coronary artery bypass grafting; Dth/MI/CABG/PTCA = freedom from death, myocardial infarction, coronary artery bypass grafting, and repeat angioplasty.

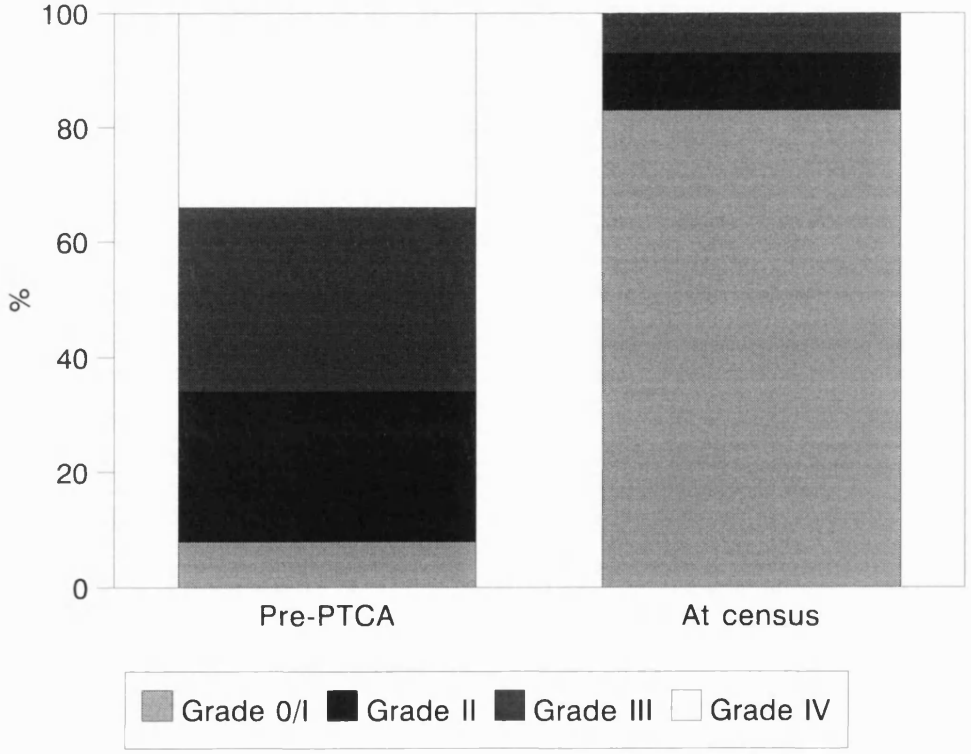

FIGURE 8.4. Angina grade before coronary angioplasty and at census in 100 survivors ($p < 0.001$).

9. *CLINICAL AND LESION MORPHOLOGICAL DETERMINANTS OF ACUTE CORONARY ANGIOPLASTY SUCCESS AND COMPLICATIONS*

9.1 INTRODUCTION

Since the introduction of percutaneous transluminal coronary angioplasty, multiple preprocedural clinical and angiographic characteristics have been identified as determinants of acute angioplasty outcome (Meier et al, 1983; Faxon et al, 1984a; de Feyter et al, 1985; Ischinger et al, 1986; Timmis et al, 1986; Zatzkis et al, 1986; Holmes et al, 1988a; Simpfendorfer et al, 1988; Ellis et al, 1988). On the basis of these observations, the American College of Cardiology/American Heart Association (ACC/AHA) Task Force issued guidelines to make recommendations regarding the appropriate selection of patients for this therapeutic procedure (Ryan et al, 1988). They proposed a classification scheme based on the morphological characteristics of lesions to estimate the likelihood of acute angioplasty success and complications, which were subsequently modified by Ellis et al (1990a) and Myler et al (1992). These classification schemes have proved to be a useful guide for operators in assessing the likelihood of success and risk of complications for a particular lesion, thus assisting in appropriate case selection.

Despite being extended to more complex cases, the continued refinement in balloon angioplasty technique, greater operator experience, and equipment evolution have led to improved acute angioplasty outcome (Kelsey et al, 1984; Myler et al, 1989b; Holmes et al, 1989; Tuzcu et al, 1989; Timmis, 1990). Currently, only a minority of lesions treated with coronary angioplasty have a morphology that would be considered ideal. Two recent reports, 1 from the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry (Detre et al, 1988) and the other from the Cleveland Clinic Foundation (Tuzcu et al, 1989), confirmed the expanded indications for this procedure and documented the improved success rate despite an increased complexity of cases. Further advances in

angioplasty technology have occurred since that period. As a result, the acute angioplasty outcome for all types of lesions has changed significantly and the applicability of these classification schemes in the setting of current angioplasty practice has been questioned.

The study presented in this chapter had 3 objectives: (1) to assess the acute success and complication rates of coronary balloon angioplasty in a recent cohort of patients; (2) to evaluate the validity of previously proposed ACC/AHA and modified classification schemes; (3) to undertake a comprehensive assessment of clinical and lesion morphological characteristics to assess the impact of each individual characteristic on acute angioplasty success and complications, and identify independent determinants of acute angioplasty outcome. Multiple logistic regression models, incorporating lesion specific characteristics to predict acute angioplasty outcome, were developed in the expectation that they could contribute to any new classification schemes that may emerge in the future.

9.2 PATIENTS AND METHODS

(a) PATIENTS

Between January 1990 and March 1993, 729 consecutive patients underwent percutaneous transluminal coronary angioplasty to 994 vessels and 1,248 lesions. Patients who underwent directional atherectomy, or stent implantation, as the primary procedure, were excluded from the study. However, patients who had stent implantation as a rescue procedure after balloon angioplasty were included and were classified as having a failed balloon angioplasty with complications.

The mean age was 57 years (SD 9, range 25 to 83 Years) and 562 (77%) were male (Table 9.1). Three hundred and eighty-seven patients (53%) had a history of previous myocardial infarction and 227 (31%) had impaired left ventricular function. One hundred and thirty-nine patients (19%) had previous coronary artery bypass grafting. Coronary angioplasty was performed as an emergency for unstable angina in 153 patients (21%). Before intervention, 418 patients (57%) had grade III or IV angina. Two hundred and eighty-two patients (39%) had single vessel disease and 447 (61%) had multivessel disease. Risk factors that were present in the patients included smoking (30%), diabetes mellitus (8%), hypertension (18%), and hypercholesterolaemia (50%).

Coronary angioplasty was attempted in 994 vessels including 6 (0.6%) protected left main stems, 390 (39%) left anterior descending arteries and their diagonal branches, 16 (1.6%) intermediate arteries, 268 (27%) circumflex arteries and their obtuse marginal branches, 255 (26%) right coronary arteries, 55 (5.5%) saphenous vein grafts, and 4 internal mammary arterial grafts (0.4%).

(b) ANGIOPLASTY PROCEDURE

Coronary angioplasty was performed according to the protocol described in Chapter 2. The femoral approach was used in all but 3 patients, in whom the brachial approach was used. The techniques used to dilate ostial lesions and total coronary occlusions have already been described in Chapter 3 and Chapter 4. The routine use of long balloons (30 to 40 mm) for dilating long and angulated lesions, and perfusion balloons for prolonged dilatation of proximal lesions, gained wide acceptance by all operators only during the latter part of the study period

(c) STUDY METHODS

Baseline clinical and angiographic characteristics of all 729 patients, 994 vessels, and 1,248 lesions were assessed. Lesion complexity was scored as type A, B or C according to the guidelines published by the ACC/AHA Task Force (Ryan et al, 1988) (Table 1.1). Type B and C lesions were further subcategorised as suggested by Ellis et al (1990a) and Myler et al (1992) (types B1 and C1 = 1 adverse characteristic; types B2 and C2 = 2 or more adverse characteristics).

Definitions

The following definitions were used.

Bifurcation lesion. Lesion involving the bifurcation of a large epicardial coronary artery. Side branches were either protected (using either a single balloon and double-wire technique or the 'kissing balloon' technique) or unprotected (with no guidewire or balloon catheter placed in the side branch).

Calcification. Presence of radioopacity present at the site of the stenosis before contrast medium injection.

Dissection. Presence of angiographically evident intimal or medial damage defined according to the National Heart, Lung, and Blood Institute coronary artery dissection classification (Dorros et al, 1983; Guiteras Val et al, 1987a): type A: nonpersistent radiolucent areas within the lumen of the vessel (tear or flap); type B: parallel tracts caused by extravasation of nonpersisting contrast medium; type C: extravasation of persisting contrast medium; type D: spiral luminal filling defect with delayed runoff of contrast; type E: new, persistent luminal filling defects with delayed antegrade flow; type F: filling defect accompanied by total coronary occlusion.

Distal ectasia. Evidence of abnormal arterial segment expansion beyond the stenosis.

Eccentricity. A ≥75% displacement of the lumen within the lesion in any projection by visual assessment (lumen in the outer one-quarter diameter of the apparent normal lumen).

High grade stenosis. Lesion with a luminal diameter narrowing of 80% to 99% relative to the adjacent normal coronary artery dimension.

Lesion length. This was measured from the proximal to distal shoulder of the lesion in the least foreshortened projection using callipers. Lesions were classified as discrete (< 10 mm), tubular (10 mm to 20 mm), or diffuse (> 20 mm).

Lesion angulation. The vessel angle formed by a centreline through the lumen proximal to the stenosis and extending beyond it, and a second centreline in the straight portion of the artery distal to stenosis. Lesions were classified as nonangulated (<45°), moderately angulated (45° to 90°), or extremely angulated (>90°).

Lesion contour. Presence or absence of irregularities or 'sawtooth' appearance on the luminal surface of the stenosis.

Lesion success. A ≤50% residual diameter stenosis at the dilated site without an abrupt closure. In the event of an abrupt occlusion, even if the reestablishment of flow was possible with prolonged balloon inflation, the lesion was still classified as having had an abrupt closure.

Ostial lesion. A lesion involving the coronary ostium arising within 0.3 cm of the aortic orifice (ie left main stem and right coronary artery ostial stenoses) or left main stem (ie left anterior descending, circumflex, or intermediate ostial stenoses).

Procedural success. This occurred when a patient had at least 1 vessel successfully dilated without a major complication (defined as the occurrence of either death, myocardial infarction, or emergency coronary artery bypass grafting) at any time during hospitalisation (invariably the result of an abrupt occlusion of the vessel being dilated).

Tandem lesion. Sequential lesions in different segments of the artery separated by angiographically disease-free segments.

Thrombus. Presence of intra-luminal filling defects or contrast medium staining within the lumen.

Tortuosity. Lesion accessibility was classified as readily accessible (no or 1 bend $>45°$ proximal to the stenosis), moderately tortuous (presence of 2 bends $>45°$ proximal to the lesion), or excessively tortuous (presence of >2 bends $>45°$ proximal to the stenosis).

Total occlusion. This was defined as 100% luminal diameter narrowing with absence of a visible intraluminal channel. This included vessels with no opacification of the distal segment and vessels with faint distal opacification through antegrade or retrograde collaterals. The duration of occlusion was estimated either from the date of myocardial infarction in the distribution of the occluded vessel, abrupt worsening of angina pectoris, or information provided by sequential angiograms.

Unstable angina pectoris. Angina occurring at rest requiring intravenous medical therapy, including postinfarction angina pectoris.

Vessel success. Successful dilatation of all lesions with luminal diameter narrowing of $>50\%$ present in the vessel without an abrupt occlusion.

(d) STATISTICAL METHODS

Continuous variables are expressed as median value (interquartile range) because of their non-Normal distribution, with the exception that the patients' ages are expressed as mean value (SD). The study patients, vessels, and lesions were divided

into subgroups, both according to initial angioplasty outcome and as to whether an untoward event had occurred. The clinical and angiographic variables analysed as possible correlates of acute angioplasty outcome were compared for each of these outcomes. Categorical variables were compared using the chi-square test or the 2-sided Fisher's exact test.

All variables found to be significantly related to acute angioplasty outcome by univariate analysis were included in a multiple logistic regression analysis. The backwards stepwise selection procedure was used to identify independent predictors of acute angioplasty outcome significant at the 1% level. Analyses were performed with and without the modified ACC/AHA classification scheme included as a predictive variable. Data concerning the technical details of the procedure were also compared: between the ACC/AHA lesion subtypes; between occluded and nonoccluded lesions; and between calcified and noncalcified lesions using the Kruskal-Wallis test.

9.3 RESULTS

(a) PROCEDURAL RESULTS

Of the 729 patients, 202 (28%) underwent multivessel coronary angioplasty and 323 (44%) underwent multilesion coronary angioplasty. A mean of 1.4 vessels and 1.7 stenoses per patient were dilated.

Procedural Outcome

Procedural success was achieved in 657 patients (90.1%). A major in-hospital complication occurred in 24 patients (3.3%). Three patients (0.4%) died and 5 (0.7%) suffered a Q-wave myocardial infarction. Fifteen patients (2.1%) underwent emergency coronary artery bypass grafting, of whom 3 also suffered a Q-wave myocardial infarction, and 3 underwent stent implantation as a "bail-out" measure before surgery. One patient (0.1%) underwent stent implantation for abrupt vessel closure without any untoward clinical sequelae. Forty-eight patients (6.6%) had an uncomplicated procedural failure (Table 9.2).

Predictors of Procedural Outcome

The clinical variables that were analysed to assess their association with procedural outcome are shown in Table 9.3. Coronary angioplasty performed as an emergency procedure for unstable angina, was associated with a lower procedural success ($p=0.002$) and a higher major in-hospital complication rate ($p=0.001$). The presence of multivessel disease was also associated with a lower procedural success rate ($p=0.02$). Multiple logistic regression analysis identified the presence of multivessel disease ($p=0.009$) and presentation with unstable angina ($p<0.001$) as

independent predictors of a lower procedural success. Unstable angina emerged as the only independent predictor of a major in-hospital complication (p=0.001).

(b) VESSEL RESULTS

A total of 994 vessels were dilated. A single lesion was dilated in 804 vessels (81%): 125 type A (13%), 215 type B1 (22%), 258 type B2 (26%), 189 type C1 (19%), and 17 type C2 (1.7%). Two lesions were dilated in 142 vessels (14%): 4 type A-A (0.4%), 32 type A-B (3.2%), 2 type A-C (0.2%), 75 type B-B (7.5%), 13 type B-C (1.3%), and 16 type C-C (1.6%) lesions. Three or more lesions were dilated in 48 (4.8%) vessels: 5 (0.5%) with predominantly type A lesions, 42 (4.2) with predominantly type B lesions, and 1 (0.1%) with predominantly type C lesions.

Vessel Outcome

Angioplasty success was achieved in 888 vessels (89.3%). An untoward event occurred in 24 vessels (2.4%). An uncomplicated angioplasty failure occurred in 82 (8.2%) vessels (Table 9.4).

Predictors of Vessel Outcome

The effects of vessel location, number of lesions dilated in each vessel and lesion morphological combinations on acute angioplasty outcome are shown in Tables 9.4 and 9.5. There was no significant correlation between vessel location or number of lesions dilated in each vessel and acute angioplasty outcome. Vessel success was lower for those with type C lesions (77%, $p<0.001$) or C-C combinations (75%, $p=0.06$).

(c) LESION RESULTS

Coronary angioplasty was attempted in 1,248 lesions, of which 1,157 were nonoccluded, and 91 were totally occluded. Of the 1,157 nonoccluded lesions, 193 (17%) were type A, 333 (29%) were type B1, 420 (36%) were type B2, 192 (17%) were type C1, and 19 (2%) were type C2. Of the 91 total occlusions, 41 (45%) were type B (<3 months) and 50 (55%) were type C (≥3 months).

Lesions Outcome

Angioplasty success was achieved in 1,132 lesions (91%). An abrupt closure occurred in 38 lesions (3%). An uncomplicated angioplasty failure occurred in 78 (6.3%) lesions (Table 9.6).

Evaluation of ACC/AHA and Modified Classification Schemes

The relationship between ACC/AHA classification scheme or its modifications and acute angioplasty outcome is shown in Table 9.6. Acute angioplasty success was achieved in 96%, 93%, and 80% of type A, B, and C lesions, respectively (A versus B, $p=0.13$; B versus C, $p<0.001$; A versus C, $p<0.001$). Comparison of success rates between the lesion subtypes showed the following: A versus B1 (96% versus 95%, $p=0.69$); A versus B2 (96% versus 91%, $p=0.03$); B1 versus B2 (95% versus 91%, $p=0.02$); B2 versus C (91% versus 80%, $p<0.001$); C1 versus C2 (82% versus 67%, $p=0.15$).

An abrupt closure occurred in 2.1%, 2.6%, and 5.0% of type A, B, and C lesions, respectively (A versus B, $p=0.8$; B versus C, $p=0.06$; A versus C, $p=0.11$). Comparison of abrupt closure rates between the lesion subtypes showed the following: A versus B1 (2.1% versus 1.1%, $p=0.46$); B1 versus B2 (1.1% versus

4.0%, p=0.01); B2 versus C1 (4.0% versus 4.2%, p=0.92); C1 versus C2 (4.2% versus 14%, p=0.04). The results are summarised in Figures 9.1 and 9.2.

Effect of Lesion Morphology on Lesion Outcome

The correlation between specific lesion morphology and angioplasty outcome is shown in Table 9.7. Univariate analysis of 13 lesion morphological features showed that angioplasty success was less common with longer lesions (<10 mm=95%, 10 mm to 20 mm=85% and >20 mm=78%, p<0.001), highly angulated lesions (<45°=94%, 45° to 90°=88%, and >90°=83%, p=0.005), lesions containing calcium (74% versus 94%, p<0.001), and lesions containing thrombus (74% versus 93%, p<0.001). Abrupt closure was also more common with longer lesions (<10 mm=1.5%, 10 mm to 20 mm=11%, and >20 mm=16%, p<0.001), highly angulated lesions (<45°=2.2%, 45° to 90°=8.8%, and >90°=13%, p<0.001), calcified lesions (14% versus 2.5%, p<0.001), and lesions containing thrombus (8.7% versus 3.1%, p=0.036). Uncomplicated failure was more common with unprotected bifurcation lesions (no bifurcation=3.8%, protected=3.0%, and unprotected=11.5%, p=0.02), lesions located at the proximal segment of the vessel (proximal=5.8%, mid=3.0%, and distal=0.8%, p=0.01), calcified lesions (12% versus 3.4%, p<0.001), and lesions containing thrombus (17% versus 3.5%, p<0.001).

