



Safety of the Deferral of Coronary Revascularization on the Basis of Instantaneous Wave-Free Ratio and Fractional Flow Reserve Measurements in Stable Coronary Artery Disease and Acute Coronary Syndromes

Javier Escaned, MD, PhD,^a Nicola Ryan, MB, BCh,^{a,*} Hernán Mejía-Rentería, MD,^{a,*} Christopher M. Cook, MD,^b Hakim-Moulay Dehbi, PhD,^c Eduardo Alegria-Barrero, MD, PhD,^d Ali Alghamdi, MD,^e Rasha Al-Lamee, MD,^b John Altman, MD,^f Alphonse Ambrosia, DO,^g Sérgio B. Baptista, MD,^h Maria Bertilsson, MSc,ⁱ Ravinay Bhindi, MB, BS, PhD,^j Mats Birgander, MD, PhD,^k Waldemar Bojara, MD,^l Salvatore Brugaletta, MD, PhD,^m Christopher Buller, MD,ⁿ Fredrik Calais, MD,^o Pedro Canas Silva, MD,^p Jörg Carlsson, MD, PhD,^q Evald H. Christiansen, MD, PhD,^r Mikael Danielewicz, MD,^s Carlo Di Mario, MD, PhD,^t Joon-Hyung Doh, MD, PhD,^u Andrejs Erglis, MD, PhD,^v David Erlinge, MD, PhD,^k Robert T. Gerber, PhD,^w Olaf Going, MD,^x Ingibjörg Gudmundsdóttir, MD, PhD,^y Tobias Härle, MD,^z Dario Hauer, MD,^{aa} Farrel Hellig, MB, BS,^{bb} Ciro Indolfi, MD,^{cc} Lars Jakobsen, MD, PhD,^r Luc Janssens, MD,^{dd} Jens Jensen, MD, PhD,^{ee} Allen Jeremias, MD,^{ff} Amra Kåregren, MD,^{gg} Ann-Charlotte Karlsson, MD,^{hh} Rajesh K. Kharbanda, MD, PhD,ⁱⁱ Ahmed Khashaba, MD,^{jj} Yuetsu Kikuta, MD,^{kk} Florian Krackhardt, MD,^{ll} Bon-Kwon Koo, MD, PhD,^{mm} Sasha Koul, MD, PhD,^k Mika Laine, MD, PhD,ⁿⁿ Sam J. Lehman, MB, BS, PhD,^{oo} Pontus Lindroos, MD,^{pp} Iqbal S. Malik, PhD,^b Michael Maeng, MD, PhD,^r Hitoshi Matsuo, MD, PhD,^{qq} Martijn Meuwissen, MD, PhD,^{rr} Chang-Wook Nam, MD, PhD,^{ss} Giampaolo Niccoli, MD, PhD,^{tt} Sukhjinder S. Nijjer, MB, BS, PhD,^b Hans Olsson, MD,^s Sven-Erik Olsson, MD,^{uu} Elmır Omerovic, MD, PhD,^{vv} Georgios Panayi, MD,^{aa} Ricardo Petraco, MB, BS, PhD,^b Jan J. Piek, MD, PhD,^{ww} Flavio Ribichini, MD,^{xx} Habib Samady, MD,^{yy} Bruce Samuels, MD,^{zz} Lennart Sandhall, MD,^{uu} James Sapontis, MB, BS,^{aaa} Sayan Sen, MD, PhD,^b Arnold H. Seto, MD,^{bbb} Murat Sezer, MD,^{ccc} Andrew S.P. Sharp, MD,^{ddd} Eun-Seok Shin, MD,^{eee} Jasvinder Singh, MD,^{fff} Hiroaki Takashima, MD, PhD,^{ggg} Suneel Talwar, MB, BS, MD,^{hhh} Nobuhiro Tanaka, MD, PhD,ⁱⁱⁱ Kare Tang, MD,^{jjj} Eric Van Belle, MD, PhD,^{kkk} Niels van Royen, MD, PhD,^{lll} Christoph Varenhorst, MD, PhD,^{mmm} Hugo Vinhas, MD,ⁿⁿⁿ Christiaan J. Vrints, MD, PhD,^{ooo} Darren Walters, MB, BS,^{ppp} Hiroyoshi Yokoi, MD,^{qqq} Ole Frøbert, MD, PhD,^o Manesh R. Patel, MD,^{rrr} Patrick Serruys, MD, PhD,^{sss} Justin E. Davies, MD, PhD,^b Matthias Götberg, MD, PhD,^k

JACC: CARDIOVASCULAR INTERVENTIONS CME/MOC

This article has been selected as this issue's CME/MOC activity, available online at <http://www.acc.org/jacc-journals-cme> by selecting the JACC Journals CME/MOC tab.

Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME/MOC activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Method of Participation and Receipt of CME/MOC Certificate

To obtain credit for this CME/MOC activity, you must:

1. Be an ACC member or JACC: *Cardiovascular Interventions* subscriber.

2. Carefully read the CME/MOC-designated article available online and in this issue of the journal.
3. Answer the post-test questions. At least 2 out of the 3 questions provided must be answered correctly to obtain CME/MOC credit.
4. Complete a brief evaluation.
5. Claim your CME/MOC credit and receive your certificate electronically by following the instructions given at the conclusion of the activity.

CME/MOC Objective for This Article: At the end of the activity the reader should be able to: 1) understand the differences of currently available physiologic indices; 2) recognize the safety of deferred patients with physiology-guided decision-making; and 3) compare the results in the present study to previous trials.

CME/MOC Editor Disclosure: JACC: *Cardiovascular Interventions* CME/MOC Editor Bill Gogas, MD, PhD, has reported that he has no disclosures.

Author Disclosures: DEFINE-FLAIR and iFR-SWEDEHEART were supported by unrestricted educational grants from Philips

(formerly Volcano) to Imperial College Trials Unit and Uppsala Clinical Research Centre, respectively. This trial received no additional funding. Dr. Escaned is a speaker and consultant for Abbott, Boston Scientific, and Philips, and received personal fees from Philips Volcano, Boston Scientific, and Abbott/St. Jude Medical outside the submitted work. Dr. Al-Lamee has received personal fees from Philips Volcano outside the submitted work. Dr. Baptista has received grants and personal fees from St. Jude Medical and Boston Scientific outside the submitted work. Dr. Cook has received personal fees from Philips Volcano outside the submitted work. Dr. Davies has received grants and personal fees from Volcano and Imperial College during the conduct of the study; has received grants and personal fees from Medtronic and ReCor Medical; and has received grants from AstraZeneca outside the submitted work. In addition, Dr. Davies has patents WO2011110817 A2, US9339348 B2, WO2015013134 A3, EP3021741 A2, and US20150025330 A1, issued to Imperial College and licensed to Volcano. Dr. Buller is a consultant to Philips Volcano. Dr. Di Mario has received personal fees from Philips Volcano outside the submitted work. Dr. Götberg has received grant support from Volcano during the conduct of the study; and personal fees from Volcano, Boston Scientific, and Medtronic outside the submitted work. Dr. Härle has received nonfinancial support from Volcano outside the submitted work. Dr. Jeremias has received personal fees from St. Jude Medical and Philips Volcano outside the submitted work. Dr. Khashaba has received support from Volcano during the conduct of the study. Dr. Kikuta has received personal fees from Philips Volcano during the conduct of the study. Dr. Laine has received grants from Imperial College London during the conduct of the study. Dr. Maeng has received grant support from Volcano during the conduct of the study. Dr. Nijjer has received grants from the Medical Research Council; and personal fees and nonfinancial support from Volcano during the conduct of the study. Dr. Omerovic has received grant support and personal fees from AstraZeneca; and grant support from Abbott outside the submitted work. Dr. Patel has received grants and

personal fees from Volcano during the conduct of the study; grants and personal fees from AstraZeneca and Janssen; and personal fees from Bayer outside the submitted work. Dr. Petracco has received personal fees from Philips Volcano outside the submitted work. Dr. Piek has received grants and personal fees from Abbott Vascular, Philips Volcano, and Miracor outside the submitted work. Dr. Sandhall has received personal fees from Philips Volcano and Boston Scientific outside the submitted work. Dr. Sen has received grants from Volcano during the conduct of the study; and grants and personal fees from Philips and grants from Medtronic outside the submitted work. Dr. Serruys has received personal fees from Abbott, AstraZeneca, Biotronik, Cardialysis, GLG Research, Medtronic, Sinomedical, Societ e Europa Digital & Publishing, Stentys, Svelte, Philips Volcano, St. Jude Medical, Qualimed, and Xeltis outside the submitted work. Dr. Seto has received grants from Volcano during the conduct of the study. Dr. Sharp has received personal fees from Philips Volcano outside the submitted work. Dr. Singh has received personal fees from Volcano during the conduct of the study; and personal fees from Volcano outside the submitted work. Dr. Tanaka has received personal fees from Volcano (Japan), St. Jude Medical, and Boston Scientific outside the submitted work. Dr. Van Belle has received personal fees from Philips Volcano and St. Jude Medical outside the submitted work. Dr. van Royen has received grants and personal fees from Volcano and St. Jude Medical outside the submitted work. Dr. Vinhas has received personal fees from Volcano outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME/MOC Term of Approval

Issue Date: August 13, 2018

Expiration Date: August 12, 2019

From the ^aHospital Cl nico San Carlos, IDISSC, and Universidad Complutense de Madrid, Madrid, Spain; ^bHammersmith Hospital, Imperial College London, London, United Kingdom; ^cCRUK & UCL Cancer Trials Centre, University College London, London, United Kingdom; ^dHospital Universitario de Torrej n and Universidad Francisco de Vitoria, Madrid, Spain; ^eKing Abdulaziz Medical City Cardiac Center, Riyadh, Saudi Arabia; ^fColorado Heart and Vascular, Lakewood, Colorado; ^gMesa, Arizona; ^hHospital Prof. Doutor Fernando Fonseca, Amadora, Portugal; ⁱUppsala Clinical Research Center, Uppsala University, Uppsala, Sweden; ^jRoyal North Shore Hospital, Sydney, Australia; ^kDepartment of Cardiology, Clinical Sciences, Lund University, Sk ne University Hospital, Lund, Sweden; ^lGemeinschaftsklinikum Mittelrhein, Kemperhof Koblenz, Koblenz, Germany; ^mCardiovascular Institute, Hospital Clinic, Institut d'Investigacions Biom diques August Pi i Sunyer, Barcelona, Spain; ⁿSt. Michaels Hospital, Toronto, Ontario, Canada; ^oDepartment of Cardiology, Faculty of Health,  rebro University,  rebro, Sweden; ^pHospital Santa Maria, Lisbon, Portugal; ^qKalmar County Hospital, and Linnaeus University, Faculty of Health and Life Sciences, Kalmar, Sweden; ^rDepartment of Cardiology, Aarhus University Hospital, Aarhus, Denmark; ^sDepartment of Cardiology, Karlstad Hospital, Karlstad, Sweden; ^tRoyal Brompton Hospital, Imperial College London, United Kingdom, and University of Florence, Florence, Italy; ^uInje University Ilsan Paik Hospital, Daehwa-Dong, South Korea; ^vPauls Stradins Clinical University Hospital, Riga, Latvia; ^wConquest Hospital, St. Leonards-on-Sea, United Kingdom; ^xSana Klinikum Lichtenberg, Lichtenberg, Germany; ^yDepartment of Cardiology, Reykjavik University Hospital, Reykjavik, Iceland; ^zKlinikum Oldenburg, European Medical School, Carl von Ossietzky University, Oldenburg, Germany; ^{aa}Departments of Cardiology and Medical and Health Sciences, Link ping University, Link ping, Sweden; ^{ab}Sunninghill Hospital, Johannesburg, South Africa; ^{ac}University Magna Graecia, Catanzaro, Italy; ^{ad}Imelda Hospital, Bonheiden, Belgium; ^{ae}Department of Clinical Science and Education, S dersjukhuset, Karolinska Institutet, and Unit of Cardiology, Capio S:t G rans Sjukhus, Stockholm, and Department of Medicine, Sundsvall Hospital, Sundsvall, Sweden; ^{af}Stony Brook University Medical Center, Stony Brook, New York; ^{ag}Department of Internal Medicine, V stmanland Hospital V ster s, V ster s, Sweden; ^{ah}Department of Cardiology, Halmstad Hospital, Halmstad, Sweden; ^{ai}John Radcliffe Hospital, Oxford University Hospitals Foundation Trust, Oxford, United Kingdom; ^{aj}Ain Shams University, Cairo, Egypt; ^{ak}Fukuyama Cardiovascular Hospital, Fukuyama, Japan; ^{al}Charite Campus Virchow Klinikum, Universitaetsmedizin, Berlin, Germany; ^{am}Seoul National University Hospital, Seoul, South Korea; ^{an}Helsinki University Hospital, Helsinki, Finland; ^{ao}Flinders University, Adelaide, Australia; ^{ap}Department of Cardiology, St. G ran Hospital, Stockholm, Sweden; ^{aq}Gifu Heart Center, Gifu, Japan; ^{ar}Amphia Hospital, Breda, the Netherlands; ^{as}Keimyung University Dongsan Medical Center, Daegu, South Korea; ^{at}Catholic University of the Sacred Heart, Rome, Italy; ^{au}Departments of Cardiology and Radiology, Helsingborg Hospital, Helsingborg, Sweden; ^{av}Department of Cardiology, Sahlgrenska University Gothenburg, Sweden; ^{aw}AMC Heart Center, Academic Medical Center, Amsterdam, the Netherlands;

Safety of the Deferral of Coronary Revascularization on the Basis of Instantaneous Wave-Free Ratio and Fractional Flow Reserve Measurements in Stable Coronary Artery Disease and Acute Coronary Syndromes