Effect of Stenosis Severity on Lesion Outcome

Coronary angioplasty of total occlusions was associated with a lower success (66% versus 93%, p<0.001) and a higher uncomplicated failure rate (34% versus 4.0%, p<0.001) when compared with nonoccluded lesions. However, the abrupt closure rate was also lower (0% versus 3.3%, p=0.05). Occlusions that were ≥3 months old (type C lesion) had a lower success (57% versus 76%, p=0.05) and a higher

uncomplicated failure rate (43% versus 24%, p=0.05) than occlusions <3 months old. In nonoccluded lesions, when the subgroups of lesion severity were compared, significant differences in the acute success (89% versus 98%, p<0.001), uncomplicated failure (5.8% versus 1.2%, p<0.001), and complication rates (5.0% versus 0.5%, p<0.001) were found between high grade stenoses (80% to 99%) and all other subgroups (Table 9.8).

Independent Determinants of Lesion Outcome

Excluding total occlusions, multiple stepwise logistic regression analysis identified increased lesion length (p=0.001), calcified lesions (p<0.001), high grade stenoses (p<0.001) and the presence of thrombus (p=0.002) as independent predictors of angioplasty failure. Increased lesion length (p<0.001), increased lesion angulation (p<0.001), high grade stenoses (p<0.001), and calcified lesions (p=0.007) emerged as independent predictors of an abrupt closure. The presence of thrombus (p=0.002) and high grade stenosis (p<0.001) also emerged as independent predictors of an uncomplicated failure (Tables 9.9 to 9.11; Figures 9.3 to 9.12). Analyses were performed with and without the modified ACC/AHA classification scheme included as a predictive variable, which was independently predictive of angioplasty success but not of an abrupt closure. When the modified ACC/AHA classification scheme was forced in the regression model, calcified lesions, high grade stenosis, and the presence of thrombus were still independently predictive of angioplasty failure. The same independent predictors of an abrupt closure and uncomplicated failure were retained.

With these models, the estimated probability of lesion success is: $\mathbf{p = e^y/(1+e^y)}$ where e = 2.72, and y = (−0.79 × lesion length of 10 mm to 20 mm) + (−1.24 × lesion length of >20 mm) + (−1.33 × calcium) + (−1.28 × thrombus) + (−1.65 ×

high grade stenosis) + 4.34. In the case of the estimated probability of absence of an abrupt closure, y = (−1.80 × lesion length 10 mm to 20 mm) + (−2.33 × lesion length >20 mm) + (−1.39 × angulation of 45° to 90°) + (−1.91 × angulation of >90°) + (−1.19 × calcium) + (−1.99 × high grade stenosis) + 6.33. In the case of the estimated probability of an uncomplicated failure, y = (1.54 × thrombus) + (1.55 × high grade stenosis) + (− 4.49).

Lesion length of 10 mm to 20 mm was scored 1 for presence and 0 for absence; lesion length of >20 mm was scored 1 for presence and 0 for absence; angulation of 45° to 90° was scored 1 for presence and 0 for absence; angulation of >90° was scored 1 for presence and 0 for absence; calcium was scored 1 for presence and 0 for absence; thrombus was scored 1 for presence and 0 for absence.

(d) EFFECT OF ANGIOGRAPHIC DISSECTION ON ABRUPT CLOSURE

Of the 1,157 nonoccluded lesions, angiographically visible dissection was seen in 221 lesions (19%) after balloon dilatation. Severity of dissection was classified according to the NHLBI criteria: 171 were type A or B, and 50 were type C to F. Presence of an angiographically visible dissection was a strong predictor of abrupt closure (8.1% versus 2.1%, $p<0.001$). However, when the dissection morphological subtypes were compared, a significant difference in the abrupt closure rate was found between type A and B dissections and all other subtypes. Type A and B dissections were not associated with an increased risk of abrupt closure when compared with lesions without angiographic dissection (1.2% versus 2.1%, $p=0.56$). The increased abrupt closure rate was a result of types C to F dissections (32% versus 2.1%, $p<0.001$).

(e) TECHNICAL CONSIDERATIONS

The technical variables involved during coronary angioplasty are presented in Table 9.12. Type C lesions required more frequent inflations ($p=0.04$) than type A or B lesions. Occluded lesions required more frequent inflations ($p=0.001$) and longer total inflation duration ($p<0.001$) than nonoccluded lesions. Calcified lesions not only required more frequent inflations ($p=0.001$) and a longer inflation duration ($p=0.007$), they also need a higher inflation pressure ($p<0.001$) than noncalcified lesions. The balloon/artery ratio did not differ significantly between the various subgroups and was not predictive of an abrupt closure (<0.9 = 2.2%, 0.9 to 1.1 = 1.2%, >1.1 = 2.0%, $p=0.54$). Mean balloon/artery ratio was 1.02 (SD=0.14) in lesions with an abrupt closure and 1.03 (SD 0.14) in lesions without ($p=0.83$).

9.4 DISCUSSION

Since its introduction, there has been a great impetus for investigators to correlate clinical and anatomical variables with acute angioplasty outcome so that patient selection can be improved. Multiple clinical and angiographic indices have thus been identified, and the ACC/AHA Task Force, responding to these observations, categorised lesion characteristics on the basis of the estimated success rate and relative risk of complication (Ryan et al, 1988). The guidelines reflect angioplasty experience and opinions between 1986 and 1988. Since that time there have been dramatic advances in balloon angioplasty technology and techniques (Kelsey et al, 1984; Myler et al, 1989; Holmes et al, 1989; Tuzcu et al, 1989; Timmis, 1990; Tenaglia et al, 1992; Banka et al, 1993), which have had a significant and favourable impact on acute angioplasty outcome. Lesions that were previously considered suboptimal, or unfavourable for the procedure are now increasingly attempted. As a result, the influence of specific clinical and lesion morphological characteristics on acute angioplasty outcome has changed significantly.

Two studies have formally examined the validity of the classification scheme, 1 representing angioplasty experience between 1986 and 1987 (Ellis et al, 1990a) and the other between 1990 and 1991 (Myler et al, 1992). This study reports on an extensive and more recent experience.

Effect of Clinical Variables on Acute Angioplasty Outcome

The procedural success and major in-hospital complication rates achieved in this study are similar to those recently reported (Anderson et al, 1985; Detre et al, 1988; Ellis et al, 1990a; Myler et al, 1992). Clinical presentation with unstable angina was strongly correlated with adverse procedural outcome, in comparison to

patients with stable angina pectoris. This too is consistent with the findings of other investigators (Timmis et al, 1987; de Feyter et al, 1988; Myler et al, 1990). Previous balloon angioplasty studies in patients with unstable angina have reported widely differing outcomes, with procedural success rates ranging from 61% to 93% and complication rates from 2% to 20% (Williams et al, 1981; Faxon et al, 1983; Meyer et al, 1983; Quigley et al, 1986; Safian et al, 1987; de Feyter et al, 1987; Timmis et al, 1987; de Feyter et al, 1988; Perry et al, 1988; Plokker et al, 1988; Kamp et al, 1989; Myler et al, 1990). Although the underlying pathological change in unstable angina pectoris is spontaneous plaque fissuring or rupture (Davies and Thomas, 1985), there is no universally accepted clinical definition. Hence, previous studies have included patients with a wide variety of clinical presentation, and this may be the cause for the disparate results reported. Although more recent reports have demonstrated improved success rates in unstable angina, the abrupt closure rates remain higher than for stable angina pectoris (Timmis et al, 1987; de Feyter et al, 1988; Perry et al, 1988; Plokker et al, 1988; Myler et al, 1990; Kamp et al, 1989).

The only other clinical variable that was correlated with a lower procedural success in the present series was the presence of multivessel disease. None of the other 12 clinical characteristics analysed was found to be associated with procedural outcome despite associations shown in previous studies. This probably reflects improved case selection in these high risk patients, on the baisi of knowledge gained from previously published reports on the effect of these clinical variables on acute angioplasty outcome.

Effect of Stenosis Location on Acute Angioplasty Outcome

In the present study, neither vessel nor lesion location emerges as an important variable in determining the acute outcome of coronary angioplasty. Although earlier studies have shown unfavourable results in the dilatation of stenoses located in the left circumflex coronary artery or at distal vessel sites (Faxon et al, 1984a), relatively nonsteerable angioplasty equipment was used in those days, resulting in difficulty in reaching and crossing such lesions. The entire epicardial coronary vasculature is now accessible to coronary angioplasty by the technical advances made possible by steerable, low profile, and more trackable catheter systems (Tuzcu et al, 1989; Anderson et al, 1985). More recently, Savage et al (1991b) reported that right coronary artery location significantly reduced the primary success rate. Hermans et al (1992a) and Cowley et al (1984a) also reported a significantly higher dissection rate in right coronary artery lesions. The present study does not support these findings. Although the occurrence rate is low, certain lesion types (ie type C2) and tandem lesion combinations (ie type C-C) appear to have an adverse effect on both the success and abrupt closure rate.

Effect of Lesion Morphology on Acute Angioplasty Outcome

Of all the morphological characteristics that were cited in the ACC/AHA classification scheme, only increased lesion length, lesion calcification, and presence of thrombus were identified as independent predictors of acute angioplasty failure. Increased lesion length, increased lesion angulation and lesion calcification were predictive of an abrupt closure. Although high grade stenosis was not included in the original classification, its presence significantly reduced the likelihood of angioplasty success and increased the likelihood of an abrupt closure in the present series (Figures 9.3 to 9.12). Even with the modified ACC/AHA classification scheme included in the regression analyses, similar results were obtained, indicating

that these variables were highly important correlates of acute angioplasty outcome. None of the other variables analysed (ie eccentricity, accessibility, contour, lesion location, and ectasia) contributed significantly to the regression models.

Lesion length. Meier et al (1983) were among the first to identify long lesion morphology as a marker of increased risk. Bredlau et al (1985a) found an increased risk following coronary angioplasty when lesion length exceeded 10 mm. More recently, Ellis et al (1988) identified lesion length equal to or exceeding 2 luminal diameters as a predictor for acute closure resulting in death, myocardial infarction, or emergency repeat angioplasty. The adverse impact of increased lesion length on angioplasty outcome has also been shown by other investigators (Cowley et al, 1984a; Bentivoglio et al, 1984; Detre et al, 1990; Ellis and Topol, 1990). Since longer lesions have a larger amount of atherosclerotic material, dissections occur more readily (Zollikofer et al, 1984), and therefore increase the chance of abrupt closure. In addition, the use of short balloons in these lesions may result in an increased risk of dissection in diseased segments immediately adjacent to the ends of the balloon.

In some recent reports, lesion length has not been found to be correlated with acute angioplasty outcome. Goundreau et al (1991) found that long lesions could be successfully treated with coronary angioplasty. Myler et al (1992) identified lesion length as a predictor of acute angioplasty failure but not a predictor of an abrupt closure. Ellis et al (1990a) and Savage et al (1991b) did not find any correlation between lesion length and acute angioplasty outcome. This may in part be attributed to the increasing use of long balloons (30 mm to 40 mm), which would allow the entire diseased segment to be adequately covered, thus reducing the incidence of dissection. The increased balloon length also afford a more gradual transition in

arterial stretch at the plaque edge-normal artery junction, a common site of dissections, as well as providing more even dispersement of pressure (Zollikofer et al, 1984). Preliminary results with long balloons have been encouraging (Slack and Pinkerton, 1987; Brymer et al, 1991; Savas et al, 1992; Zidar et al, 1992; Tenaglia et al, 1993), and if substantiated by further clinical evaluation, their increasing utilisation may overcome the adverse effect of lesion length on acute angioplasty outcome.

Lesion Angulation. The adverse influence of lesion angulation on acute angioplasty outcome has been shown by previous investigators (Ischinger et al, 1986; Ellis et al, 1988; Ellis et al, 1990a; Ellis and Topol, 1990; Hermans et al, 1992a). The underlying mechanism appears to be arterial dissection from noncoaxial stress caused by the straightening of the angulated atherosclerotic segment when the balloon catheter is inflated. We generally use gradual inflation with low pressure to dilate highly angulated lesions.

Several new advances in angioplasty technology have shown promising results in improving acute angioplasty outcome. There has been growing enthusiasm for the use of long balloons (30 mm to 40 mm) in treating angulated lesions, regardless of the lesion length. Longer balloons appear to have better conformability compared to shorter balloons, and favourable results on their use have been reported (Savas et al, 1992). In addition, certain balloon material, in particular polyethylene terephthalate, confers superior conformable properties, hence reducing straightening stress and risk of dissection (Ellis and Topol, 1990). Lastly, a specially designed balloon with a preshaped angle of 135° to 145° at its midportion has also been developed for angulated stenosis. This balloon reduces the trauma that may result from straightening of the angled segment. Results on its use have been encouraging

(Slack and Pinkerton, 1987; Vivekaphirat et al, 1989; Bajwa et al, 1990). However, angled balloon catheters have a higher profile and are less trackable than conventional balloon systems, frequently restricting their application to proximal stenoses in large calibre vessels. The routine use of long and conformable balloons has gained wide acceptance by all operators at our institution only during the latter part of the study period. This may explain the significantly lower success rate and an unacceptably high abrupt closure rate in lesions with angulation of $\geq 90°$ in the present series.

Calcification. Calcified lesions, by virtue of their rigidity, often require multiple balloon inflations at higher pressures to eliminate the "waist" of the stenoses. Animal studies have shown that vessels exposed to high inflation pressure had a significantly higher incidence of mural thrombus, dissection and medial necrosis when compared to those exposed to low inflation pressure (Sarembock et al, 1989). Frequently, the contralateral, plaque-free wall segment is stretched without cracking or compressing the calcified atheroma; elastic recoil of the normal wall segment ensues and a high grade residual stenosis remains. Furthermore, if the burst pressure is exceeded, rupture of the balloon catheter in the coronary artery can lead to extensive coronary dissection, coronary rupture, and balloon entrapment. These factors may have led to the unfavourable outcome observed in the present and previous studies (Faxon et al, 1984a; Bredlau et al, 1985a; Tuzcu et al, 1988; Savage et al, 1991b; Myler et al, 1992; Sharma et al, 1993). Polyethylene terephthalate balloons have a low compliance and allow a very high inflation pressure, with little overexpansion of the balloons. Reports on the use of these high pressure balloons have shown encouraging results, and may be the optimal type of balloon for calcified lesions (Bush et al, 1991; Willard et al, 1991).

Thrombus. Preexisting intraluminal thrombus is a marker of lesion instability, and has been shown to pose an increased risk to angioplasty (Mabin et al, 1985b; Surgue et al, 1986; Deligonul et al, 1988b; Ellis et al, 1988; Detre et al, 1990; de Feyter et al, 1991; Savage et al, 1991b; Myler et al, 1992). Although the frequency of occurrence in the present study was low (<4%), its presence was strongly correlated with unsuccessful angioplasty and abrupt closure. The association of intracoronary thrombus with unstable angina is well established (Davies and Thomas, 1985; Falk, 1985; Fuster et al, 1988). Virtually all of the intracoronary thrombus seen in the present study occurred in patients who presented with unstable angina. The mechanism of acute vessel closure is due to balloon trauma to the vessel wall, exposing collagen and thrombotic factors and releasing vasoactive substances, causing thrombus propagation (Weiss, 1975). Others have suggested that it may simply be a marker for a hypercoagulable state (Chesebro et al, 1981). Aggressive periprocedural antiplatelet and anticoagulant therapy has been shown to reduce the risk of abrupt occlusion in some studies (Surgue et al, 1986; Laskey et al, 1990; Lukas et al, 1990) but not all (Deligonul et al, 1988b). Non-randomised studies have also suggested an important role for intracoronary thrombolytic therapy when thrombus is present prior to coronary angioplasty (Chapekis et al, 1991; Pavlides et al, 1991).

Stenosis Severity. In the present study, the presence of a high grade stenosis appears to adversely affect acute angioplasty outcome, reducing the chance of success and increasing the risk of abrupt closure, and confirms previous findings (Dorros et al, 1983; Faxon et al, 1984a; Ellis et al, 1990a; Detre et al, 1990; Savage et al, 1991b). Coronary angioplasty of total occlusions, especially those that were ≥3 months old, was associated with a significantly lower success rate but also

a lower risk of complication. The success and complication rates of coronary angioplasty of chronic total occlusions have already been discussed in Chapter 3.

Evaluation of the ACC/AHA and Modified Classification Schemes

Angioplasty Success. Given that 79% were either type A or B lesions, the ACC/AHA classification scheme was unable to stratify the majority of the lesions according to the probability of success. There was no significant difference in the success rate between type A and B lesions, and both were associated with a success rate of >90%. However, type C lesions had a significantly lower success rate of 80%. The modified ACC/AHA classification scheme, by subtyping type B lesions, as suggested by Ellis et al (1990a), was able to identify a subgroup of type B2 lesions with a significantly lower success rate than either type A or B1 lesions. Although further subtyping of type C lesions, as suggested by Myler et al (1992), identified a subgroup of type C2 lesions, of which only 67% were successfully dilated, this was not significantly different from the success rate achieved with type C1 lesions.

Hence, the modified ACC/AHA classification scheme, as suggested by Ellis et al (1990a), appears to provide useful lesion stratification into categories of high (types A and B1, ≥95%), intermediate (type B2, 91%) and low (type C, 80%) probability of success. However, lesions that were categorised as having an intermediate probability of success (type B2) were nevertheless associated with a success rate >90%. Lesions that were categorised as having a low probability of success (type C) had a success rate of 80%, which is much higher than the 60% suggested by the ACC/AHA Task Force.