Javier Escaned, MD, PhD,^a Nicola Ryan, MB, BCH,^{a,*} Hernán Mejía-Rentería, MD,^{a,*} Christopher M. Cook, MD,^b Hakim-Moulay Dehbi, PhD,^c Eduardo Alegria-Barrero, MD, PhD,^d Ali Alghamdi, MD,^e Rasha Al-Lamee, MD,^b John Altman, MD,^f Alphonse Ambrosia, DO,^g Sérgio B. Baptista, MD,^h Maria Bertilsson, MSc,ⁱ Ravinay Bhindi, MB, BS, PhD,^j Mats Birgander, MD, PhD,^k Waldemar Bojara, MD,^l Salvatore Brugaletta, MD, PhD,^m Christopher Buller, MD,ⁿ Fredrik Calais, MD,^o Pedro Canas Silva, MD,^p Jörg Carlsson, MD, PhD,^q Evald H. Christiansen, MD, PhD,^r Mikael Danielewicz, MD,^s Carlo Di Mario, MD, PhD,^t Joon-Hyung Doh, MD, PhD,^u Andrejs Erglis, MD, PhD,^v David Erlinge, MD, PhD,^k Robert T. Gerber, PhD,^w Olaf Going, MD,^x Ingibjörg Gudmundsdóttir, MD, PhD,^y Tobias Hårlé, MD,^z Dario Hauer, MD,^{aa} Farrel Hellig, MB, BS,^{bb} Ciro Indolfi, MD,^{cc} Lars Jakobsen, MD, PhD,^r Luc Janssens, MD,^{dd} Jens Jensen, MD, PhD,^{ee} Allen Jeremias, MD,^{ff} Amra Kåregren, MD,^{gg} Ann-Charlotte Karlsson, MD,^{hh} Rajesh K. Kharbanda, MD, PhD,ⁱⁱ Ahmed Khashaba, MD,^{jj} Yuetsu Kikuta, MD,^{kk} Florian Krackhardt, MD,^{ll} Bon-Kwon Koo, MD, PhD,^{mm} Sasha Koul, MD, PhD,^k Mika Laine, MD, PhD,ⁿⁿ Sam J. Lehman, MB, BS, PhD,^{oo} Pontus Lindroos, MD,^{pp} Iqbal S. Malik, PhD,^b Michael Maeng, MD, PhD,^r Hitoshi Matsuo, MD, PhD,^{qq} Martijn Meuwissen, MD, PhD,^{rr} Chang-Wook Nam, MD, PhD,^{ss} Giampaolo Niccoli, MD, PhD,^{tt} Sukhjinder S. Nijjer, MB, BS, PhD,^b Hans Olsson, MD,^s Sven-Erik Olsson, MD,^{uu} Elmira Omerovic, MD, PhD,^{vv} Georgios Panayi, MD,^{aa} Ricardo Petraco, MB, BS, PhD,^b Jan J. Piek, MD, PhD,^{ww} Flavio Ribichini, MD,^{xx} Habib Samady, MD,^{yy} Bruce Samuels, MD,^{zz} Lennart Sandhall, MD,^{uu} James Sapontis, MB, BS,^{aaa} Sayan Sen, MD, PhD,^b Arnold H. Seto, MD,^{bbb} Murat Sezer, MD,^{ccc} Andrew S.P. Sharp, MD,^{ddd} Eun-Seok Shin, MD,^{eee} Jasvinder Singh, MD,^{fff} Hiroaki Takashima, MD, PhD,^{ggg} Suneel Talwar, MB, BS, MD,^{hhh} Nobuhiro Tanaka, MD, PhD,ⁱⁱⁱ Kare Tang, MD,^{jjj} Eric Van Belle, MD, PhD,^{kkk} Niels van Royen, MD, PhD,^{lll} Christoph Varenhorst, MD, PhD,^{mmm} Hugo Vinhas, MD,ⁿⁿⁿ Christiaan J. Vrints, MD, PhD,^{ooo} Darren Walters, MB, BS,^{ppp} Hiroyoshi Yokoi, MD,^{qqq} Ole Fröbert, MD, PhD,^o Manesh R. Patel, MD,^{rrr} Patrick Serruys, MD, PhD,^{sss} Justin E. Davies, MD, PhD,^b Matthias Götzberg, MD, PhD,^k

^{xx}University Hospital Verona, Verona, Italy; ^{yy}Emory University, Atlanta, Georgia; ^{zz}Cedars-Sinai Heart Institute, Los Angeles, California; ^{aaa}MonashHeart and Monash University, Melbourne, Australia; ^{bbb}Veterans Affairs Long Beach Healthcare System, Long Beach, California; ^{ccc}Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey; ^{ddd}Royal Devon and Exeter Hospital and University of Exeter, Exeter, United Kingdom; ^{eee}Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea; ^{fff}Washington University School of Medicine, St. Louis, Missouri; ^{ggg}Aichi Medical University Hospital, Aichi, Japan; ^{hhh}Royal Bournemouth General Hospital, Bournemouth, United Kingdom; ⁱⁱⁱTokyo Medical University, Tokyo, Japan; ^{jjj}Essex Cardiothoracic Centre, Basildon and Anglia Ruskin University, Chelmsford, United Kingdom; ^{kkk}Institut Coeur Poumon, Lille University Hospital, and INSERM Unité 1011, Lille, France; ^{lll}VU University Medical Center, Amsterdam, the Netherlands; ^{mmm}Department of Medical Sciences, Uppsala University, Uppsala, Sweden; ⁿⁿⁿHospital Garcia de Horta, Lisbon, Portugal; ^{ooo}Antwerp University Hospital, Antwerp, Belgium; ^{ppp}Prince Charles Hospital, Brisbane, Australia; ^{qqq}Fukuoka Sannou Hospital, Fukuoka, Japan; ^{rrr}Duke University, Durham, North Carolina; and ^{sss}Department of Cardiology, Imperial College London, London, United Kingdom. DEFINE-FLAIR and iFR-SWEDEHEART were supported by unrestricted educational grants from Philips (formerly Volcano) to Imperial College Trials Unit and Uppsala Clinical Research Centre, respectively. This trial received no additional funding. Dr. Escaned is a speaker and consultant for Abbott, Boston Scientific, and Philips, and received personal fees from Philips Volcano, Boston Scientific, and Abbott/St. Jude Medical outside the submitted work. Dr. Al-Lamee has received personal fees from Philips Volcano outside the submitted work. Dr. Baptista has received grants and personal fees from St. Jude Medical and Boston Scientific outside the submitted work. Dr. Cook has received personal fees from Philips Volcano outside the submitted work. Dr. Davies has received grants and personal fees from Volcano and Imperial College during the conduct of the study; has received from grants and personal fees from Medtronic and ReCor Medical; and has received grants from AstraZeneca outside the submitted work. In addition, Dr. Davies has patents WO2011110817 A2, US9339348 B2, WO2015013134 A3, EP3021741 A2, and US20150025330 A1, issued to Imperial College and licensed to Volcano. Dr. Buller is a consultant to Philips Volcano. Dr. Di Mario has received personal fees from Philips Volcano outside the submitted work. Dr. Götzberg has received grant support from

ABSTRACT

OBJECTIVES The aim of this study was to investigate the clinical outcomes of patients deferred from coronary revascularization on the basis of instantaneous wave-free ratio (iFR) or fractional flow reserve (FFR) measurements in stable angina pectoris (SAP) and acute coronary syndromes (ACS).

BACKGROUND Assessment of coronary stenosis severity with pressure guidewires is recommended to determine the need for myocardial revascularization.

METHODS The safety of deferral of coronary revascularization in the pooled per-protocol population ($n = 4,486$) of the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR-SWEDEHEART (Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome) randomized clinical trials was investigated. Patients were stratified according to revascularization decision making on the basis of iFR or FFR and to clinical presentation (SAP or ACS). The primary endpoint was major adverse cardiac events (MACE), defined as the composite of all-cause death, nonfatal myocardial infarction, or unplanned revascularization at 1 year.

RESULTS Coronary revascularization was deferred in 2,130 patients. Deferral was performed in 1,117 patients (50%) in the iFR group and 1,013 patients (45%) in the FFR group ($p < 0.01$). At 1 year, the MACE rate in the deferred population was similar between the iFR and FFR groups (4.12% vs. 4.05%; fully adjusted hazard ratio: 1.13; 95% confidence interval: 0.72 to 1.79; $p = 0.60$). A clinical presentation with ACS was associated with a higher MACE rate compared with SAP in deferred patients (5.91% vs. 3.64% in ACS and SAP, respectively; fully adjusted hazard ratio: 0.61 in favor of SAP; 95% confidence interval: 0.38 to 0.99; $p = 0.04$).