Angioplasty Complications. In this study, the ACC/AHA classification scheme provided a poor stratification of lesions into risk groups of abrupt closure. There was no difference in the abrupt closure rate among type A, B, or C lesions. However, the modified scheme, by subtyping type B lesions, as suggested by Ellis et al (1990a), identified a subgroup of type B2 lesions with a significantly higher abrupt closure rate than type B1 lesions. Further subtyping of type C lesions, as suggested by Myler et al (1992), identified a subgroup of type C2 lesions with a significantly higher abrupt closure rate than type C1 lesions.

Hence, the modified classification scheme, as suggested by Myler et al (1992), provided useful stratification of lesions into categories with low (types A and B1, ≤ 2.1%), intermediate (types B2 and C1, ≤4.2%), and high (type C2, 14%) risk of abrupt closure. Although both the low and intermediate risk categories were associated with an abrupt closure rate of <5%, the high risk lesions had an unacceptable abrupt closure rate of 14%.

A classification scheme should be an aid for ordering separate but closely related data. It should also allow the identification of lesions which have an unacceptably low probability of success or high risk of abrupt closure, so that an alternative mode of revascularisation could be considered. With these proviso, this study suggests that the ACC/AHA classification scheme appears to be outdated, perhaps because of improvement in angioplasty technique and equipment evolution, and this was predicted by the initial committee (Faxon et al, 1992a). The modified classification schemes seem to fulfil this role, in allowing useful stratification of stenoses into categories with significantly different, albeit closely related, outcomes. However, the lesion subtypes under the categories stratified according to probability of success and those according to risk of abrupt closure did not correlate with each other.

Furthermore, the estimated success and risk ascribed to each category may need to be amended to be applicable to current practice since they are not typical of results that are achievable with contemporary balloon technology.

More importantly, although listed under the same category in the ACC/AHA classification scheme, the impact of each individual morphological characteristic on angioplasty outcome is not equal. In this series, type B characteristics were associated with success rates ranging from 74% (calcified stenosis) to 95% (protected bifurcation stenosis), and abrupt closure rates ranging from 2.2% (protected bifurcation stenosis) to 14% (calcified stenosis). Similarly, type C characteristics were associated with success rates ranging from 57% (chronic occlusions) to 88% (old saphenous grafts), and abrupt closure rates ranging from 0% (chronic occlusions) to 16% (lesion length >20 mm). Similar findings have been shown by other investigators (Myler et al, 1992). High grade stenosis, although not listed in the ACC/AHA classification scheme, was a significant independent predictor of acute angioplasty outcome, consistent with the findings of Ellis et al (1990a). It appears that the original ACC/AHA classification scheme grouped a motley array of lesions with heterogeneous morphological patterns and very dissimilar angioplasty results. Hence, some of the morphological characteristics listed in the original ACC/AHA classification scheme may need to be deleted or recategorised, and others incorporated when the guidelines are updated in the light of recent reports and the present study.

Effect of Angiographic Dissection on Abrupt Closure

Although coronary angioplasty results in an angiographically visible dissection in 20% to 45% (Guiteras Val et al, 1987a; Quigley et al, 1989a) of the stenoses dilated, ischaemic complications occur in only 4% to 11% of cases (Marquis et al,

1984; Ellis et al, 1988; Ryan et al, 1988; Detre et al, 1990). However, given the grave consequences that are associated with abrupt closure, and the availability of new treatment modalities such as stents (Sigwart et al, 1988), perfusion balloon angioplasty (Leitschuh et al, 1991), laser balloon angioplasty (Jenkins and Spears, 1990), and coronary atherectomy (Lee et al, 1990), the ability to distinguish those dissections that are "therapeutic" (minor dissections), from those that are likely to cause major ischaemic complications (major dissections), could have important clinical implications. In a recent review, Waller et al (1992) have attempted to make this distinction with histological descriptors. Although this method provides an accurate definition of dissections, it is not feasible in the vast majority of patients. Intravascular ultrasound has also provided a unique opportunity to detect and assess the severity of dissections, but this new technology is not widely available (Tobis et al, 1989).

Various angiographic parameters have been used to characterise the severity of dissections. Previous studies have indicated that, in the presence of an angiographic dissection, residual diameter stenosis, dissection length, and certain morphological features are correlated with an adverse outcome (Black et al, 1989; Huber et al, 1991). In the present study, dissection type C to F were associated with an increased incidence of abrupt closure, but not dissection types A and B, as are consistent with the findings of Huber et al (1991). Hence, in conjunction with the patient's symptoms, electrocardiographic changes and haemodynamic status, the NHLBI coronary artery dissection criteria provides an additional method for guiding the management of patients with dissection. Recently, progressive coronary dilation using incremental balloon size, and prolonged inflation, have both been shown to reduce the incidence of dissection and acute closure (Tenaglia et al, 1992; Ohman et al, 1992; Banka et al, 1993).

Technical Considerations

Despite the greater technical requirement, a less satisfactory final angiographic result was seen with calcified, totally occluded and type C stenoses, reflecting the complexity of these lesions. As previously discussed, more dilatations, higher inflation pressures, and longer total inflation times were necessary for rigid, calcified lesions when compared to noncalcified lesions. More frequent dilatations and longer total inflation times were also seen in totally occluded lesions, but the pressures needed were no different to those of nonoccluded lesions, suggesting that the consistency of occluded lesions was no different in the absence of calcification. More inflation frequency was also seen with type C lesions. In contrast to previous studies (Roubin et al, 1988; Nichols et al, 1989), the balloon/artery ratio was not correlated with angioplasty complications. This probably reflects careful balloon sizing by operators on the basis of the findings of previous investigators.

Study Limitations

Although this study reports on a nonselected, consecutive series of patients, it is a retrospective analysis of data and is subject to the limitations inherent in any retrospective study. Ideally, the ACC/AHA classification scheme and its modifications should be validated prospectively. The frequency of occurrence of some of the variables analysed as determinants of angioplasty outcome was low. Diabetes mellitus was present in only 53 patients (7%), distal ectasia was present in only 42 lesions (3%), and only 58 (5%) were graft lesions. These variables may have been significant determinants of acute angioplasty outcome had a greater number of patients been present in the study. Multiple subgroup comparisons were made, and the possibility of a type II statistical error should be acknowledged.

9.5 SUMMARY AND CONCLUSIONS

With currently available angioplasty technology and adequate operator experience, >90% of coronary stenoses can be successfully dilated with balloon angioplasty with an acceptable complication rate of <5% (Anderson et al, 1985). This study has shown that the ACC/AHA and modified classification schemes, although useful tools in aiding patient stratification, need to be amended to be applicable to current angioplasty practice. First, the ascribed estimated success and risk for each category may need to be revised in light of the improved results achieved with recent technological advances. Second, some of the original lesion characteristics listed in the ACC/AHA classification scheme may need to be deleted or recategorised, given the significant change in the morphological predictors of acute angioplasty outcome. Third, previously unconsidered lesion characteristics may need to be incorporated into the scheme in light of recent reports and the present study. Even with these modifications, there exist multiple problems intrinsic to a classification scheme. Therefore, identifying and analysing specific lesion morphological characteristics, rather than applying a simple lesion classification score when evaluating angioplasty outcome, may be more useful because they provide a more precise profile of the lesion and allow better patient stratification and selection. In support of this, the present study has shown that the probability of acute angioplasty success and complication can be predicted from easily identifiable lesion morphological features. Careful case selection, with specific attention to these morphological features, is all important in ensuring continued improvement in acute angioplasty outcome.

New devices have recently been introduced as an alternative to balloon angioplasty for specific lesion characteristics, although the initial enthusiasm has diminished as experience was gained (Myler, 1992). There remain some morphological

characteristics where the current results from balloon angioplasty could be further improved, especially long, calcified, and angulated lesions. Whether these lesions should be treated with new balloon angioplasty technology (eg long balloons, angled balloons, and high pressure balloons) or new devices (eg rotational atherectomy, directional atherectomy, and laser angioplasty) (Iyer et al, 1991; Ellis et al, 1991; Cook et al, 1991) will need to be resolved by randomised trials. Until then, any new devices that may be introduced for the nonoperative revascularisation of these complex lesions will need to be compared with this contemporary experience, with attention given to case selection and lesion morphological characteristics related to procedural success.

Table 9.1. Patient and Angiographic Characteristics.

	Number	%
Total	729	100
Mean age (years)	57	SD 9 (range 25-83)
Male gender	562	77
Angina grade		
0/I	109	15
II	202	28
III	188	26
IV	230	31
Previous MI	387	53
Abnormal LV (EF<45%)	227	31
Previous CABG	139	19
Risk factors		
Smoking	218	30
Family history	282	39
Diabetes mellitus	57	8
Hypertension	133	18
Hypercholesterolaemia	366	50
Emergency procedure	153	21
Multivessel disease	447	61
Single vessel PTCA	527	72
Multivessel PTCA	202	28
Multilesion PTCA	323	44

CABG=coronary artery bypass grafting; EF=ejection fraction; LV=left ventricular function; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty; SD=standard deviation.

Table 9.2. Primary Success and Complications Rates of all 729 Patients.

	Number	%
Procedural success	657	90.1
Any major complication	24	3.3
Procedural death	3	0.4
Non-fatal Q-wave MI	5	0.7
Emergency CABG	15	2.1
'Bail-out' stent	1	0.14

Abbreviations as for Table 9.1.

Table 9.3. Clinical Characteristics Predictive of Procedural Success, Uncomplicated Failure, and Complications. Value are Number (%).

Variable	Number	Success	p Value	UAF	p Value	Compl.	p Value
Gender							
Male	562	511 (91)		34 (6.0)		17 (3.0)	
Female	167	146 (87)	NS	14 (8.4)	NS	7 (4.2)	NS
Angina grade III/IV							
Yes	418	376 (90)		25 (6.0)		17 (4.0)	
No	311	281 (90)	NS	23 (7.4)	NS	7 (2.3)	NS
Previous MI							
Yes	387	343 (89)		29 (7.5)		15 (3.9)	
No	342	314 (92)	NS	19 (5.6)	NS	9 (2.6)	NS
Previous CABG							
Yes	139	121 (87)		16 (12)		2 (1.4)	
No	590	536 (91)	NS	32 (5.4)	0.009	22 (3.7)	NS
Abnormal LV							
Yes	227	198 (87)		18 (7.9)		11 (4.8)	
No	502	459 (91)	NS	30 (6.0)	NS	13 (2.6)	NS
Emergency procedure							
Yes	153	127 (83)		14 (9.2)		12 (7.8)	
No	576	530 (92)	0.002	34 (5.9)	NS	12 (2.1)	0.001
Multivessel disease							
Yes	447	394 (88)		34 (7.6)		19 (4.3)	
No	282	263 (93)	0.02	14 (5.0)	NS	5 (1.8)	NS
Smoking							
Yes	218	191 (88)		17 (7.8)		10 (4.6)	
No	137	120 (88)	NS	12 (8.8)	NS	5 (3.6)	NS
Ex	374	346 (93)		19 (5.1)		9 (2.4)	
Diabetes mellitus							
Yes	57	53 (93)		4 (7.0)		0 (0)	
No	672	604 (90)	NS	44 (6.5)	NS	24 (3.6)	NS
Family history							
Yes	282	253 (90)		18 (6.4)		11 (3.9)	
No	447	404 (90)	NS	30 (6.7)	NS	13 (2.9)	NS
Hypertension							
Yes	133	118 (89)		8 (6.0)		7 (5.3)	
No	596	539 (90)	NS	40 (6.7)	NS	17 (2.9)	NS
Hyper-cholesterolaemia							
Yes	366	333 (91)		21 (5.7)		12 (3.3)	
No	363	324 (89)	NS	27 (7.4)	NS	12 (3.3)	NS

CABG = coronary artery bypass grafting, Compl. = complications, LV = left ventricular function, MI = myocardial infarction, UAF = uncomplicated angioplasty failure.

Table 9.4. Angioplasty Success and Complications According to Vessel Location and Number of Lesions in Each Vessel. Values are Number (%).

Vessel	Number	Success	UAF	Abrupt closure
LMS	6	6 (100)	0 (0)	0 (0)
LAD	390	346 (89)	27 (7)	17 (4)
INT	16	16 (100)	0 (0)	0 (0)
CX	268	242 (90)	23 (9)	3 (1)
RCA	255	226 (89)	26 (10)	3 (1)
SVG/IMA	59	52 (88)	6 (10)	1 (2)
No. of lesions dilated in each vessel				
1	804	713 (89)	73 (9.1)	18 (2.2)
2	142	132 (93)	7 (4.9)	3 (2.1)
3	36	34 (94)	1 (2.8)	1 (2.8)
4	10	7 (70)	1 (10)	2 (20)
6	2	2 (100)	0 (0)	0 (0)
Total	994	888 (89)	82 (8)	24 (2)

CX = circumflex, INT = intermediate, LAD = left anterior descending, LMS = left main stem, RCA = right coronary, SVG/IMA = saphenous vein graft/internal mammary artery graft, UAF = uncomplicated angioplasty failure.

Table 9.5. Effect of Lesion Morphological Combinations on Acute Angioplasty Outcome of all 994 vessels. Values are Number (%).

Lesion combination	Number	Success	UAF	Abrupt closure
A	125	119 (95)	5 (4.0)	1(0.8)
B1	216	198 (92)	12 (5.6)	6 (2.8)
B2	259	233 (90)	20 (7.7)	6 (2.3)
C1	186	152 (82)	30 (16)	4 (2.1)
C2	18	11 (61)	6 (33)	1 (5.6)
A-A	4	4 (100)	0 (0)	0 (0)
A-B	32	29 (91)	1 (3.1)	2 (6.3)
A-C	2	2 (100)	0 (0)	0 (0)
B-B	74	72(97)	2 (2.7)	0 (0)
B-C	14	13 (93)	1 (7.1)	0 (0)
C-C	16	12 (75)	3 (19)	1 (6.3)
Mainly A	5	4 (80)	1 (20)	0 (0)
Mainly B	42	38 (90)	1 (2.4)	3 (7.1)
Mainly C	1	1 (100)	0 (0)	0 (0)
Total	994	888 (89)	82 (8)	24 (2)

Abbreviations as for Table 9.3.

Table 9.6. Effect of ACC/AHA and Modified Classification Schemes on Acute Angioplasty Outcome on all 1248 Lesions. Values are Number (%).

Lesion morphology	Number	Success	UAF	Abrupt closure
A	193	185 (96)	4 (2.0)	4 (2.1)
B	794	737 (93)	36 (4.5)	21 (2.6)
C	261	210 (80)	38 (15)	13 (5.0)
A	193	185 (96)	4 (2.1)	4 (2.1)
B1	369	351 (95)	14 (3.8)	4 (1.1)
B2	425	386 (91)	22 (5.2)	17 (4.0)
C1	240	196 (82)	34 (14)	10 (4.2)
C2	21	14 (67)	4 (19)	3 (14)
Total	1248	1132 (91)	78 (6.3)	38 (3.0)

Abbreviations as for Table 9.3.

Table 9.7. Effect of Individual Lesion Morphology on Acute Angioplasty Outcome (Based on 1157 Non-occluded Lesions). Values are Number (%).

Lesion morphology	Number	Success	p Value	UAF	p Value	Abrupt closure	p Value
Length							
< 10 mm	959	907 (95)		38 (4.0)		14 (1.5)	
10-20 mm	153	130 (85)	<0.001	6 (3.9)	NS	17 (11)	<0.001
>20 mm	45	35 (78)		3 (6.7)		7 (16)	
Eccentric							
Yes	666	615 (92)		26 (3.9)		25 (3.8)	
No	491	457 (93)	NS	21 (4.3)	NS	13 (2.6)	NS
Tortuosity							
No	965	898(93)		38 (3.9)		29 (3.0)	
Moderate	142	132 (93)	NS	4 (2.8)	NS	6 (4.2)	NS
Severe	50	42 (84)		5 (10)		3 (6.0)	
Angulation							
<45°	991	928 (94)		41 (4.1)		22 (2.2)	
45-90°	136	119 (88)	0.005	5 (3.7)	NS	12 (8.8)	<0.001
>90°	30	25 (83)		1 (3.3)		4(13)	
Contour							
Smooth	762	712 (93)		29 (3.8)		21 (2.8)	
Irregular	395	360 (91)	NS	18 (4.6)	NS	17 (4.3)	NS
Calcium							
Yes	81	60 (74)		10 (12.3)		11 (14)	
No	1076	1012 (94)	<0.001	37 (3.4)	<0.001	27 (2.5)	<0.001
Ostial							
Yes	77	72 (94)		5 (6.5)		0 (0)	
No	1080	1000 (93)	NS	42 (3.9)	NS	38 (3.5)	NS
Bifurcation							
No	970	900 (93)		37 (3.8)		33 (3.4)	
Protected	135	128 (95)	NS	4 (3.0)	0.018	3 (2.2)	NS
Unprotected	52	44(85)		6 (12)		2 (3.8)	
Thrombus							
Yes	46	34 (74)		8 (17)		4 (8.7)	
No	1111	1038 (93)	<0.001	39 (3.5)	<0.001	34 (3.1)	0.036
Vein graft lesion							
Yes (<3 years)	17	16 (94)		1 (5.9)		0 (0)	
Yes (>3 years)	41	36 (88)	NS	2 (4.9)	NS	3 (7.3)	NS
No	1099	1020 (93)		44 (4.0)		35 (3.2)	
Lesion location							
Proximal	533	488 (92)		31 (5.8)		14 (2.6)	
Mid	501	465 (93)	NS	15 (3.0)	0.01	21 (4.2)	NS
Distal	123	119 (97)		1 (0.8)		3 (2.4)	
Distal ectasia							
Yes	42	38 (90)		1 (2.2)		3 (6.7)	
No	1115	1034 (93)	NS	46 (4.1)	NS	35 (3.1)	NS
Tandem Lesion							
Yes	450	425 (94)		13 (2.9)		12 (2.7)	
No	707	647 (92)	NS	34 (4.8)	NS	26 (3.7)	NS

Abbreviations as for Table 9.3.

Table 9.8. Effects of Lesion Severity on Acute Angioplasty Outcome. Values are Numbers (%).

Lesion severity	Number	Success	p Value	UAF	p Value	Abrupt closure	p Value
Occlusions							
No	1157	1072 (93)		47 (4.0)		38 (3.3)	
Yes	91	60 (66)	<0.001	31 (34)	<0.001	0 (0)	0.05
Occlusions							
<3 months	42	32 (76)		10 (24)		0	
≥3 months	49	28 (57)	0.05	21 (43)	0.05	0	NA
Stenosis							
80-99%	726	648 (89)		42 (5.8)		36 (5.0)	
51-79%	431	424 (98)	<0.001	5 (1.2)	<0.001	2 (0.5)	<0.001

NA = not applicable; Other abbreviations as for Table 9.3.

Table 9.9. Multiple Stepwise Logistic Regression Model to Predict Lesion Success (Based on 1157 Non-occluded Lesions).

Variable	Coefficient	Standard error	Odds ratio	95% Confidence interval for odds ratio	p Value
Length					
10-20 mm	−0.79	0.28	0.45	0.26 to 0.79	
>20 mm	−1.24	0.41	0.29	0.13 to 0.64	0.001
Calcium	−1.33	0.30	0.27	0.15 to 0.48	<0.001
Thrombus	−1.28	0.38	0.28	0.13 to 0.58	0.002
High grade stenosis	−1.65	0.41	0.19	0.09 to 0.43	<0.001

Table 9.10. Multiple Stepwise Logistic Regression Model to Predict Absence of Abrupt Closure (Based on 1157 Non-occluded Lesions).

Variable	Coefficient	Standard error	Odds ratio	95% Confidence interval for odds ratio	p Value
Length					
10-20 mm	−1.80	0.39	0.16	0.08 to 0.35	
>20 mm	−2.33	0.52	0.10	0.03 to 0.27	<0.001
Angulation					
45-90°	−1.39	0.41	0.25	0.11 to 0.55	
>90°	−1.91	0.64	0.15	0.04 to 0.52	<0.001
Calcium	−1.19	0.42	0.30	0.13 to 0.69	0.007
High grade stenosis	−1.99	0.74	0.14	0.03 to 0.59	<0.001

Abbreviations as for Table 9.9.

Table 9.11. Multiple Stepwise Logistic Regression Model to Predict Uncomplicated Failure (Based on 1157 Non-occluded Lesions).

Variable	Coefficient	Standard error	Odds ratio	95% Confidence interval for odds ratio	p Value
Thrombus	1.54	0.43	4.64	2.01 to 10.72	0.002
High grade stenosis	1.55	0.48	4.70	1.84 to 12.00	<0.001

Abbreviations as for Table 9.9.

Table 9.12. Technical Data on the 1132 Successfully Dilated Lesions. Values are Median (Inter-quartile Range).

Lesion	Pre-PTCA stenosis (%)	Post-PTCA stenosis (%)	Inflation. frequency	Inflation. pressure (atmosphere)	Inflation duration (seconds)	Balloon/ artery ratio
Type						
A	82 (72-90)	11 (4-18)	2 (2-3)	6 (6-8)	180 (120-240)	1.03 (0.93-1.12)
B	83 (75-91)	14 (8-22)	2 (2-3)	7 (6-8)	180 (120-240)	1.02 (0.93-1.10)
C	87 (78-97)	14 (7-26)	3 (2-4)	7 (6-8)	180 (120-270)	1.00 (0.93-1.10)
p Value	<0.001	<0.001	0.04	0.56	0.18	0.37
Occluded						
Yes	100 (100-100)	13 (10-31)	3 (2-5)	8 (6-8)	240 (180-360)	0.98 (0.91-1.09)
No	83 (74-90)	13 (8-21)	2 (2-3)	7 (6-8)	180 (120-240)	1.02 (0.93-1.10)
p Value	<0.001	0.007	0.001	0.41	<0.001	0.20
Calcified						
Yes	86 (81-92)	18 (8-31)	3 (2-4)	8 (6-10)	180 (135-300)	1.02 (0.96-1.11)
No	83 (74-92)	12 (8-21)	2 (2-3)	6 (6-8)	180 (120-240)	1.02 (0.93-1.10)
p Value	0.04	0.02	0.001	<0.001	0.007	0.55
Total	83 (75-92)	13 (8-22)	2 (2-3)	7 (6-8)	180 (120-244)	1.02 (0.93-1.10)

Pre-PTCA=pre-angioplasty; Post-PTCA=post-angioplasty.

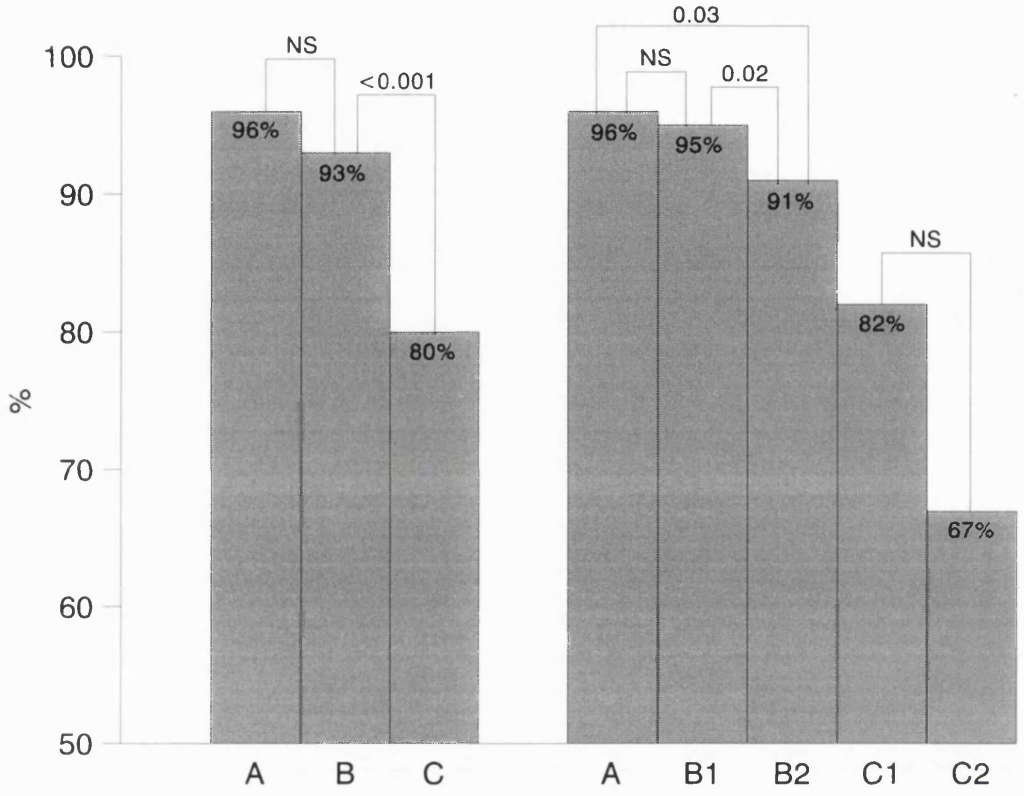

FIGURE 9.1. Effect of ACC/AHA and modified scores on acute success rate.

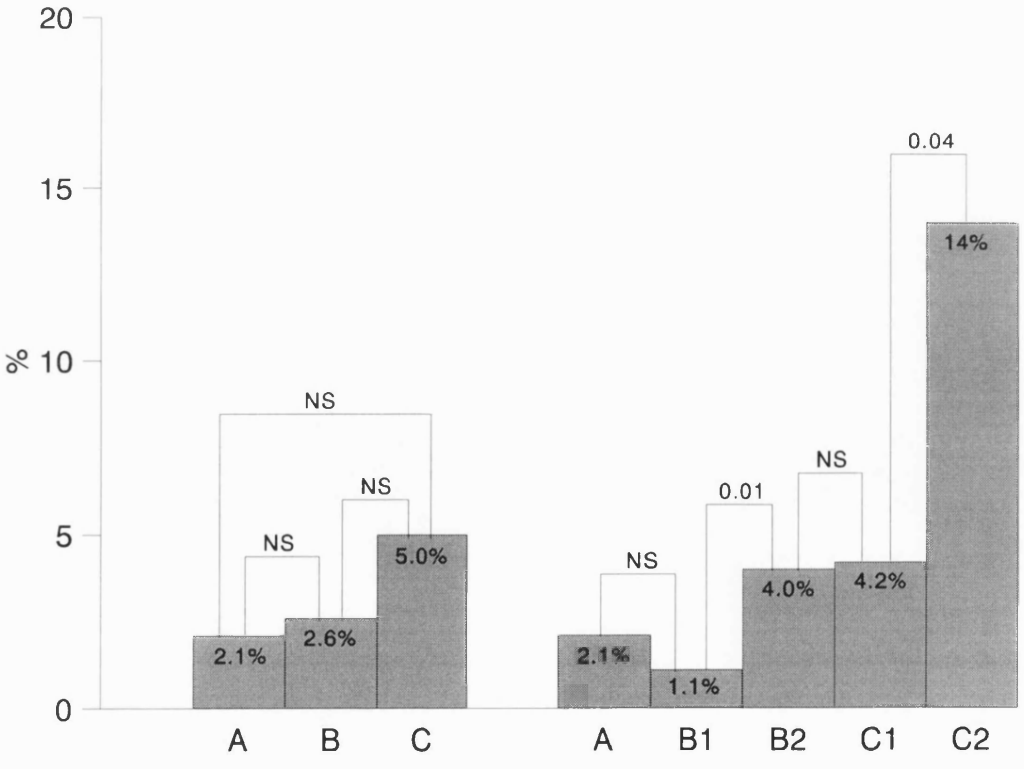

FIGURE 9.2. Effect of ACC/AHA and modified scores on abrupt closure rate.

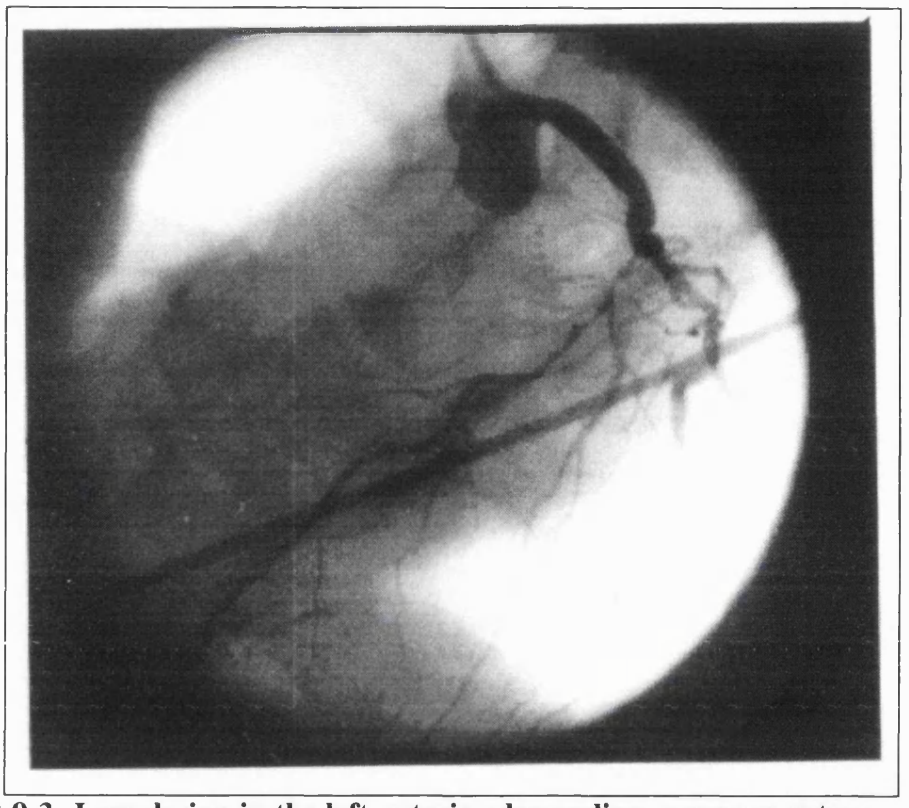

FIGURE 9.3. Long lesion in the left anterior descending coronary artery.

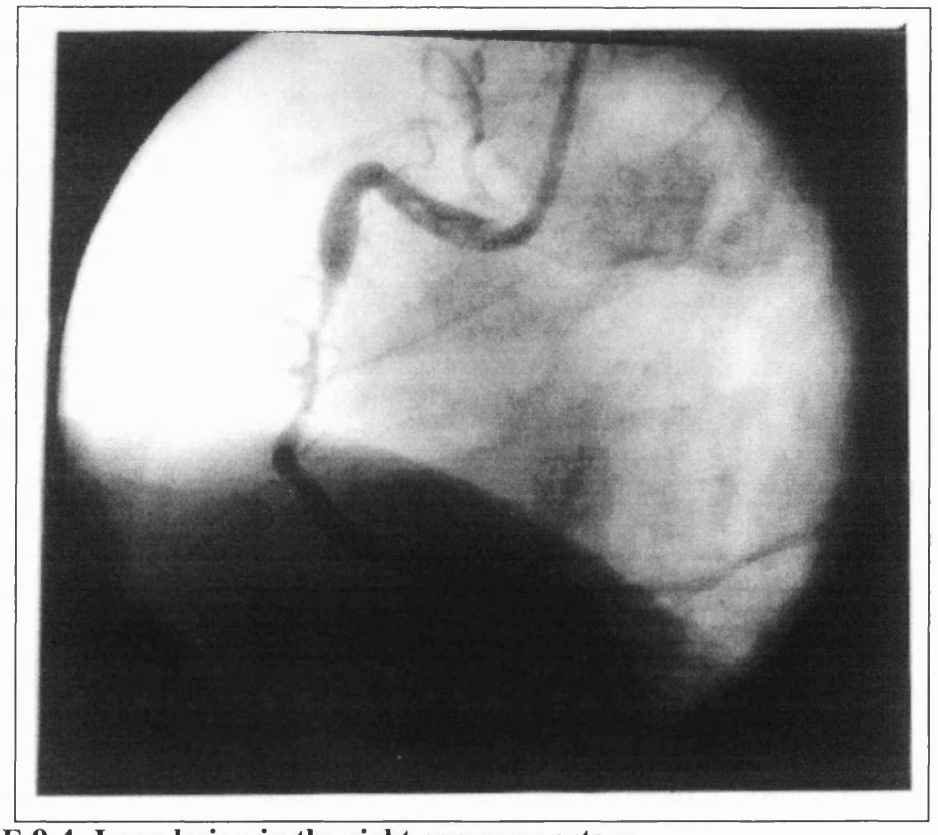

FIGURE 9.4. Long lesion in the right coronary artery.

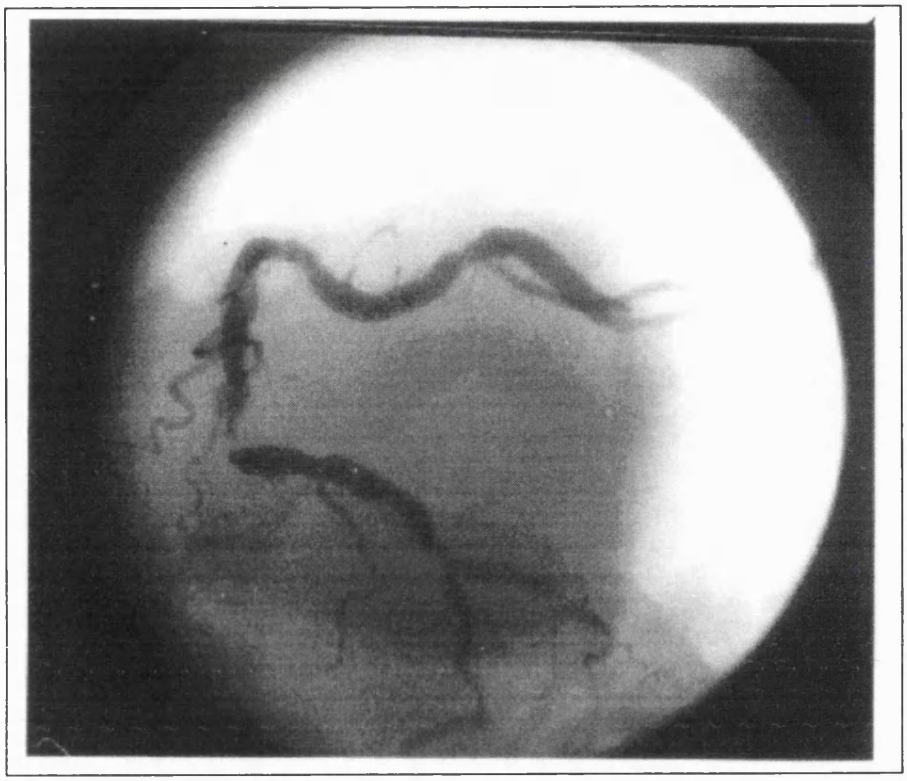

FIGURE 9.5. Angulated lesion in the right coronary artery.