CONCLUSIONS Overall, deferral of revascularization is equally safe with both iFR and FFR, with a low MACE rate of about 4%. Lesions were more frequently deferred when iFR was used to assess physiological significance. In deferred patients presenting with ACS, the event rate was significantly increased compared with SAP at 1 year. (J Am Coll Cardiol Intv 2018;11:1437-49) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Volcano during the conduct of the study; and personal fees from Volcano, Boston Scientific, and Medtronic outside the submitted work. Dr. Härle has received nonfinancial support from Volcano outside the submitted work. Dr. Jeremias has received personal fees from St. Jude Medical and Philips Volcano outside the submitted work. Dr. Khashaba has received support from Volcano during the conduct of the study. Dr. Kikuta has received personal fees from Philips Volcano during the conduct of the study. Dr. Laine has received grants from Imperial College London during the conduct of the study. Dr. Maeng has received grant support from Volcano during the conduct of the study. Dr. Nijjer has received grants from the Medical Research Council; and personal fees and nonfinancial support from Volcano during the conduct of the study. Dr. Omerovic has received grant support and personal fees from AstraZeneca and grant support from Abbott outside the submitted work. Dr. Patel has received grants and personal fees from Volcano during the conduct of the study, grants and personal fees from AstraZeneca and Janssen, and personal fees from Bayer outside the submitted work. Dr. Petraco has received personal fees from Philips Volcano outside the submitted work. Dr. Piek has received grants and personal fees from Abbott Vascular, Philips Volcano, and Miracor outside the submitted work. Dr. Sandhall has received personal fees from Philips Volcano and Boston Scientific outside the submitted work. Dr. Sen has received grants from Volcano during the conduct of the study; and grants and personal fees from Philips and grants from Medtronic outside the submitted work. Dr. Serruys has received personal fees from Abbott, AstraZeneca, Biotronik, Cardialysis, GLG Research, Medtronic, Sinomedical, Société Europe Digital & Publishing, Stentys, Svelte, Philips Volcano, St. Jude Medical, Qualimed, and Xeltis outside the submitted work. Dr. Seto has received grants from Volcano during the conduct of the study. Dr. Sharp has received personal fees from Philips Volcano outside the submitted work. Dr. Singh has received personal fees from Volcano during the conduct of the study and personal fees from Volcano outside the submitted work. Dr. Tanaka has received personal fees from Volcano (Japan), St. Jude Medical, and Boston Scientific outside the submitted work. Dr. Van Belle has received personal fees from Philips Volcano and St. Jude Medical outside the submitted work. Dr. van Royen has received grants and personal fees from Volcano and St. Jude Medical outside the submitted work. Dr. Vinhas has received personal fees from Volcano outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. *Drs. Ryan and Mejia-Renteria contributed equally to this research.

Manuscript received April 11, 2018; revised manuscript received May 14, 2018, accepted May 16, 2018.

Physiology-guided coronary revascularization is currently recommended in clinical practice guidelines on the grounds of ample evidence supporting its clinical value (1). Compared with angiography alone, decision making using fractional flow reserve (FFR) improves patient outcomes and procedural cost efficiencies (2). These benefits are due largely to deferral of myocardial revascularization in hemodynamically nonsignificant stenosis (3-5). The 15-year follow-up of the DEFER (Deferral vs. Performance of Percutaneous Coronary Intervention of Functionally Non-Significant Coronary Stenosis) trial, the pivotal study assessing the safety of FFR-based revascularization deferral, has shown favorable very long term outcomes (4). However, the results of that study are difficult to translate into current clinical practice because of the small sample size, the use of a different FFR cutoff (0.75), and major developments in percutaneous coronary intervention (PCI) and medical therapy in the intervening 17 years (3).

SEE PAGE 1450

Recently, 2 large randomized clinical trials, DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR-SWEDEHEART (Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome), compared the clinical outcomes of 4,529 patients with coronary stenoses undergoing either FFR-based or instantaneous wave-free ratio (iFR)-based revascularization, the latter a novel adenosine-free index of stenosis severity (6,7). The combined dataset of both studies provides a unique opportunity to revisit the safety of physiology-guided deferral of revascularization in contemporary clinical practice, with the added value of depicting the predominant clinical use of FFR, which is interrogation of stenoses with intermediate angiographic severity (8-10).

In this study, we investigated the 1-year clinical outcomes of patients who were included in the per-protocol populations of the DEFINE-FLAIR and iFR-SWEDEHEART randomized trials. As both trials included patients with stable angina pectoris (SAP) and acute coronary syndromes (ACS), the safety of revascularization deferral in both clinical scenarios could be compared. This may shed light on conflicting reports regarding the comparable safety of revascularization deferral in patients in stable condition and in those presenting with ACS (11-15).

METHODS

STUDY DESIGN. The DEFINE-FLAIR and iFR-SWEDEHEART trial designs have been previously

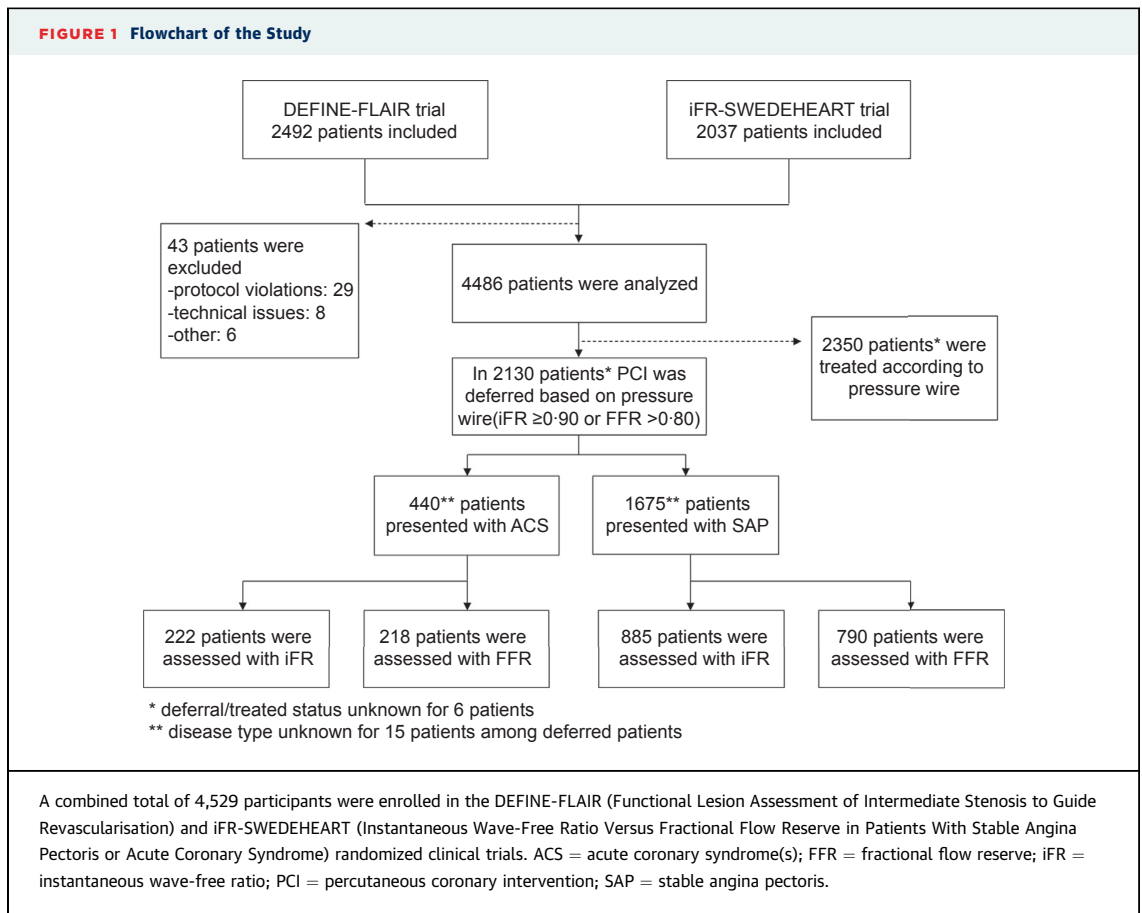
reported (6,7). In brief, both are multicenter, prospective, randomized trials comparing clinical outcomes and cost-effectiveness of iFR- and FFR-based decision making in physiologically guided coronary revascularization. Eligible patients were randomly assigned to undergo revascularization decision making guided by either iFR or FFR. Patients enrolled in iFR-SWEDEHEART were included in the SCAAR (Swedish Coronary Angiography and Angioplasty Registry), which was used to obtain immediate and continuous feedback on processes and quality-of-care measures (Online Appendix). Whereas iFR-SWEDEHEART had an open-label design, DEFINE-FLAIR was a double-blind trial with patients and follow-up teams blinded to the use of iFR or FFR. Both trials confirmed their primary hypothesis, that iFR was noninferior to FFR for major adverse cardiac events (MACE) at 1 year in patients undergoing physiologically guided revascularization decision making.