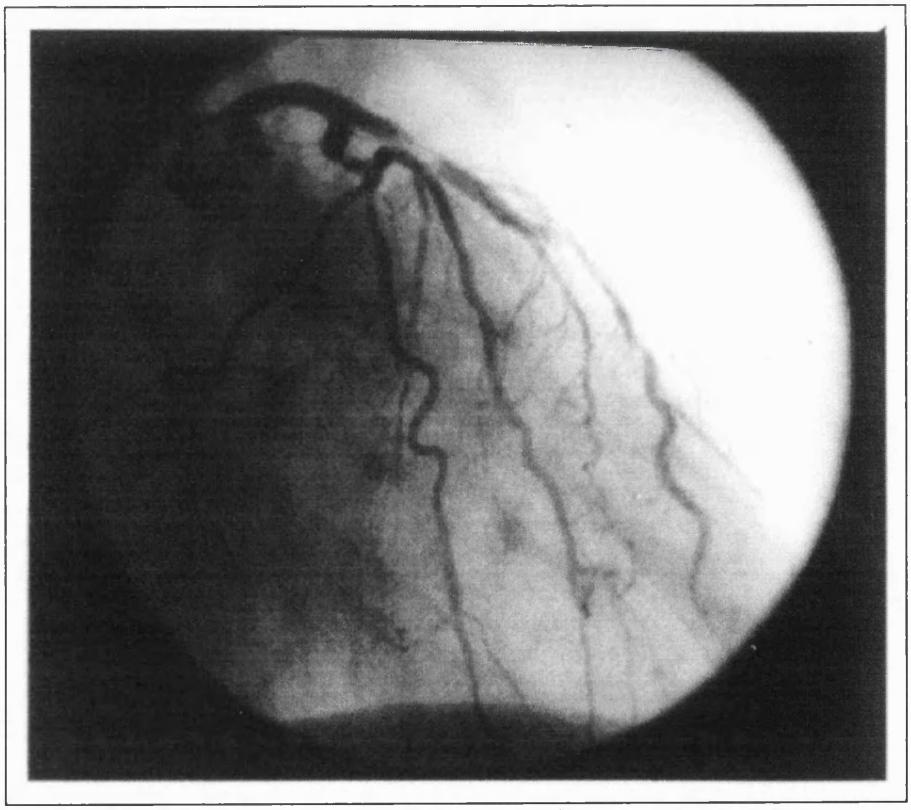

FIGURE 9.6. Angulated lesion in the left circumflex coronary artery.

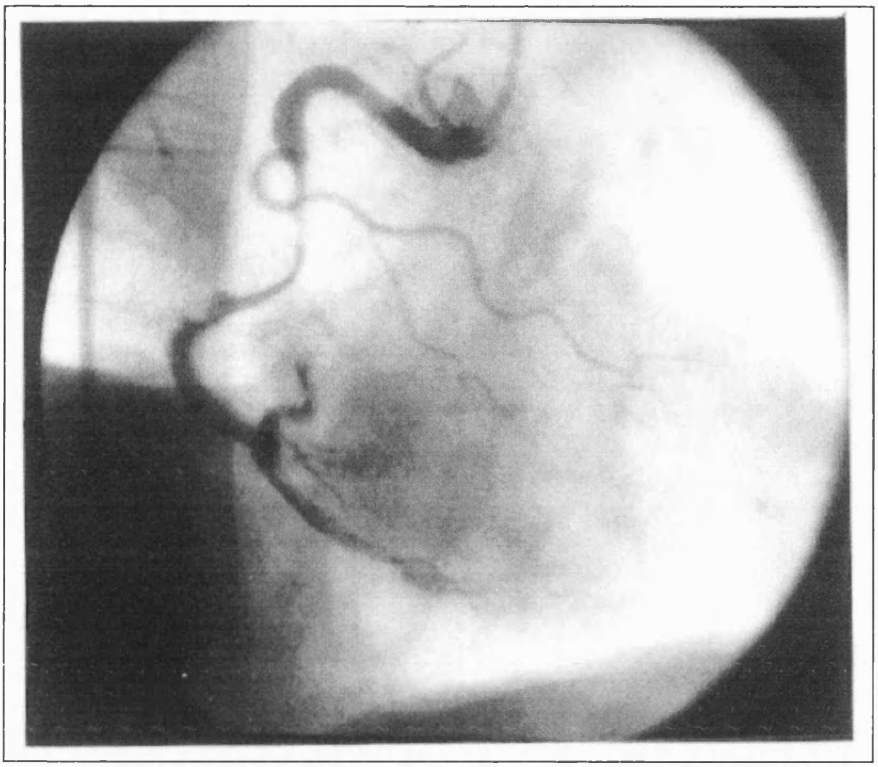

FIGURE 9.7. Long and angulated lesion in the right coronary artery.

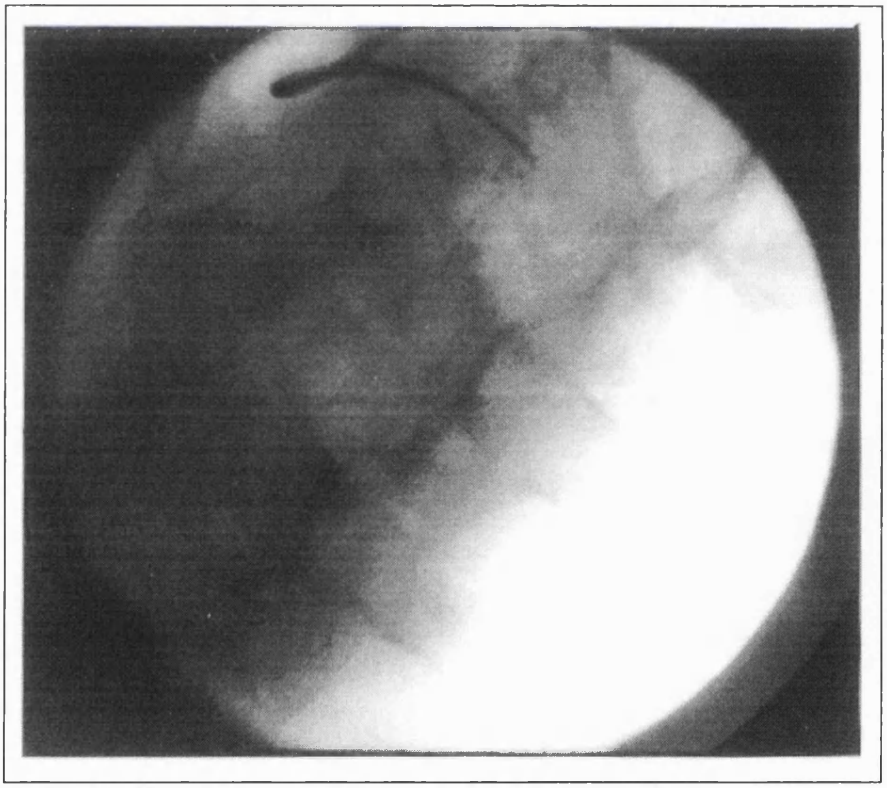

FIGURE 9.8. Calcified lesion in the left anterior descending coronary artery.

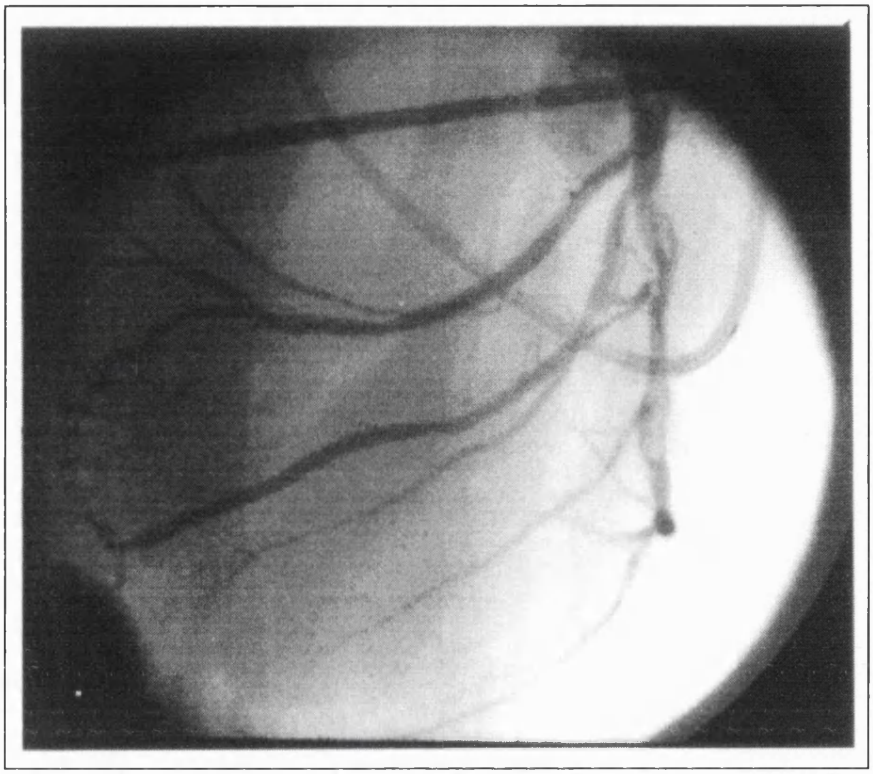

FIGURE 9.9. Thrombus containing lesion in the left anterior descending coronary artery.

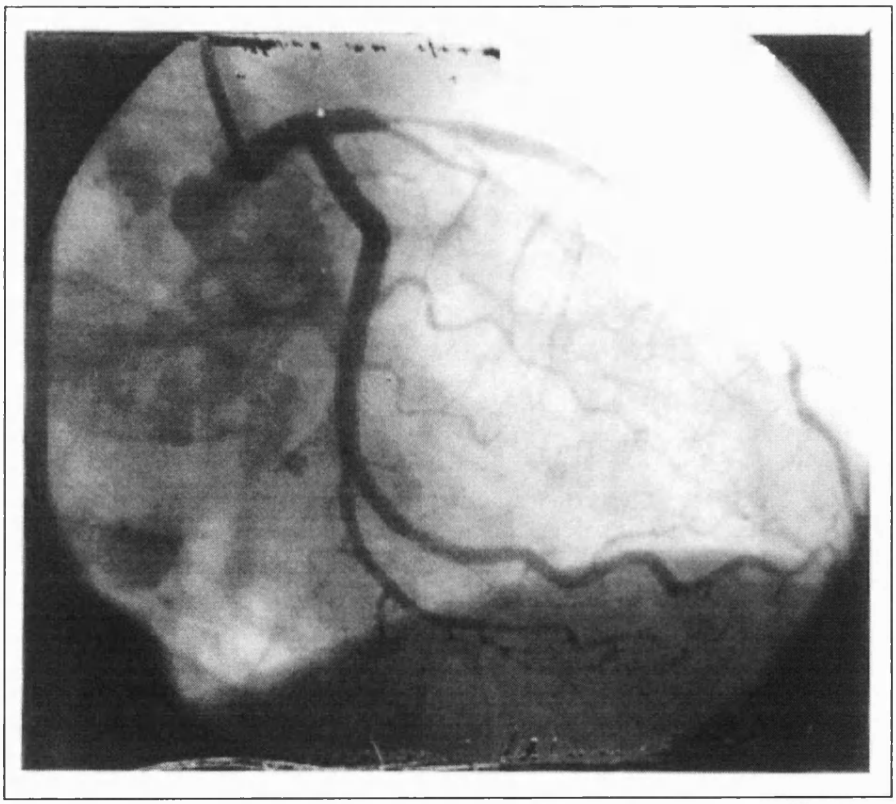

FIGURE 9.10. High grade stenosis in the left anterior descending coronary artery.

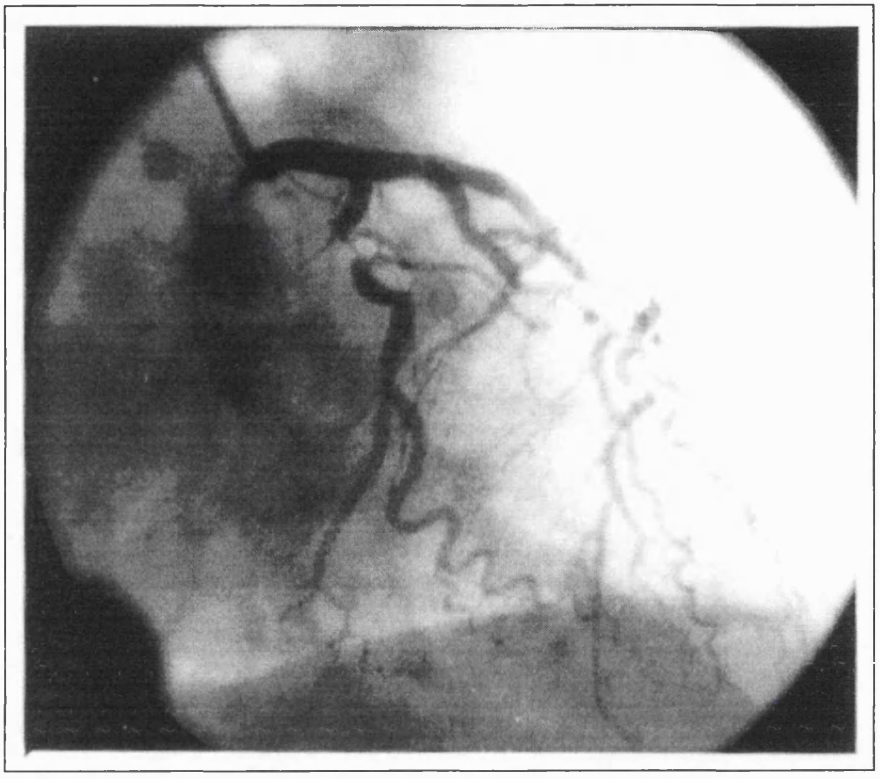

FIGURE 9.11. High grade stenosis in the left circumflex coronary artery.

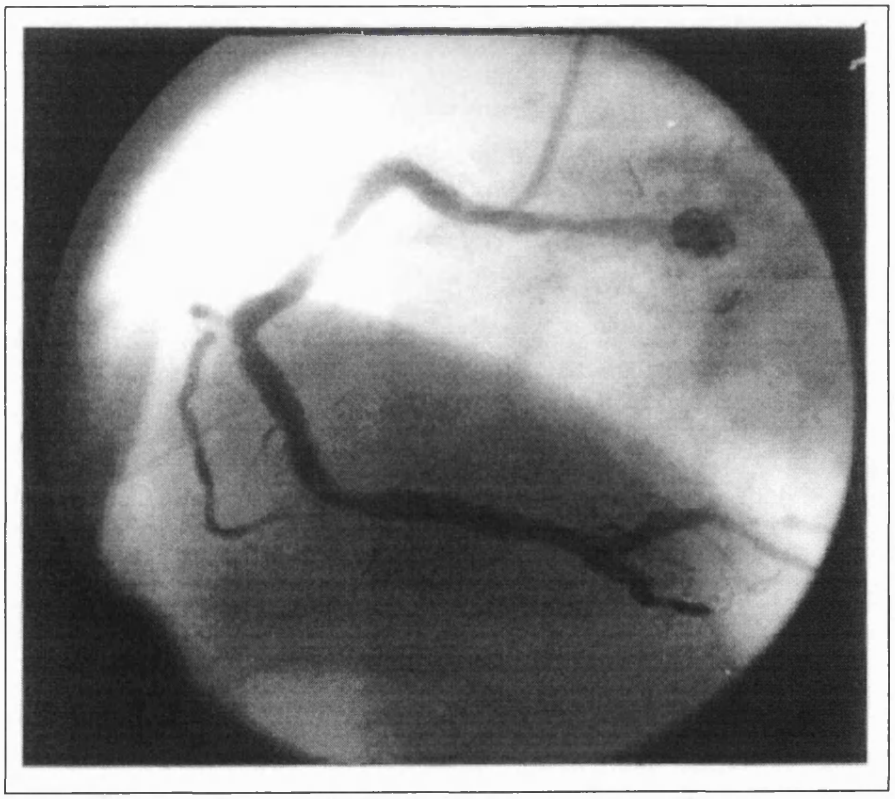

FIGURE 9.12. High grade stenosis in the right coronary artery.

10. ANGIOGRAPHIC FINDINGS WHEN CHEST PAIN RECURS AFTER SUCCESSFUL CORONARY ANGIOPLASTY

10.1 Introduction

10.2 Patients and Methods

(a) Patients

(b) Angioplasty Procedure

(c) Study Methods

(d) Statistical Methods

10.3 Results

(a) Angiographic Outcome

(b) Determinants of Angiographic Outcome

(c) Location of New Coronary Artery Stenosis

10.4 Discussion

10.5 Summary and Conclusions

Figures and Tables

10.1 INTRODUCTION

Percutaneous transluminal coronary angioplasty is an established revascularisation technique in patients with symptomatic coronary artery disease. In the early days, it has been used predominantly in patients with single vessel coronary artery disease, although more recently it has also been applied successfully in multiple coronary arteries (Cowley et al, 1985; Myler et al, 1987; O'Keefe et al, 1990; Hollman et al, 1992; Le Feuvre et al, 1993). Despite its effectiveness in relieving anginal symptoms, recurrence of chest pain after a successful procedure is a common occurrence, and clinical or electrocardiographic signs of myocardial ischaemia occur in 20% to 25% of patients within the first 6 months (Stammen et al, 1991; Glazier et al, 1989b).

Recurrence of chest pain is frequently due to restenosis, but for a significant proportion of patients, other mechanisms may be responsible. Other possible causes include incomplete revascularisation, progression of coronary atherosclerosis, or dynamic coronary stenosis (Joelson et al, 1987). The ability to predict the likelihood of any of these angiographic outcomes occurring on the basis of baseline patient-, lesion-, and procedure-related variables, would have important implications for the selection of patients for repeat coronary angiography when chest pain recurs after successful angioplasty.

Previous studies have evaluated the frequency of coronary artery disease progression after percutaneous transluminal coronary angioplasty. There have been many reports of isolated cases of accelerated development of coronary stenosis proximal to the site of previous dilatation (Slack and Pinkerton, 1985; Waller et al, 1987; Wayne et al 1988; Kells et al, 1990). However, few studies have systematically evaluated this

potentially serious problem, as to whether it could be a direct complication of the procedure (Hwang et al, 1988).

The study presented in this chapter reports on the angiographic findings, in a consecutive series of patients who underwent repeat coronary angiography for recurrence of chest pain, after an initially successful coronary angioplasty procedure. Comprehensive assessment of patient-, lesion-, and procedure-related variables is undertaken to identify the determinants of angiographic outcome. In patients who have progression of atherosclerosis, the relationship between the location of the new coronary stenosis and the vessels that had coronary angioplasty is also examined.