STUDY POPULATION. Our study combined and analyzed the merged populations of the DEFINE-FLAIR and iFR-SWEDEHEART randomized clinical trials. These patients had an indication for physiological assessment of at least 1 coronary lesion in which the functional severity was questionable (40% to 80% stenosis by visual assessment). This study included patients with SAP and ACS (unstable angina pectoris, non-ST-segment elevation myocardial infarction [MI], and ST-segment elevation MI). In patients with SAP, any lesion could be assessed. In patients with ACS, physiological interrogation was performed only in the nonculprit artery once the culprit vessel was revascularized. In the case of ST-segment elevation MI, nonculprit vessels were evaluated >48 h after primary PCI. Inclusion and exclusion criteria are listed in the Online Appendix. In both trials, all participants provided written informed consent before enrollment.

PROCEDURE. Physiological measurements were performed in the usual manner using the same coronary pressure guidewire (Verrata, Philips Volcano, San Diego, California). Before measurement, intracoronary nitrates were administered to control vasomotor tone. Pre-specified treatment thresholds were 0.89 for iFR and 0.80 for FFR. Stenoses were revascularized with either PCI or coronary artery bypass grafting. When iFR or FFR exceeded these pre-specified thresholds, treatment was deferred. Pressure drift was assessed using the pressure ratio at the catheter tip after each physiological measurement.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
CI = confidence interval
FFR = fractional flow reserve
HR = hazard ratio
iFR = instantaneous wave-free ratio
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
SAP = stable angina pectoris



If the pressure ratio exceeded ± 0.02 , physiological measurements were repeated. For patients assigned to FFR, hyperemia was obtained with intravenous or intracoronary hyperemic agents as previously described (6,7). When multivessel revascularization was required, investigators could stage procedures within 60 days of the index measurement. Revascularization was performed according to standard clinical practice, with pharmacological therapy left to the discretion of the treating physician.

ENDPOINTS. The primary safety endpoint of the study was the composite of MACE, defined as all-cause death, nonfatal MI, or unplanned revascularization within 12 months of the index procedure. Secondary endpoints were the individual components of MACE. In both DEFINE-FLAIR and iFR-SWEDEHEART, death and MI were adjudicated with anonymized source documentation by independent clinical event adjudication committees, whose members were unaware of the group assignments. A consensus decision was made on the basis of the pre-specified endpoint definitions. Unplanned revascularization events and secondary angiographic

outcomes were adjudicated by the clinical event adjudication committee in DEFINE-FLAIR and by an independent experienced observer who was unaware of the group assignments in iFR-SWEDEHEART.

STATISTICAL ANALYSIS. The objective of this study was to compare event rates between physiological techniques (iFR vs. FFR) in patients for whom revascularization was deferred on the grounds of physiological measurements. Additionally, we investigated whether clinical presentation (SAP vs. ACS) influenced event rates and subsequently if this was modified by which physiological technique was used to guide decision making.

For MACE and its components, a time-to-event analysis was performed in the per-protocol population by Cox survival modeling. Participants who withdrew from the study before reaching 1 year of follow-up and who were event free at their last visit were censored at their time of last visit. Testing of the validity of the proportional hazards assumption was done using Schoenfeld residuals. There were no signs of violations of proportional hazards assumption.

TABLE 1 Baseline Characteristics of the Deferred Population

	iFR (n = 1,117)	FFR (n = 1,013)	p Value
Age (yrs)	66.1 ± 10.7	66.6 ± 9.9	0.55
Male	72.0 (804)	68.0 (689)	0.05
Body mass index (kg/m ²)	27.5 ± 4.7	27.5 ± 5.0	0.51
Diabetes mellitus	21.8 (243)	24.8 (251)	0.19
Hypertension	71.1 (794)	71.7 (726)	0.32
Hyperlipidemia	68.5 (765)	66.3 (672)	0.52
Current smoker	19.0 (212)	17.8 (180)	
Previous MI	30.1 (336)	30.4 (308)	0.09
Previous PCI	42.6 (476)	43.4 (440)	0.57
CCS angina class			<0.01
I	26.8 (299)	22.5 (228)	
II	32.8 (366)	27.9 (283)	
III	4.8 (54)	7.8 (79)	
IV	1.8 (20)	2.3 (23)	
Clinical presentation			0.36
Acute coronary syndrome	19.9 (222)	21.5 (218)	
Stable angina pectoris	79.2 (885)	78.0 (790)	
No information	0.9 (10)	0.5 (5)	

Values are mean ± SD or % (n).
 CCS = Canadian Cardiovascular Society; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Results are reported using hazard ratios (HRs), 95% 2-sided confidence intervals (CIs), and cumulative hazard curves. Analyses were performed in an unadjusted manner as well as adjusted for the following baseline characteristics that were chosen a priori for their known associations with cardiovascular events: age, sex, body mass index, clinical presentation,

Canadian Cardiovascular Society class for grading of angina pectoris, diabetes, hypertension, hyperlipidemia, smoking status, previous MI, and previous PCI. Fully adjusted results are presented in the text and both unadjusted and fully adjusted in the tables.

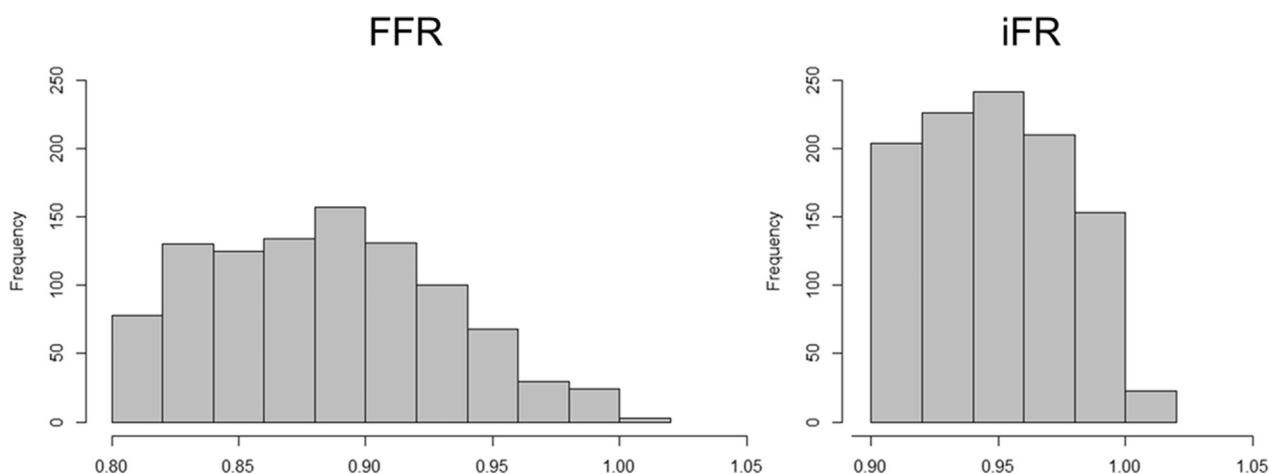
RESULTS

STUDY POPULATION. A combined total of 4,529 participants were enrolled in both trials; 2,261 were assigned to the iFR group and 2,268 to the FFR group (Figure 1). Data for 43 patients were excluded from the analyses because of unacceptable side effects associated with adenosine, technical issues, incorrect group assignment, or other reasons; data for the remaining 4,486 patients were included in the analyses.

BASELINE CHARACTERISTICS. In the overall study population, the mean age was 66.3 years, 26.6% of patients had diabetes mellitus, 72.2% had SAP, and 31.0% had history of MI. No differences were found in baseline characteristics between the iFR and FFR groups (Online Table 1).

Coronary revascularization was deferred in 2,130 patients. Deferral was performed in 1,117 patients (50%) in the iFR group and 1,013 patients (45%) in the FFR group (p < 0.01). The baseline characteristics of patients deferred by iFR and FFR methods are displayed in Table 1. The iFR group included a higher proportion of male patients than the FFR group (72.0% vs. 68.0%; p = 0.05). Canadian Cardiovascular Society grading of angina pectoris was significantly higher in the iFR group (26.8% in class I and 32.8% in

FIGURE 2 Distribution of Physiological Values



Histograms of FFR (left) and iFR (right) values in the deferred pooled patient population of the DEFINE-FLAIR and iFR-SWEDEHEART randomized clinical trials. Abbreviations as in Figure 1.

	iFR (n = 1,117)	FFR (n = 1,013)	p Value
Site of access			0.60
Radial	76.2 (851)	75.2 (762)	
Procedure time (min)			0.02
Median	30	34	
Interquartile range	20-45	24-48	
Total number of vessels evaluated	1,478	1,317	
Mean iFR/FFR value	0.95 ± 0.03	0.89 ± 0.05	
Values are % (n) or mean ± SD, unless otherwise indicated. Abbreviations as in Table 1.			

class II) than in the FFR group (22.5% in class I and 27.9% in class II) ($p < 0.01$ for the difference between groups). The remaining baseline characteristics were otherwise well balanced between the iFR- and FFR-deferred groups.

When the deferred population was stratified according to clinical presentation, overall less lesions were deferred in ACS compared with clinical presentation with SAP (36% vs. 50%; $p < 0.001$). In SAP, more lesions were deferred with iFR than FFR (55% vs. 48%; $p < 0.001$). In ACS, deferral rates were similar for both iFR and FFR guidance (36% vs. 36%; $p = 0.91$).

PROCEDURAL CHARACTERISTICS. In the deferred population, mean iFR was 0.95 ± 0.03 and mean FFR was 0.89 ± 0.05 . The distribution of iFR and FFR values is displayed in Figure 2. The procedural characteristics for the deferred populations are displayed in Table 2. The numbers of physiological evaluations per patient were 1.32 ± 0.67 for iFR and 1.30 ± 0.62 for FFR ($p = 0.67$). Total procedure time was significantly shorter in the iFR group (median 30 min; interquartile

range: 20 to 45 min) than in the FFR group (median 34 min; interquartile range: 24 to 48 min) ($p = 0.02$).

PRIMARY ENDPOINT AND COMPONENTS. There was no censoring before 12 months in iFR-SWEDEHEART; 150 patients (6.1% of 2,467) in DEFINE-FLAIR voluntarily withdrew from the study before 12 months and were censored at the time of their last visit. In the overall study population, at 1 year, the primary endpoint had occurred in 145 of 2,240 patients (6.47%) in the iFR group and in 144 of 2,246 (6.41%) in the FFR group (unadjusted HR: 1.03; 95% CI: 0.81 to 1.31; $p = 0.81$) (Online Figure 1). No significant differences were noted in terms of the components of the primary endpoint in both study arms (Online Table 2). The number of deaths from any cause at 12 months did not differ significantly between the iFR group (36 deaths, including 15 from cardiovascular causes) and the FFR group (25 deaths, including 10 from cardiovascular causes) ($p = 0.14$). The rates of nonfatal MI and unplanned revascularization did not differ significantly between the 2 groups.

When stratified according to clinical presentation, the overall MACE rate in patients with ACS (7.7%) was higher than in patients with SAP (6.0%) (fully adjusted HR: 0.72 in favor of SAP; 95% CI: 0.55 to 0.93; $p = 0.01$) (Online Table 3). In the deferred population, this difference was driven mainly by a higher 1-year MACE rate among the deferred patients with ACS (26 of 440 [5.9%]) compared with deferred patients with SAP (61 of 1,675 [3.6%]) (fully adjusted HR: 0.61 in favor of SAP; 95% CI: 0.38 to 0.99; $p = 0.04$) (Table 3).

In the deferred population, at 1 year, the primary endpoint occurred in 46 of 1,117 patients (4.12%) in the iFR group and in 41 of 1,013 patients (4.05%) in the FFR group (fully adjusted HR: 1.13; 95% CI: 0.72 to 1.79; $p = 0.60$) (Figure 3). The HRs for the individual components of MACE for iFR- versus FFR-guided deferral are displayed in Table 4. Unplanned revascularization was the biggest contributor numerically to the total MACE rate for both iFR- and FFR-deferred groups (2.78% and 3.26%, respectively; $p = 0.63$). There were no significant differences in the components of MACE between the 2 physiological techniques.

Within the deferred group, the MACE rate was more influenced by clinical presentation in patients evaluated with FFR (unadjusted HR: 0.52 in favor of SAP; 95% CI: 0.27 to 1.00; $p < 0.05$) than in those evaluated with iFR (unadjusted HR: 0.74 in favor of SAP; 95% CI: 0.38 to 1.43; $p = 0.37$) (Table 5), with a statistically nonsignificant interaction (Figure 4). The effect of clinical presentation on MI rate was more

	SAP (n = 1,675)	ACS (n = 440)	SAP vs. ACS		p Value
			Unadjusted HR (95% CI)	Fully Adjusted HR (95% CI)	
MACE	3.64 (61)	5.91 (26)	0.62 (0.39-0.99)	0.61 (0.38-0.99)	0.04
All-cause death	0.66 (11)	1.36 (6)	0.50 (0.19-1.36)	0.44 (0.16-1.23)	0.12
Cardiovascular death	0.18 (3)	0.45 (2)	0.41 (0.07-2.45)	0.21 (0.02-1.71)	0.14
Noncardiovascular death	0.48 (8)	0.91 (4)	0.55 (0.16-1.82)	0.46 (0.13-1.59)	0.22
Myocardial infarction	0.90 (15)	2.50 (11)	0.34 (0.16-0.76)	0.36 (0.16-0.79)	0.01
Unplanned revascularization	2.87 (48)	3.64 (16)	0.81 (0.46-1.43)	0.83 (0.46-1.49)	0.53
Values are % (n), unless otherwise indicated. ACS = acute coronary syndrome(s); CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event(s); SAP = stable angina pectoris.					

marked in the FFR group (unadjusted HR: 0.28 in favor of SAP; 95% CI: 0.09 to 0.88) than in the iFR group (unadjusted HR: 0.42 in favor of SAP; 95% CI: 0.14 to 1.27), but the interaction was not statistically significant.