10.2 PATIENTS AND METHODS

(a) PATIENTS

Between January 1981 and December 1992, percutaneous transluminal balloon angioplasty was performed in 2691 consecutive patients. It is the policy of our department to strongly recommend repeat diagnostic coronary angiography when chest pain recurs during follow-up, after an initially successful angioplasty procedure. Six hundred and seven patients underwent repeat diagnostic coronary angiography for recurrence of chest pain suggestive of angina pectoris. All those patients who required repeat angiography in the first 48 hours after the angioplasty procedure were excluded. In patients who underwent more than 1 angiographic study for the evaluation of chest pain after angioplasty, only the first follow-up study was included in the analysis.

On the basis of findings at follow-up coronary angiography, patients were classified as having restenosis, incomplete revascularisation, progression of atherosclerosis, or no significant coronary artery stenosis. Thirty-eight patients had more than 1 possible mechanism for the recurrence of chest pain. These patients were excluded from further analysis since determination of the exact mechanism for recurrence of symptoms was not possible. The remaining 569 patients form the study group of this chapter.

The mean age was 54 years (SD 9, range 27 to 86 years) and 476 (84%) were male (Table 10.1). A previous myocardial infarction had occurred in 265 patients (47%) resulting in left ventricular dysfunction in 197 patients (35%). Sixty-nine patients (12%) had previous coronary artery bypass grafting. Coronary angioplasty was

performed as an emergency for unstable angina in 58 patients (10%). Before intervention, 380 patients (67%) suffered grade III or IV angina. Two hundred and ninety-six patients (52%) had multivessel disease, 108 (19%) underwent multivessel coronary angioplasty, and 164 (29%) underwent multilesion coronary angioplasty during the same procedure. A mean of 1.2 vessels and 1.4 stenoses per patient were attempted. Risk factors that were present in the patients included hypertension (31%), diabetes mellitus (5%), hypercholesterolaemia (50%), and smoking (58%).

(b) ANGIOPLASTY PROCEDURE

Coronary angioplasty was performed according to the protocol described in Chapter 2.

(c) STUDY METHODS

The baseline patient-, lesion-, and procedure-related data on all 569 patients and 803 lesions were assessed. Complete follow-up angiographic data were available on all 569 patients. Patients were classified as having restenosis, incomplete revascularisation, progression of atherosclerosis, or no significant coronary artery stenosis, depending on the findings at follow-up coronary angiography. In patients who had progression of atherosclerosis, the exact location of the new coronary stenosis was noted, and its relationship to the vessel that had coronary angioplasty was examined.

The patient-related parameters analysed as possible determinants of angiographic outcome included age, gender, angina grade, extent of coronary artery disease, left ventricular function, and whether multivessel or multilesion coronary angioplasty

was performed. Other clinical factors considered were a history of smoking, hypertension, diabetes mellitus, hypercholesterolaemia, previous myocardial infarction, prior coronary artery bypass surgery, and the presence of a family history. The lesion-related parameters analysed included lesion location, vessel diameter, pre-angioplasty lesion severity, post-angioplasty lesion severity, and lesion length. The procedure-related parameters analysed included inflation frequency, inflation duration, inflation pressure, and balloon to artery ratio.

Procedural success was defined as ≤50% residual diameter stenosis at the dilated sites without a major in-hospital complication, defined as the occurrence of death, myocardial infarction, or emergency coronary artery bypass grafting. Angiographic restenosis was defined as a recurrence of a >50% luminal diameter narrowing at a previously successfully dilated site. Incomplete revascularisation was defined as the continued presence of a significant lesion (>50% luminal diameter narrowing) at follow-up angiography at a site that was not dilated. Progression of atherosclerosis was defined as the development of a new, significant lesion (>50% luminal diameter narrowing) not present during the initial angioplasty procedure. Patients whose repeat angiograms revealed no lesion of >50% luminal diameter narrowing were classified as having no significant coronary artery stenosis.

(d) STATISTICAL ANALYSIS

Continuous variables are expressed as mean (SD). The study patients were divided into sub-groups according to the 4 angiographic outcome groups. Seventeen patient-related variables were analysed as determinants of the 4 angiographic outcome groups. There were separate analyses of determinants of restenosis in the study lesions. Study lesions were also divided into sub-groups according to whether

restenosis had occurred. Fifteen lesion- and procedure-related variables were analysed as possible correlates of restenosis. Categorical variables between patient and lesion groups were compared using the chi-squared test and comparisons of continuous variables were performed using the Mann-Whitney U test.

All patient-related variables were included in a Fisher's linear discriminant analysis to distinguish between the 4 angiographic outcome groups, using forward stepwise selection of variables significant at the 1% level. To predict which group a patient belongs to, one calculates the classification function for each of the 4 groups and the largest of the 4 values will indicate the patient's most likely group. The performance of Fisher's discriminant function on the data was assessed by the jacknife method to compensate for the fact that the same data were being used to test the prediction rule as had been used to derive it. All lesion- and procedure-related variables were included in a multiple logistic regression analysis to identify independent determinants of restenosis in individual lesions, again using forwards stepwise selection of variables at the 1% level.

10.3 RESULTS

(a) ANGIOGRAPHIC OUTCOME

The median interval from coronary angioplasty to recurrent chest pain was 16 weeks (mean 43, SD 69) and ranged up to 384 weeks. The median interval from coronary angioplasty to follow-up angiography was 24 weeks (mean 53, SD 72) and ranged up to 384 weeks. On the basis of findings at follow-up angiography, 250 patients (44%) were classified as having restenosis, 72 (13%) as having incomplete revascularisation, 115 (20%) as having new significant coronary artery lesions, and 132 (23%) as having no significant coronary artery narrowing (Figure 10.1).

Of the 132 patients with no significant coronary artery narrowing, 45 patients were considered to have chest pain with features atypical of angina pectoris by the assessing clinician, but serious enough to warrant angiography. A symptom limited exercise treadmill or thallium test was available in 114 patients, and evidence of reversible ischaemia was detected in 27% of patients.

Of the 250 patients with angiographic restenosis, 189 (76%) underwent repeat angioplasty, 30 (12%) had coronary artery bypass surgery, and 31 (12%) were managed with medical therapy. Of the 115 patients with new coronary artery stenoses, 71 (62%) underwent repeat angioplasty, 19 (16%) had coronary artery bypass surgery, and 25 (22%) were managed with medical therapy. Of the 72 patients who had incomplete revascularisation, 39 (54%) underwent repeat angioplasty, 13 (18%) had coronary artery bypass surgery, and 20 (28%) continued to be managed with medical therapy.

(b) DETERMINANTS OF ANGIOGRAPHIC OUTCOME

The patient-related characteristics analysed to assess their association with angiographic outcome are shown in Table 10.2. Univariate analysis of seventeen patient-related variables showed that angiographic outcome was significantly related to 7 variables: history of diabetes mellitus, history of previous coronary artery bypass grafting, number of diseased vessels, number of vessels dilated, number of lesions dilated, time from coronary angioplasty to recurrent chest pain, and time from coronary angioplasty to follow-up angiography.

Linear stepwise discriminant analysis identified number of diseased vessels ($p<0.001$), number of vessels dilated ($p<0.001$), and time from coronary angioplasty to recurrent chest pain ($p<0.001$) as significant predictors of angiographic finding (Table 10.3). None of the other variables analysed contributed significantly to this classification rule. To predict which group a patient belongs to, one calculates the classification function for each of the 4 groups and the largest of the 4 values will indicate the patient's most likely group. For example, using the earlier model:

Number of diseased vessels (VDIS)	= 1 if patient has single vessel disease, = 2 if patient has multivessel disease.
Number of dilated vessels (VDIL)	= 1 if patient has single vessel dilatation, = 2 if patient has multivessel dilatation.
Time from coronary angioplasty to recurrent chest pain (TP4)	= 1 if time to chest pain is between 4-24 weeks, = zero otherwise.
Time from coronary angioplasty to recurrent chest pain (TP24)	= 1 if time to chest pain >24 weeks, = zero otherwise.

Consider a patient with only single vessel disease and single vessel dilatation, with a 7 month delay to recurrent chest pain.

VDIS=1, VDIL=1, TP4=0, TP24=1.

The value of the incomplete revascularisation classification function is: $(7.86 \times 1) + (3.22 \times 1) + (0.59 \times 0) + (0.78 \times 1) - 11.68 = 0.18$

The values of the other classification functions are:

No disease: 6.24

New disease: 6.99

Restenosis: 5.07

So the predicted group for this patient is new disease, followed closely by no disease.

The performance of the classification rule was assessed by the jacknife method. Table 10.4 shows the number of patients in the original sample both correctly and incorrectly classified by the derived discriminant function. The model correctly predicted 84% of the new disease group, 67% of the incomplete revascularisation group, and 66% of the restenosis group. The highest misclassification rate was seen in predicting patients with no significant coronary artery stenosis (74%).

The relationship, between time from coronary angioplasty to recurrent chest pain and angiographic outcome groups, is shown in Table 10.2. Of the patients in whom chest pain developed within 4 weeks after angioplasty, the majority had either incomplete revascularisation or no significant coronary artery stenosis (70%). A significant proportion of patients (28%) had developed restenosis but only 2% of

patients developed new coronary artery lesions in this time period. For patients in whom chest pain developed between 4 and 24 weeks after coronary angioplasty, restenosis (71%) was the most common finding. New disease and incomplete revascularisation were seen in only 6% and 4% of these patients, respectively. In contrast, for recurrent chest pain beginning more than 24 weeks after coronary angioplasty, new coronary artery stenosis (53%) was the most common finding although a significant proportion of patients had restenosis (18%) or had no significant coronary artery stenosis (27%). Patients with multivessel disease were also associated with a higher incidence of incomplete revascularisation (23% versus 1%) and a lower incidence of no significant coronary stenosis (12% versus 35%) when compared to patients with single vessel disease at follow-up. Patients who underwent multivessel dilatation were also associated with a higher incidence of restenosis than those who had single vessel dilatation (57% versus 41%).

The lesion- and procedure-related variables analysed to assess their association with angiographic restenosis of individual lesions are shown in Table 10.5 and Table 10.6. Univariate analysis of 15 variables showed that restenosis was significantly related to 10 variables: lesion location, vessel dilated, pre-angioplasty lesion severity, post-angioplasty lesion severity, dilatation of total occlusion, inflation frequency, total inflation duration, and balloon to artery ratio.

Multiple logistic regression analysis identified pre-angioplasty percentage stenosis ($p<0.001$), post-angioplasty percentage stenosis ($p<0.001$), and lesion location ($p=0.008$) as independent predictors of angiographic restenosis (Table 10.7). None of the other variables analysed contributed significantly to this regression model.

(c) LOCATION OF NEW CORONARY ARTERY STENOSIS

The 115 patients who developed new coronary artery lesions had 10 chronically occluded native major epicardial vessels, and 20 patent coronary artery bypass grafts (10 were grafted to occluded major epicardial vessels, and 10 to major branches), giving a total of 355 patent major epicardial vessels present at the time of coronary angioplasty. Coronary angioplasty was performed on 133 vessels, and 222 vessels were not dilated. At repeat angiography, 81 of the 133 vessels (61%) that had coronary angioplasty and 109 of the 222 vessels (49%) that did not have angioplasty had new lesions; this difference was significant at $p=0.03$. The location of the new lesions in the 81 coronary angioplasty vessels was proximal to the dilated site in 50 (62%) vessels and distal to the dilated site in 31 vessels (38%).

10.4 DISCUSSION

Despite continuing improvement in the primary success rate, restenosis continues to be the major limitation of percutaneous transluminal coronary angioplasty. Multiple studies have attempted to determine the incidence and factors contributing to restenosis so that appropriate measures may be taken to modify them (Holmes et al, 1984; Levine et al, 1985; Leimgruber et al 1986; Ernst et al, 1987a; Guiteras Val et al 1987a). Although recurrence of chest pain is frequently due to restenosis, other mechanisms may be responsible, including incomplete revascularisation, progression of coronary atherosclerosis, or dynamic coronary stenosis (Joelson et al, 1987). Little attention have been given to these other mechanisms of recurrent chest pain which are examined in this study.

Angiographic Outcome

The present study has shown that restenosis was the most common angiographic finding, accounting for 44% of patients with recurrence of chest pain after an initially successful angioplasty procedure. Since repeat angiography was only performed on symptomatic patients, this would account for the high incidence of restenosis, consistent with results of earlier reports. However, 56% of patients did not have restenosis at follow-up. The cause of recurrence of chest pain in most of these patients was either incomplete revascularisation or development of new coronary artery stenosis.

A significant proportion of patients had no significant coronary artery narrowing at follow-up angiography. Although 36% of these patients had atypical chest pain, the majority were considered by the assessing cardiologist to have symptoms typical of angina pectoris. Non-invasive investigations were only partially successful in

differentiating these patients, since 27% had reversible ischaemia documented on exercise treadmill testing or thallium scintigraphy. The recurrence of chest pain in these patients may be due to the development of coronary artery spasm at the site of angioplasty. This phenomenon has been reported by other investigators (Hollman et al, 1983b; David et al, 1982), who have also suggested that patients with coronary artery spasm usually present within 2 months of angioplasty. In the present series, about 40% of these patients presented with recurrence of chest pain within 2 months of angioplasty. Since ergonovine provocation was not undertaken during follow-up angiography, coronary artery spasm as a mechanism of recurrent chest pain cannot be confirmed in this series.

Determinants of Angiographic Outcome

In a health service with limited resources, it is vital that such resources are put to use in the most efficient and cost effective ways. The ability to accurately predict each angiographic outcome would have important implications in selecting patients for repeat angiography if chest pain recurs after an initially successful angioplasty procedure.

In this study, linear stepwise discriminant analysis of patient-related variables identified time from successful coronary angioplasty to the onset of recurrent chest pain, as the strongest predictor of angiographic outcome. Within 4 weeks of successful coronary angioplasty, 70% of patients with recurrent chest pain had either incomplete revascularisation or no significant coronary artery disease. In these patients, not only would a knowledge of the completeness of revascularisation at coronary angioplasty, and the reason for failure to achieve complete revascularisation, help to differentiate them, it could also help decide whether a repeat coronary angiogram is necessary.

Restenosis was the most common angiographic finding when chest pain recurred between 4 weeks and 6 months after coronary angioplasty, consistent with the findings of other investigators (Holmes et al, 1984; Kaltenbach et al, 1985; Roubin et al, 1987; Cequier et al, 1988; Kent et al, 1988; Nobuyoshi et al, 1988; Serruys et al, 1988b). A notable proportion of patients had no significant coronary artery stenosis (19%) and only 6% developed new coronary artery stenosis during this period. A knowledge of the angiographic details and technical difficulties encountered during the initial angioplasty may avoid unnecessary repeat angiography in certain individuals, for example, following angioplasty of a non-dominant circumflex stenosis which was difficult to negotiate in a patient with single vessel disease. Continuing medical treatment may be the preferred option in these individuals, even if restenosis had occurred. Six months after successful coronary angioplasty, recurrence of chest pain was most frequently attributed to the development of new coronary stenosis. Coronary angiography is necessary to assess the extent of coronary artery disease in these patients (Holmes et al, 1988b).

It is not surprising that patients with multivessel disease were associated with a higher incidence of incomplete revascularisation and a lower incidence of no significant coronary stenosis, when compared to patients with single vessel disease. The most common cause for failure to achieve complete revascularisation was the presence of a chronic total occlusion, as has been shown by other studies (Deligonul et al, 1988a; Bell et al, 1990; Shaw et al, 1990b; Bourassa et al, 1992). The higher incidence of restenosis in patients who had undergone multivessel dilatation, has also been shown by other investigators (Mata et al, 1985; Hollman et al, 1986; Guiteras Val et al, 1987a; de Feyter et al, 1988; Le Feuvre et al, 1993). This may be related to the fact that these patients had more coronary segments at risk (Le Feuvre et al, 1993).

Multiple logistic regression analysis of lesion- and procedure-related variables identified pre-angioplasty percentage stenosis, post-angioplasty percentage stenosis, and lesion location as independent predictors of angiographic restenosis. The adverse impact of pre-angioplasty lesion severity on restenosis has been noted previously (Holmes et al, 1984; David et al, 1984; Hollman et al, 1986; Myler et al, 1987; Black et al, 1988; Pepine et al, 1990; Hirshfeld et al, 1991). Recurrence in lesions with severe initial stenosis may be the result of inadequate plaque compaction, despite apparently satisfactory angiographic and haemodynamic results (Myler et al, 1987).

The association between residual stenosis severity and restenosis have also been shown by other investigators (David et al, 1984; Levine et al, 1985; Mata et al, 1985; Leimgruber et al, 1986; Hollman et al, 1986; Guiteras Val et al, 1987a; Lambert et al, 1988; Pepine et al, 1990, Renkin et al, 1990; Bourassa et al, 1991). This is particularly true when the residual lesion and the restenosis criterion used are measured in terms of percent diameter stenosis. A smaller change in diameter is needed to exceed 50% luminal diameter narrowing if the residual narrowing is greater initially. Furthermore, this greater residual stenosis may result in increased turbulence, increased platelet activation and ultimately restenosis. Recently, the concept of "relative gain" (a measure of vessel wall injury) and "relative loss" (a measure of the restenosis process) was introduced for assessing the restenosis process, by relating the absolute change in minimal luminal diameter after intervention and during follow-up to the interpolated reference diameter of the coronary segment in question (Beatt et al, 1992; Rensing et al, 1992; Hermans et al, 1992b). Using this concept, some investigators have shown that the greater the relative gain in minimal luminal diameter achieved by dilatation, the greater the subsequent relative loss, hence the phrase "the more you gain, the more you lose".

(Rensing et al, 1992; Beatt et al, 1992; Kuntz and Baim, 1993). This probably reflects the combination of deep arterial injury and reversible stretch imposed on the diseased wall, both of which are known stimuli for smooth muscle cell proliferation. However, Kuntz et al (1993) have shown that the increment in late loss is only about 45% of the immediate gain for balloon angioplasty. Therefore, further improvement in immediate gain should result in improved net gain and thus better late results even though the absolute late loss is increased, hence the phrase "the bigger, the better" (Kuntz and Baim, 1993).

The higher restenosis rate in lesions that occur proximally compared with those that occur distally has also been shown by other investigators (Vandormael et al, 1987; Roubin et al, 1987). Proximal lesion location often involves the origin of the vessel and branch points (Halon et al, 1983). Balloon dilatation of these sites often results in an unsatisfactory initial angiographic outcome. Multiple inflations are frequently necessary resulting in increased intimal trauma and a greater cellular proliferative response (Hearn et al, 1991; Glazier et al, 1989a). Furthermore, there may be an intrinsic propensity for these sites to develop restenosis (Whitworth et al, 1985; Miller et al, 1986; Health and Public Policy Committee, American College of Physician, 1983).

Location of New Coronary Artery Stenosis

In patients with normal or only mildly diseased coronary arteries, progression or development of new disease is uncommon, approximately 1.7% to 8% every year (Genesini and Kelly, 1972). There have been isolated reports suggesting that accelerated development of atherosclerosis can occur as a complication of percutaneous transluminal coronary angioplasty.

Slack and Pinkerton (1985) reported on 3 patients who developed left main stem stenosis after coronary angioplasty of the left anterior descending artery. Wayne et al (1988) also described 3 patients who had accelerated left main stenosis after percutaneous transluminal coronary angioplasty. Waller et al (1987) described accelerated development of left main stem stenosis 4 months after successful dilatation of the proximal left anterior descending artery. They also reported focal loss of luminal endothelium in the left main coronary artery in 9 of 11 patients who died 4 to 72 hours after percutaneous transluminal coronary angioplasty. All 11 patients had a normal or minimally diseased left main coronary artery. Schweiger et al (1984) described an example of subtotal occlusion developing distal to the area of angioplasty. Hwang et al (1988) reported on 39 patients who underwent repeat angiography after successful angioplasty. They noted that 13 of the 40 vessels (33%) that underwent angioplasty and only 10 of the 77 vessels (13%) that did not undergo angioplasty had new lesions or marked progression of existing lesions ($p < 0.02$).

In the present series, the incidence of new lesion development was higher in the vessels that had instrumented angioplasty (61%) than in vessels that did not have angioplasty (49%). In addition, new lesion development within the angioplasty vessel occurred more often proximally (62%) than distally (38%) to the dilated site. These data suggest that instrumentation of the coronary arteries during angioplasty may have contributed to the early development of new lesions. Injury to the intima during manipulation and transit of the guiding catheter, guidewire, and balloon dilatation catheter in the coronary arteries proximal and distal to the dilated site, is only 1 of several proposed mechanisms for this phenomenon. The trauma may initiate thrombosis, atherogenesis, or fibrocellular tissue proliferation in such areas (Schweiger et al, 1984; Waller et al, 1987). Simple retrograde extension or growth

of the fibrocellular tissue into the adjacent coronary artery segments proximal and distal to the dilated site has also been suggested as a possible mechanism (Waller et al, 1987). In addition, antegrade and retrograde propagation of a coronary artery dissection, induced by coronary angioplasty, has also been implicated in the development of new coronary stenoses (Graf and Verani, 1984). The introduction of new balloon angioplasty technology, such as lower profile, more flexible balloon and guidewire systems, as well as smaller diameter guiding catheters, may reduce the incidence of this complication. However, the association between disease progression and vessel instrumentation is not a consistent finding. Nugent et al (1986) have shown no acceleration of disease progression in nondilated segments of the dilated vessels compared with segments of nondilated vessels in 86 patients at 21 months of follow-up. Hence, whether this phenomenon is a true complication of the procedure can only be answered by a much larger scale study.

Study Limitations

This study is a retrospective analysis of data and is subject to the limitations inherent in any retrospective study. In addition, although the model was developed from a large data base and validated on the database from which it was derived using the jacknife method, it needs to be tested prospectively and against other populations. We are currently collecting new data for this purpose.

10.5 SUMMARY AND CONCLUSIONS

This study has shown that the most common cause of recurrence of chest pain after initially successful coronary angioplasty was restenosis, although other mechanisms may also be responsible, including incomplete revascularisation, development of new coronary artery stenosis, and dynamic coronary stenosis. The time from coronary angioplasty to onset of recurrent chest pain was the most powerful predictor of angiographic outcome. In conjunction with a knowledge of the angiographic and technical details during the initial angioplasty procedure, the completeness of revascularisation, and the reason for failure to achieve complete revascularisation can help decide whether a repeat coronary angiogram is necessary. This study has also shown that the incidence of new lesion development was higher in the vessels that had instrumented angioplasty, possibly reflecting accelerated atherosclerosis or increased fibrocellular proliferation from intimal injury.

Table 10.1. Patient and Angiographic Characteristics.

	Number	%
Total	569	100
Mean age (years)	54	SD 9 (range 27-86)
Male gender	476	84
Angina grade		
0/I	35	6
II	154	27
III	208	37
IV	172	30
Previous MI	265	47
Abnormal LV (EF<45%)	197	35
Previous CABG	69	12
Risk factors		
Smoking	327	58
Family history	261	46
Diabetes mellitus	26	5
Hypertension	174	31
Hypercholesterolaemia	283	50
Emergency procedure	96	17
Multivessel disease	296	52
Single vessel PTCA	461	81
Multivessel PTCA	108	19
Multilesion PTCA	164	29

CABG=coronary artery bypass grafting; EF=ejection fraction; LV=left ventricular function; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty; SD=standard deviation.

Table 10.2. Patient-related Variables as Predictors of Angiographic Findings With Univariate Analyses. Values are Numbers (%).

Variable	Number	Restenosis	No disease	New disease	Incompl. revasc.	p Value
Age (years)						
≤55	301	130 (43)	78 (26)	59 (20)	34 (11)	0.37
>55	268	120 (45)	54 (20)	56 (21)	38 (14)	
Gender						
Male	93	37 (40)	29 (31)	14 (15)	13 (14)	0.16
Female	476	213 (45)	103 (22)	101 (21)	59 (12)	
Angina class						
0/I/II	189	93 (49)	41 (22)	36 (19)	19 (10)	0.29
III/IV	380	157 (41)	91 (24)	79 (21)	53 (14)	
Previous MI						
No	304	144 (47)	70 (18)	57 (15)	33 (9)	0.25
Yes	265	106 (40)	62 (23)	58 (22)	39 (15)	
Previous CABG						
No	500	225 (45)	120 (24)	99 (20)	56 (11)	0.02
Yes	69	25 (14)	12 (2)	16 (3)	16 (3)	
Impaired LV						
No	372	164 (44)	90 (24)	76 (20)	42 (11)	0.56
Yes	197	86 (44)	42 (21)	39 (20)	30 (15)	
Peri-infarct angina						
No	511	223 (44)	12 (2)	103 (20)	65 (13)	0.96
Yes	58	27 (47)	12 (21)	12 (21)	7 (12)	
Family history						
No	308	139 (45)	72 (23)	59 (19)	38 (12)	0.89
Yes	261	111 (43)	60 (23)	56 (21)	34 (13)	
Smoking						
No	174	68 (39)	46 (26)	37 (21)	23 (13)	0.64
Yes	327	147 (45)	75 (23)	65 (20)	40 (12)	
Diabetes mellitus						
No	543	245 (45)	127 (23)	103 (19)	68 (13)	0.004
Yes	26	5 (19)	5 (19)	12 (46)	4 (15)	
Hypertension						
No	395	175 (44)	96 (24)	77 (19)	47 (12)	0.65
Yes	174	75 (43)	36 (21)	38 (22)	25 (14)	
Hypercholesterolaemia						
No	286	124 (43)	69 (24)	61 (21)	32 (11)	0.66
Yes	283	126 (45)	63 (22)	54 (19)	40 (14)	

continued

Table 10.2. Patient-related Variables as Predictors of Angiographic Findings With Univariate Analyses (Continued). Values are Numbers (%).

Variable	Number	Restenosis	No disease	New disease	Incompl. revasc.	p Value
No. of diseased vessels						
SV dilation	273	119 (44)	96 (35)	55 (20)	3 (1)	<0.001
MV dilation	296	131 (44)	36 (12)	60 (20)	69 (23)	
No. of vessels dilated						
SV dilation	461	188 (41)	116 (25)	98 (21)	59 (13)	0.01
MV dilation	108	62 (57)	16 (15)	17 (16)	13 (12)	
No. of lesions dilated						
SL dilation	405	158 (39)	107 (26)	88 (22)	52 (13)	0.001
ML dilation	164	92 (56)	25 (15)	27 (16)	20 (12)	
Time from PTCA to recurrent chest pain						
<4 weeks	134	37 (28)	35 (26)	3 (2)	59 (44)	<0.001
4-24 weeks	253	180 (71)	47 (19)	15 (6)	11 (4)	
>24 weeks	182	33 (18)	50 (27)	97 (53)	2 (1)	
Time from PTCA to repeat angiography						
<4 weeks	74	29 (39)	23 (31)	1 (1)	21 (28)	<0.001
4-24 weeks	229	137 (60)	44 (19)	12 (5)	36 (16)	
>24 weeks	266	84 (37)	65 (29)	102 (45)	15 (7)	

Incompl. revasc.=incomplete revascularisation; ML=multilesion; MV=multivessel; SL=single lesion; SV=single vessel; Other abbreviations as for Table 10.1.

Table 10.3. Coefficients of Fisher's Linear Discriminant Functions to Predict Angiographic Outcome.

Variable	Restenosis	No disease	New disease	Incompl. revasc.	p Value
No of vessels diseased	4.78	3.63	4.91	7.86	<0.001
No of vessels dilated	5.41	5.40	5.05	3.22	<0.001
Time from PTCA to chest pain					
4-24 weeks	5.48	3.97	4.82	0.59	<0.001
>24 weeks	4.85	5.70	9.63	0.78	<0.001
Constant	−9.97	−8.49	−12.60	−11.68	–

Abbreviations as for Table 10.1 and Table 10.2.

Table 10.4. Performance of Linear Discriminant Function as Assessed by Jacknife Method. Values are Numbers Except Percent Correct (%).

		Angiographic outcome allocated by discriminant rule			
Actual angiographic outcome	Percent correct (%)	Restenosis	No disease	New disease	Incompl. revasc.
Restenosis	66	165	25	33	27
No disease	26	40	34	50	8
New disease	84	14	1	97	3
Incompl. revasc.	67	19	3	2	48
Total	61	238	63	182	86

Abbreviations as for Table 10.2.

Table 10.5. Lesion-related Variables as Predictors of Angiographic Restenosis. Values are Mean (SD) Except for Lesion Location, Total Occlusions, and Vessels Dilated (number (%)).

Variables	Restenosis (n=281)	No Restenosis (n=522)	p Value
Arterial size (millimetre)	3.04 (0.36)	3.06 (0.39)	0.42
PrePTCA stenosis (%)	86 (10)	83 (11)	<0.001
PostPTCA stenosis (%)	20 (10)	16 (10)	<0.001
PrePTCA diameter (millimetre)	0.42 (0.32)	0.51 (0.35)	<0.001
PostPTCA diameter (millimetre)	2.44 (0.44)	2.56 (0.45)	<0.001
Lesion length (millimetre)	7.22 (2.59)	6.89 (2.37)	0.20
Lesion location			
Proximal (n=421)	165 (39)	256 (61)	
Mid (n=317)	101 (32)	216 (68)	0.03
Distal (n=65)	15 (23)	50 (77)	
Vessel dilated			
Left main stem (n=7)	6 (86)	1 (14)	
Left anterior descending (n=431)	169 (39)	262 (61)	
Circumflex (n=178)	49 (28)	129 (72)	0.002
Right coronary artery (n=164)	49 (30)	115 (70)	
Saphenous vein graft (n=23)	8 (35)	15 (65)	
Total occlusions			
No (n=714)	238 (33)	476 (67)	0.004
Yes (n=88)	43 (49)	45 (51)	

Abbreviations as for Table 10.1.

Table 10.6. Procedure-related Variables as Predictors of Angiographic Restenosis. Values are Mean (SD).

Variables	Restenosis (n=281)	No Restenosis (n=522)	p Value
Number of inflations	4.9 (2.4)	4.5 (2.7)	0.002
Total inflation duration (seconds)	276 (126)	251 (129)	0.001
Longest inflation duration (seconds)	62 (11)	62 (14)	0.61
Maximum inflation pressure (atmosphere)	8.1 (1.7)	8.1 (1.6)	0.92
Balloon size (millimetre)	3.02 (0.37)	3.07 (0.38)	0.08
Balloon to artery ratio	0.99 (0.07)	1.01 (0.07)	0.04

Abbreviations as for Table 10.1.

Table 10.7. Multiple Logistic Regression Model to Predict Angiographic Restenosis.

Variable	Coefficient	Standard error	Odds ratio	95% Confidence interval for odds ratio	p Value
Pre-PTCA % stenosis	0.025	0.01	1.025	1.010 to 1.040	<0.001
Post-PTCA % stenosis	0.037	0.01	1.037	1.021 to 1.054	<0.001
Lesion location					
Proximal	-0.27	0.16	0.76	0.56 to 1.04	
Mid	-0.77	0.32	0.46	0.25 to 0.87	0.008
Distal	2.25	1.10	9.46	1.10 to 81.23	

Abbreviations as for Table 10.1.

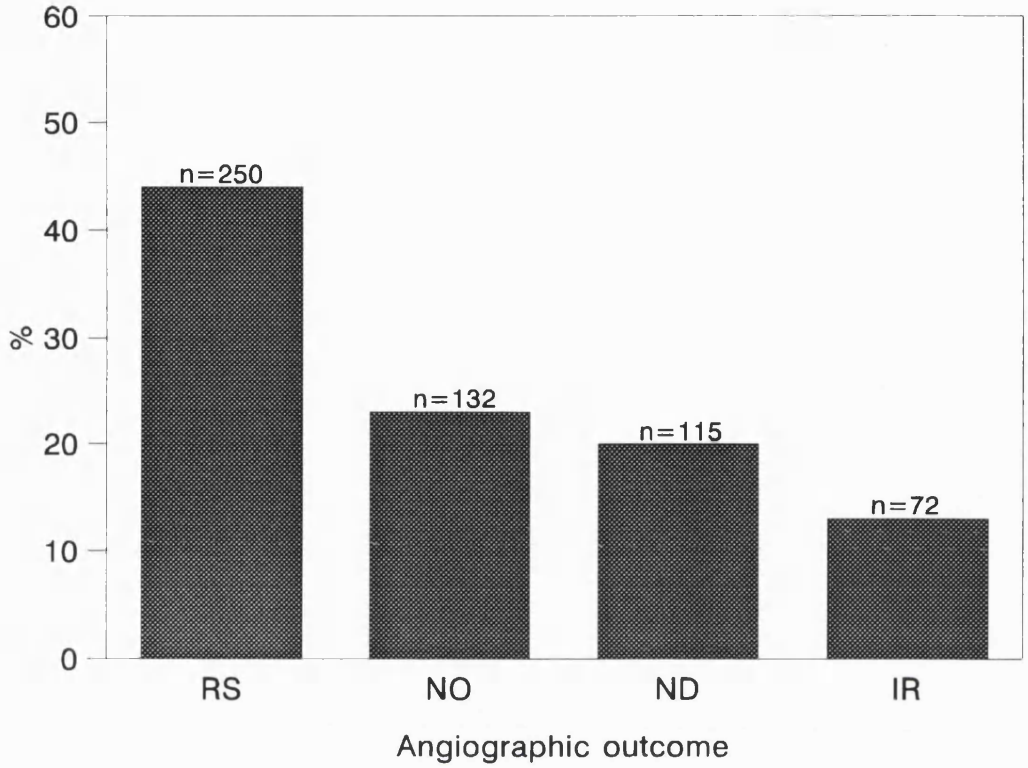

FIGURE 10.1. Angiographic outcome of all 569 patients. RS=restenosis; NO=no significant coronary artery disease; ND=new disease; IR=incomplete revascularisation.

11. CONCLUDING REMARKS

11.1 Introduction

11.2 Summary of Thesis Results

11.3 Overview of New Coronary Interventional Devices

(a) Acute Success and Complications

(b) Management of Abrupt Closure

(c) Avoidance of Restenosis

(d) Expansion to Complex Anatomic Subsets

(e) The Size of the Niche

11.4 Summary and Conclusions

Figures and Tables

11.1 INTRODUCTION

When Andreas Grüntzig introduced percutaneous transluminal coronary angioplasty in 1977, he could not have foreseen how quickly this technique would develop and become accepted as part of routine clinical practice. His pioneering work opened the era of interventional cardiology, and since then, angioplasty has emerged as a major tool in the armamentarium for treating coronary artery disease. However, despite marked advances in the design of percutaneous transluminal coronary balloon angioplasty hardware, optimisation of procedural variables, and use of adjunctive pharmacotherapy, deficiencies persist which have restricted the application of this technique. As a result, there remain many unresolved issues concerning the type of patient or lesion that should be treated by conventional balloon angioplasty.