DISCUSSION

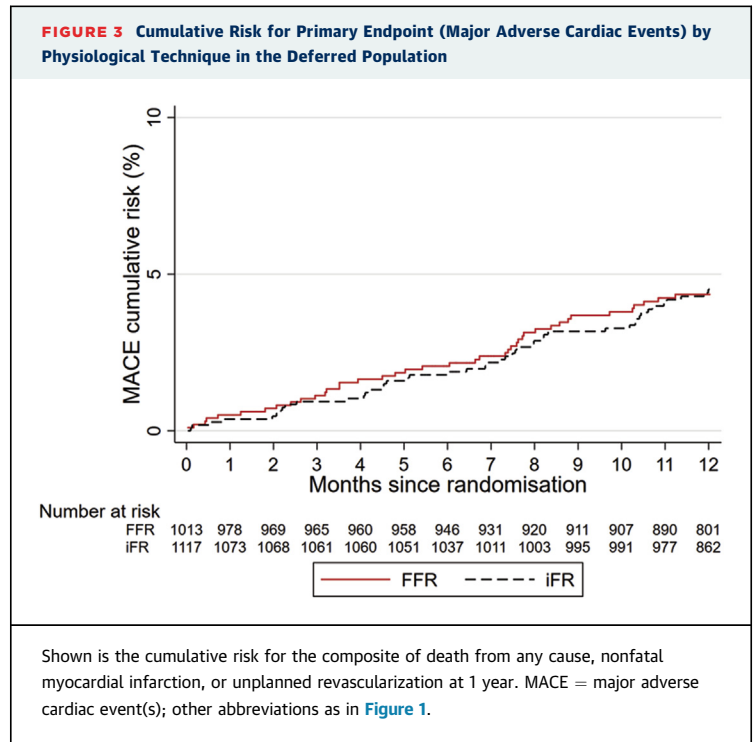
The present study demonstrates that the revascularization of intermediate stenoses in patients with SAP can be safely deferred on the grounds of iFR or FFR measurements. In patients with ACS, deferral was associated with more cardiovascular events at follow-up, compared to patients with SAP.

DEFERRAL OF REVASCLARIZATION: A KEY ASPECT OF PHYSIOLOGY-GUIDED REVASCLARIZATION.

Physiology-guided revascularization is the current main application of coronary physiology in the catheterization laboratory. It aims to improve patient outcomes by restricting revascularization to stenoses that cause myocardial ischemia (2,16). Because coronary angiography is an inadequate diagnostic tool for estimating functional stenosis severity, particularly in intermediate stenoses (17), the predominant role of intracoronary physiology is to serve as a gatekeeper to revascularization in intermediate stenoses (18).

The pivotal DEFER trial, in which 92 of the 325 patients included were randomized to PCI deferral, consolidated the concept that FFR-based postponement of revascularization is safe (3). However, translation of the trial to contemporary clinical practice is hampered not only by the fact that the 0.75 FFR cutoff in the study has been abandoned from treatment guidelines but also primarily by the evolution of treatment over the past 20 years: balloon angioplasty as a stand-alone therapy has virtually been abandoned, drug-eluting stents have been developed, and more potent antiplatelet agents and other medical therapies have become available. Furthermore, subsequent randomized studies such as the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial, although performed in the stent era, were conducted in study populations that do not align with guidelines for the recommended use of coronary physiology to guide decision making. Mean FFR in FAME was 0.71, while FFR in DEFINE-FLAIR and iFR-SWEDEHEART studies was close to the 0.80 cutoff, which is in agreement with all other contemporary registries and trials (8-10).

In the FAME trial, 513 lesions were deferred in 509 patients. At 2 years, 1.8% of patients had presented



with MI, and 10.4% required repeat revascularization (19). In the FAME II trial, 166 registry patients (those with FFR >0.80) were followed up. At 2 years, 9% of patients had reached the primary endpoint. Looking at the components of the primary endpoint, the mortality rate was 1.2%, the MI rate 5.4%, and the urgent revascularization rate 5.4% (16). Ahn et al. (20) enrolled 5,846 patients in a prospective multi-center study from 2009 to 2015 who had revascularization guided by FFR (6,468 deferred lesions, 2,165 treated lesions). In this study, the risk for cardiac events in deferred lesions, at a median

TABLE 4 Outcomes in the Overall Deferred Population According to Instantaneous Wave-Free Ratio or Fractional Flow Reserve

	iFR (n = 1,117)	FFR (n = 1,013)	iFR vs. FFR		p Value
			Unadjusted HR (95% CI)	Fully Adjusted HR (95% CI)	
MACE	4.12 (46)	4.05 (41)	1.05 (0.69-1.60)	1.13 (0.72-1.79)	0.60
All-cause death	0.98 (11)	0.59 (6)	1.68 (0.62-4.55)	2.21 (0.68-7.13)	0.19
Cardiovascular death	0.36 (4)	0.10 (1)	3.66 (0.41-32.76)	2.53 (0.23-28.32)	0.45
Noncardiovascular death	0.63 (7)	0.49 (5)	1.29 (0.41-4.05)	2.04 (0.51-8.13)	0.31
Myocardial infarction	1.16 (13)	1.28 (13)	0.99 (0.45-2.18)	1.00 (0.44-2.28)	1.00
Unplanned revascularization	2.78 (31)	3.26 (33)	0.86 (0.53-1.40)	0.88 (0.52-1.49)	0.63

Values are % (n), unless otherwise indicated.
Abbreviations as in Tables 1 and 3.

TABLE 5 Outcomes in the Overall Deferred Population According to Clinical Presentation (Stable Angina Pectoris Versus Acute Coronary Syndrome) and Effect Modification by Physiological Technique

	SAP (n = 1,675)	ACS (n = 440)	SAP vs. ACS Unadjusted HR (95% CI)	p Value	Interaction p Value
MACE	3.64 (61)	5.91 (26)	0.62 (0.39-0.99)	0.04	0.46
FFR	3.42 (27)	6.42 (14)	0.52 (0.27-1.00)		
iFR	3.84 (34)	5.41 (12)	0.74 (0.38-1.42)		
All-cause death	0.66 (11)	1.36 (6)	0.50 (0.19-1.36)	0.17	0.83
FFR	0.51 (4)	0.92 (2)	0.57 (0.10-3.13)		
iFR	0.79 (7)	1.80 (4)	0.46 (0.13-1.57)		
Cardiovascular death	0.18 (3)	0.45 (2)	0.41 (0.07-2.45)	0.33	0.38
FFR	0.00 (0)	0.46 (1)			
iFR	0.34 (3)	0.45 (1)	0.78 (0.08-7.52)		
Noncardiovascular death	0.48 (8)	0.91 (4)	0.55 (0.16-1.82)	0.32	0.38
FFR	0.51 (4)	0.46 (1)	1.14 (0.13-10.24)		
iFR	0.45 (4)	1.35 (3)	0.35 (0.08-1.56)		
Myocardial infarction	0.90 (15)	2.50 (11)	0.34 (0.16-0.76)	0.01	0.64
FFR	0.89 (7)	2.75 (6)	0.28 (0.09-0.88)		
iFR	0.90 (8)	2.25 (5)	0.42 (0.14-1.27)		
Urgent revascularization	2.87 (48)	3.64 (16)	0.81 (0.46-1.43)	0.47	0.15
FFR	2.78 (22)	5.05 (11)	0.56 (0.27-1.16)		
iFR	2.94 (26)	2.25 (5)	1.36 (0.52-3.53)		

Values are % (n), unless otherwise indicated.
Abbreviations as in Tables 1 and 3.

follow-up of 1.9 years, was linearly associated with FFR values. When FFR was >0.70, the higher the FFR value, the lower the incidence of cardiac events. However, contemporary evidence supporting the safety of FFR-based revascularization deferral is