The major limitations associated with conventional balloon angioplasty include: (a) unsuitable coronary anatomy that cannot be dilated by angioplasty; (b) abrupt vessel closure at the time of angioplasty that causes complications; and (c) restenosis of the lesion in the months following the procedure that leads to recurrent ischaemia. Primary procedural success and complication rates remain problematic for certain anatomic subsets including: chronic total occlusions; old degenerated saphenous vein grafts; ostial stenoses; long or tandem lesions; calcified lesions; angulated lesions; and thrombus containing lesions. Furthermore, restenosis, occurring in 35% to 50% of cases, has limited the long-term efficacy attributable to conventional balloon angioplasty. Many new non-balloon interventional devices, such as atherectomy systems, laser systems, and stents, have been introduced in an effort to improve upon these deficiencies and expand the application of percutaneous revascularisation technology. The results achieved with these new devices have frequently been compared to those obtained with conventional balloon angioplasty

before the recent refinement in balloon angioplasty technique, improvement in operator experience, and equipment evolution. Furthermore, direct comparison between studies may be misleading because it is not possible to take account of differences in baseline and procedural variations. This thesis has examined some of these topics which have been the subject of controversy during the past decade. Although the studies reported in this thesis are limited by their retrospective and non-randomised design, they bring ancillary data to areas of particular interest in the field of interventional cardiology, with many important, but yet unresolved issues. Until the results of randomised trials are available, newer devices introduced for the non-operative revascularisation of the various patient and lesion subsets will need to be compared with this contemporary experience

11.2 SUMMARY OF THESIS RESULTS

In chapter 3, the role of conventional balloon angioplasty in patients with a chronic total occlusion was examined. Although the primary success rate was less favourable than that expected of non-occluded lesions, coronary balloon angioplasty of chronic total occlusion was found to be associated with a low risk of acute complication. Furthermore, an improved success rate was found with the most recent cases, confirming reports from other large centres. Certain clinical and angiographic variables that were easily identifiable, were found to be highly predictive of procedural outcome. Successful recanalisation of chronic total occlusions also reduced the need for subsequent elective coronary artery bypass graft surgery when compared with patients with a failed procedure. With present techniques and sufficient operator experience, $>70\%$ of chronic total occlusions can be successfully recanalised by coronary balloon angioplasty with a complication rate of $<2\%$. The long-term results were also encouraging with favourable late clinical outcome. New interventional devices introduced for the nonoperative recanalisation of totally occluded coronary arteries, such as mechanical rotational atherectomy (Kaltenbach et al, 1991) and excimer laser angioplasty (Bowes et al, 1989), will need to be compared with this contemporary experience, with careful attention given to clinical and angiographic variables related to procedural outcome and long-term clinical outcome.

Chapter 4 provided evidence that 80-90% of aorta ostial, non-aorta ostial, and branch ostial stenoses can be successfully dilated by conventional balloon angioplasty with an acceptable complication rate, providing good symptomatic relief and a favourable long-term outcome. The technique involved in dilating ostial stenoses differed depending on the site of the lesion, and this in turn influences the

likelihood of a successful dilatation. New devices such as excimer laser angioplasty (Tcheng et al, 1992; Lawson et al, 1993), mechanical rotational atherectomy (Popma et al, 1993, Kent et al, 1992), directional atherectomy (Popma et al, 1991; Garratt et al, 1991; Robertson et al, 1991), and coronary stenting (Teirstein et al, 1991a) have recently been introduced as alternatives to balloon angioplasty for coronary ostial lesions. Although the application of some of these new devices in coronary ostial lesions have shown favourable results, and potentially overcome some of the technical problems encountered using balloon angioplasty, randomised trials will be needed to prove their efficacy.

The feasibility of a third conventional balloon angioplasty, of a single coronary arterial segment at which restenosis had occurred after 2 previous angioplasty procedures, was studied in chapter 5. The study has shown that a third coronary balloon angioplasty for a second restenosis can be performed safely and effectively in selected patients. Multiple repeat angioplasty for recurrent restenosis should therefore be accepted as an integral part of the overall coronary angioplasty revascularisation strategy, and provides an attractive alternative to coronary bypass surgery. However, the preferred mode of revascularisation for such patients is yet to be resolved with randomised trials. The time interval between previous procedures may help to identify patients with a high risk of subsequent restenosis, and hence allow an alternative mode of revascularisation to be considered.

Chapter 6 examined the use of conventional balloon angioplasty in treating patients with recurrence of symptoms after prior coronary artery bypass surgery. The high peri-operative mortality and morbidity associated with repeat bypass surgery, and the less satisfactory symptom relief has prompted an increasing use of coronary balloon angioplasty to treat such patients. The acute mortality and morbidity

achieved with coronary balloon angioplasty compared favourably with those of repeat coronary artery bypass surgery, although direct comparisons may be misleading given the differences in baseline characteristics. Many new devices have been introduced to overcome some of the major limitations following saphenous vein graft balloon angioplasty, in particular, the increased risk of distal embolisation and restenosis. Early experience employing a number of stenting devices has shown promising results with high procedural success rates, low complication and restenosis rates (Popma et al, 1991; Garratt et al, 1991; Robertson et al, 1991; Leon et al, 1991a). The use of directional coronary atherectomy to treat focal saphenous graft lesions has also been associated with high procedural success and low complication rates (Kaufmann et al, 1990; Selmon et al, 1991). However, it is contraindicated in degenerated and diffusely thrombotic vein grafts where it is associated with a high embolisation rate, although this limitation may be circumvented by using a transluminal extraction atherectomy device (O'Neill et al, 1991; Meany et al, 1992). The long-term results of many of these new devices remain uncertain and further randomised trials are necessary to select the best device therapy for treating saphenous vein graft lesions.

The approach towards treating elderly patients with symptomatic coronary artery disease was discussed in chapter 7. The limitations of medical and operative treatment in this group of patients were outlined, and the attractiveness of the less invasive nature of conventional balloon angioplasty was underscored by the encouraging acute and long-term results. The use of balloon angioplasty in the treatment of 'tandem lesions', and the role of systemic or local factors in determining restenosis were investigated in chapter 8. The results of this study showed that systemic factors are probably less important than local factors in influencing restenosis, and in particular, multiple inflations should be avoided.

Chapter 9 looked critically at the value of a classification scheme in stratifying lesions into categories according to the likelihood of procedural success and complications. Determinants of acute balloon angioplasty outcome were also examined by using multiple logistic regression models incorporating easily identifiable angiographic parameters. Because the guidelines issued by the American College of Cardiology/American Heart Association Task Force reflected balloon angioplasty experience and opinions between 1986-88 (Ryan et al, 1988), it is not surprising that the classification scheme proposed is no longer applicable in the setting of current angioplasty practice, given the dramatic strides made in balloon angioplasty technique, operator experience, and equipment evolution. The results in this chapter provided data on lesion morphological determinants of acute angioplasty outcome that represented a more recent experience circa 1990-92. They established that lesion morphology has a major impact on acute success and complication rates after conventional balloon angioplasty. Lesions with morphological features that have been identified as adverse predictors of coronary balloon angioplasty outcome should probably be treated by other devices. However, the initial enthusiasm of the use of some of these new devices has diminished when experience was gained. Furthermore, new balloon angioplasty technology that is being developed may help overcome some of the limitations that are encountered by the currently available angioplasty equipment. Examples include: long balloons (Savas et al, 1992; Tenaglia et al, 1993b); angled balloons (Vivekaphirat et al, 1989; Bajwa et al, 1990); and high pressure balloons (Bush et al, 1991; Willard et al, 1991).

Chapter 10 examined the mechanisms for recurrence of chest pain, and frequency of coronary artery disease progression after initially successful conventional balloon angioplasty. Possible mechanisms for recurrence of chest pain include restenosis, incomplete revascularisation, development of new coronary artery stenosis, and

dynamic coronary stenosis. The time from coronary angioplasty to onset of recurrent chest pain was shown to be the most powerful predictor of angiographic outcome. In conjunction with a knowledge of the number of diseased vessels present at coronary angioplasty, the completeness of revascularisation, and the reason for the failure to achieve it, can help decide whether a repeat coronary angiogram is necessary. The incidence of new lesion development was also shown to be higher in the vessels that had instrumented angioplasty, possibly reflecting accelerated atherosclerosis or increased fibrocellular proliferation from intimal injury.

11.3 OVERVIEW OF NEW CORONARY INTERVENTIONAL DEVICES

The growth of conventional balloon angioplasty has triggered the development of additional new coronary revascularisation technology in the field of interventional cardiology, which includes: atherectomy systems; laser systems; and stents. There are many potential promises and pitfalls associated with these new non-balloon devices. The proliferation of these new devices has occurred in order to fulfil certain niches, that were not apparently filled by conventional balloon angioplasty, or where further initial or long-term improvements were considered possible. The major limitations associated with conventional balloon angioplasty include: unsuitable coronary anatomy; abrupt closure; and restenosis. For new devices to establish their roles, they must be able to effectively demonstrate some clear cut superior advantages over balloon angioplasty where the latter tends to do poorly (complex lesion morphology) or prove their clinical utility in overcoming some of the residual problems of conventional angioplasty (abrupt closure and restenosis).

(a) Acute Success and Complications

As more experience is obtained from the application of these new devices, it is becoming clear that, although the immediate success rates have been uniformly high, an aftermath has been the emergence of a new set of complications. Examples of such complications include: coronary artery perforation that has occurred with laser angioplasty and the atherectomy procedures (Stack et al, 1990, Hinohara et al, 1992); late coronary aneurysm formation after directional atherectomy, which may be related to deep tissue resection compromising the vessel's supporting infrastructure (Prewitt et al, 1993); subacute thrombosis days after stent deployment with or without apparent adequate anticoagulation (Ellis et al, 1990b, Haude et al, 1993); bleeding problems, manifesting as major peripheral vascular complications

or need for transfusions, associated with anticoagulation after stent deployment (Serruys et al, 1994); and the coronary "no-reflow" phenomenon after the high-speed drilling and emulsification process of rotational angioplasty (Niazi et al, 1990), which is related to distal embolisation of microparticles. Each of these is extremely serious, can lead to death or myocardial infarction, and represents new complications, that are rarely if ever reported, with the use of conventional balloon angioplasty.

(b) Management of Abrupt Closure

Although not specifically designed to manage abrupt closure after conventional balloon angioplasty, most of the new non-balloon devices have shown promise in this area, including stents, directional atherectomy, and laser balloon angioplasty. Because of their scaffolding nature, stents are best designed to repair a dissected and occluded coronary artery. All the stents now under investigation have been successfully used for this purpose with good results. Sigwart et al (1988) using the Medinvent wall stent, Haude et al (1991) using the Palmaz-Schatz stent, Roubin et al (1992) using the Gianturco-Roubin stent, and Reifart et al (1992b) using the Strecker stent, have all demonstrated that coronary stenting is effective in restoring an occluded artery to near normal geometry by pushing plaque material and flaps aside. Currently in progress is the **GRACE** trial (Gianturco Roubin Stent Acute Closure Evaluation), which is a prospective, randomised trial, comparing the immediate and long-term efficacy of bailout stenting using the Gianturco-Roubin stent with long balloon inflation or other interventional devices. Directional atherectomy has also been used to manage abrupt closure, by removing dissection flaps and obstructing plaque material (Warner et al, 1991; Webb et al, 1992). However, the application of this particular technology has led to coronary artery perforation (Vetter et al, 1992). This raises caution about the application of this

device in this setting, especially in spiral dissections when the vessel wall integrity is suspect. Spears et al (1990) have shown that laser balloon angioplasty may also be effective in managing abrupt closure, by a "welding" like effect of neodinium: yttrium- aluminium-garnet laser energy.

(c) Avoidance of Restenosis

Most of the non-balloon devices have, until now, failed to reduce the problem of restenosis and provide better long-term outcome than balloon angioplasty. Preliminary data available for each of the new devices indicate that the overall rate of restenosis is quite similar to that of conventional balloon angioplasty (Ellis et al, 1990b; Litvack et al, 1990; Hinohara et al, 1992). Recent randomised trials, comparing directional coronary atherectomy versus balloon angioplasty have confirmed these findings (Topol et al, 1993; Adelman et al, 1993). However, randomised trials comparing stent implantation, using the Palmaz-Schatz device, versus balloon angioplasty, have shown a reduction in the risk of restenosis in favour of *de novo* stent placement (Serruys et al, 1993; Fischman et al, 1994). Although these preliminary results from *de novo* stent implantation are encouraging, further results should be awaited before drawing final conclusions on the merits of primary stenting.

(d) Expansion to Complex Anatomical Subsets

Since their introduction, recommendations for new interventional devices have been modified, and the initial enthusiasm has waned when experience is gained. When it comes to acute success and freedom from complication, proponents of new devices are striving to show that the new devices are as good as the balloon when applied to lesions for which the balloon is well suited. Because of this, the expectations for new devices have been scaled back from replacing the balloon to complementing the

balloon technique, in particular, by filling in gaps where the balloon is weak. The greatest impact of new interventional devices so far has been on influencing the acute result in a variety of complex problem lesions. Some of these complex lesions, which clearly represent a potential contraindication to balloon angioplasty, seem particularly well suited for therapy with new non-balloon devices.
Directional atherectomy may be superior to the balloon when used for treatment of eccentric, ostial, bifurcational, ulcerated or thrombotic lesions in large arteries (Ellis et al, 1991; Hinohara et al, 1991; Robertson et al, 1991; Selmon et al, 1991).

The niche for mechanical rotational atherectomy is less well defined. It may be most efficacious among lesions generally considered refractory to conventional balloon angioplasty, which include: calcified, ostial, or bifurcational lesions; lesions requiring high inflation pressure; tortuous lesions; eccentric lesions; and long, diffuse segments in smaller vessels (Teirstein et al, 1991b; Stertzer et al, 1993; Popma et al, 1993). It has also shown merits in treating rigid chronic occlusions that cannot be traversed or dilated by balloon angioplasty (Kaltenbach et al, 1991).

The transluminal extraction atherectomy device circumvents the limitation of downstream embolisation by aspirating atheromatous debris back through the atherectomy catheter. It seems particularly well suited for treatment of thrombus-containing lesions and degenerated saphenous vein grafts that are large in diameter, for which downstream embolisation is a potential problem with balloon angioplasty (Leon et al, 1991b; O'Neill et al, 1991).

The clinical implementation of excimer laser coronary angioplasty cannot be made with certainty at the moment until further data are gathered. However, it may be superior to the balloon for treatment of heavily calcified lesions, long or diffuse

lesions, degenerated saphenous vein grafts, ostial, and chronically occluded lesions (Bowes et al, 1989; Untereker et al, 1991; Cook et al, 1991; Bittl et al, 1992a).

Intra-coronary stents appear to be unmatched in their ability to improve acute lumen dimensions, and may be considered the treatment of choice for focal or tubular lesions in saphenous vein grafts (Popma et al, 1991; Garratt et al, 1991; Robertson et al, 1991; Leon et al, 1991a).

(e) The Size of the Niche

The value of any new device is related to the indications for and frequency of usage, as well as the outcome when it is used. To determine the new device niche for a particular lesion, one could multiply the frequency of occurrence of the lesion by the balloon angioplasty failure rate (Myler et al, 1992). In chapter 9, the frequency of occurrence of long lesions (>10mm) was 17% and the balloon angioplasty failure rate was 17%. Hence, the new device niche for long lesions is only 2.9%. The efficacy and safety of these new interventional devices, and their lesion specific indications are summarised in Table 11.1 and Table 11.2.

11.4. SUMMARY AND CONCLUSIONS

With such an extensive armamentarium, the interventional cardiologist has a wide array of newly developed equipment from which to select. This has resulted in confusion as to which interventional technology should be used to achieve the optimal acute and long-term outcome. Considering available data and extensive institutional experience, it appears that each interventional device has its own success and complication profile, lesion-specific applications, and may ultimately have a role in the interventional armamentarium. This is undoubtedly an exciting era for the development and application of coronary interventional procedures. However, maintaining an awareness of the multiplicity of problems and deficiencies will hopefully facilitate meaningful progress in this vital field. Needless to say, all the recommendations will need confirmation by well conducted prospective randomised trials, designed in a format that permits comparison of the various devices in matched lesions (Umans et al, 1991). To date, only a few randomised trials comparing new devices and balloon angioplasty have been reported and the long-term results of these devices remain uncertain. Based on available data, conventional balloon angioplasty appears to have planted itself assuredly in the armamentarium of interventional therapeutic cardiology. For numerous reasons, not the least of which is the cost of new interventional devices, conventional balloon angioplasty will remain the "work horse" of the percutaneous coronary revascularisation technique for the foreseeable future.

Table 11.1. Efficacy and Safety of the New Interventional Devices

	PTCA	DCA	TEC	MRA	ELCA	LBA	STENT
Success	>90%	↔	↔	↔	↔	↔	↔
Abrupt Closure	5%	↔	↔/↓	↔	↔	↓	↔
Subacute Closure	<1%	↔	↔	↔	↔	↔	
Dissection	30%	↓↓	↓	↓↓	↓	↓↓	↓↓
Spasm	2%	↔	↑	↑	↑	↑	↓↓
Death	1%	↔	↔	↔	↔	*	↔
MI	2%	↔	↔	↔	↔	*	↔
CABG	2%	↔/↓	↔	↔	↔	*	↔
Perforation	<1%	↑	↑	↔	↑	↔	↔
Restenosis	35-50%	↔	↔	↔	↔	↑	↔/↓

CABG=Emergency coronary artery bypass grafting; DCA=Directional coronary atherectomy; ELCA=Excimer laser coronary angioplasty; LBA=Thermal-laser balloon angioplasty; MRA=Mechanical rotational atherectomy; PTCA=Percutaneous transluminal coronary angioplasty. ↑=increased risk; ↓=decreased risk; ↔=equivalent risk, *=used primarily as a bailout device for refractory acute closure.

Table 11.2. New Devices and Niches

Lesion Morphology	DCA	TEC	MRA	ELCA	LBA	LASTAC	STENT
Eccentric	+	+	+	–	+	–	+
Ulcerated	+	+	+	–	+	–	+
Ostial	+	+	+	+	–	–	+/–
Thrombus	+/–	+	–	–	+	–	–
Long/diffuse	–	+/–	+	+	–	–	–
Calcified/rigid	+	+	+	+	–	–	–
Bifurcation	+	+	+	+	–	–	–
Old SVG	–	+	–	+	–	–	+
Uncrossable CTO	–	–	+	+	–	+	–
Dissection	+	–	–	–	+	–	+

CTO=chronic total occlusion; LASTAC=Argon-laser transluminal angioplasty catheter; SVG=saphenous vein graft. Other abbreviations as for Table 11.1. + = favourable; – = unfavourable;

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