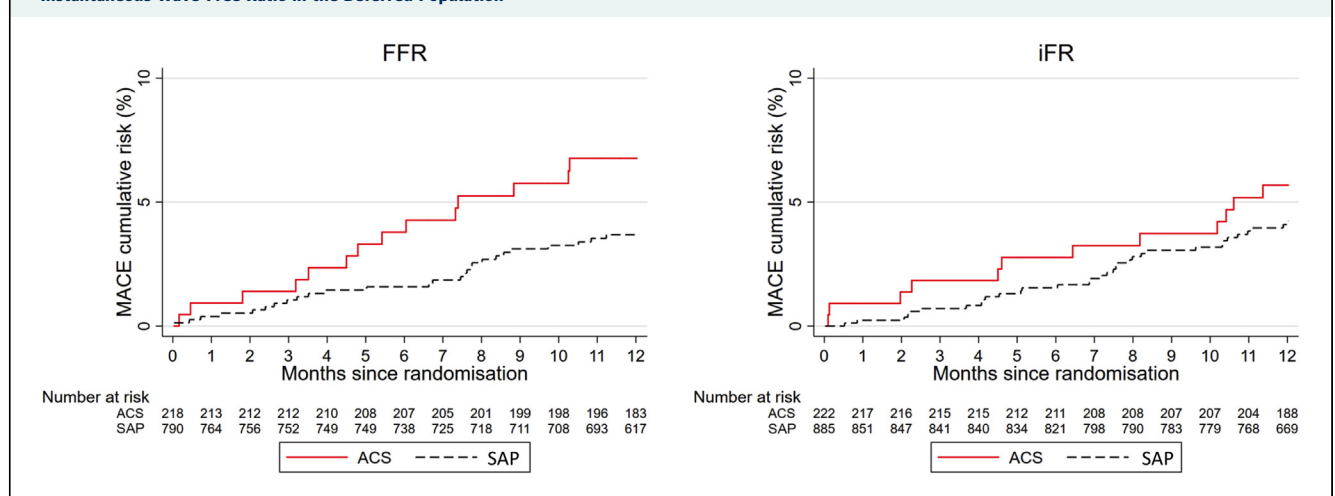
based largely on registry data, not randomized clinical trials comparing outcomes in patients with ACS compared with those with SAP.

DEFERRAL OF REVASCULARIZATION WITH EITHER FFR OR iFR. The recently published DEFINE-FLAIR and iFR-SWEDEHEART trials demonstrated that iFR is noninferior to FFR in terms of clinical outcomes associated with ischemia-driven revascularization (6,7). These trials provide the first opportunity to assess the validity of PCI deferral with a pressure-derived index of stenosis severity other than FFR. Of note, both studies consistently demonstrated that fewer stenoses were deemed hemodynamically significant when iFR was used. As this implies a higher rate of PCI deferral when iFR is used as a diagnostic tool, comparing the outcomes of patients who had iFR or FFR determined PCI deferral is an objective of the utmost clinical importance.

Overall, iFR and FFR are equally safe in deferring revascularization, with event rates in our study of 4.12% and 4.05%, respectively (fully adjusted HR: 1.13; 95% CI: 0.72 to 1.79; p = 0.60). These event rates, at 1-year follow-up, are virtually one-half of those reported for deferred patients in the DEFER trial (8%) (3), reflecting the evolution of interventional and medical therapy.

DEFERRAL OF REVASCULARIZATION IN PATIENTS WITH ACS. The evidence supporting the safety of deferral of PCI in patients with ACS on the basis of

FIGURE 4 Cumulative Risk for Primary Endpoint (Major Adverse Cardiac Events) by Clinical Presentation in Patients Assessed With Fractional Flow Reserve and Instantaneous Wave-Free Ratio in the Deferred Population



Shown is the cumulative risk for the composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization at 1 year, stratified according to clinical presentation with either stable angina pectoris (SAP) or acute coronary syndrome (ACS). Data for fractional flow reserve (FFR) (left) and instantaneous wave-free ratio (iFR) (right) are displayed.

pressure-derived measurements is limited. The conclusions of the DEFER trial, based on patients with SAP, are therefore not applicable in contemporary clinical practice, in which ACS is a very common indication for PCI. A substudy of the FAME trial documented a higher prevalence of 2-year MACE in 150 patients with ACS who had physiology-guided PCI performed (21.3%), compared with 359 patients with SAP included in the trial (16.4%); importantly, that study did not report separately the outcomes of deferred patients according to clinical presentation (21). Recent randomized trials addressing the safety of FFR-guided revascularization of nonculprit stenoses in patients with ACS and multivessel disease (11,12) have focused only on the ACS subset, not comparing the long-term outcomes with patients with SAP when revascularization is deferred on the basis of FFR (2,16). Furthermore, these trials included small numbers of patients presenting with non-ST-segment elevation MI, therefore contributing to the paucity of data on this important topic. A further limitation is that much evidence in this population comes from observational data rather than randomized clinical trials.

The present analysis confirms that among patients who had revascularization deferred, those presenting with ACS had a higher 1-year MACE rate than those presenting with SAP (5.91% vs. 3.64%; fully adjusted HR: 0.61; 95% CI: 0.38 to 0.99; $p = 0.04$) (Table 3). These findings are in agreement with recently reported studies (13,14). Hakeem et al. (14) found that FFR-based deferral of PCI in patients with ACS was associated with a more than 2-fold increase in the combined endpoint of MI or target vessel revascularization at 3.4-year follow-up compared with patients with SAP (23% vs. 11%, respectively, $p < 0.0001$). Masrani Mehta et al. (13) reported similar findings in a retrospective analysis of a series of 674 patients, of whom 334 presented with ACS. At a mean follow-up of 4.5 years, patients with ACS had a significantly higher MACE rate than those with SAP (32% vs. 23%, respectively, $p = 0.02$). Lee et al. (15) reported, as part of a prospective, international registry on FFR use, the long-term outcomes (mean 2.1 years) after FFR-based deferral of revascularization in 1,596 patients, of whom 301 presented with ACS. Deferral of revascularization in nonculprit stenoses in patients with ACS ($n = 409$) was associated with a more than 2-fold increase in MACE compared with deferral of stenoses in patients with SAP (adjusted HR: 2.97; 95% CI: 1.33 to 7.17; $p = 0.026$). Clinical

presentation with ACS was identified in a multivariate Cox model as the most powerful independent predictor of MACE after FFR-based intervention deferral (adjusted HR: 2.74; 95% CI: 1.13 to 6.64; $p = 0.026$). In contrast, our findings are not concordant with those obtained in the pooled population of 2 separate registries, including 1,983 patients, of whom 533 presented with ACS (22). At 1-year follow-up, FFR-based deferral was associated with similar MACE rates in patients presenting with ACS and SAP (8.0% vs. 8.5% with ACS and SAP, respectively; $p = 0.83$). Of note, MACE rates in that registry were markedly higher than in our study, particularly in patients with SAP (8.5% vs. 3.6% in our study).

INFLUENCE OF CLINICAL PRESENTATION ON THE SAFETY OF PRESSURE-DERIVED INDEXES OF STENOSIS SEVERITY. Whether the observed higher event rates among patients with ACS are due to their inherent higher risk or to inadequate stenosis assessment with pressure guidewires is unclear. From contemporary trial data (23) patients presenting with ACS have increased cardiovascular risk after stabilization, with respective 1-year rates of MI and death of 5.8% and 2.4%.

In our analysis, we found that MACE in deferred patients with ACS were driven largely by coronary revascularization, although both MI and death also contributed. This might provide indirect support for the concept that in patients with ACS, pressure-based indexes do not consistently identify the stenoses for which revascularization can be safely deferred. Furthermore, other studies have reported repeat revascularization as an important contributor to MACE in patients presenting with ACS who had revascularization deferred on the grounds of FFR interrogation (13-15). As we did not assess the characteristics of the atheromatous plaques in nonculprit vessels in patients with ACS, an increased risk attributable to vulnerable lesions in these patients cannot be ruled out. Such risk might be amplified by the presence of systemic inflammation, which has been documented in patients with ACS (24).

The excess of risk for physiology-based stenosis deferral in patients with ACS may reflect the substantially different physiological conditions found in these patients from those in patients with SAP. Although FFR has been extensively validated as a clinical tool in patients with SAP, its value in patients with ACS is less well described. Microcirculatory vasodilation during hyperemia can be transiently blunted in the acute phase of ACS, affecting also

myocardial territories remote to those subtended by nonculprit stenoses (25). We explored whether iFR or FFR resulted in better long-term outcomes of stenosis deferral in patients with ACS. However, the negative outcome associated with ACS presentation on 1-year outcomes after revascularization deferral was not significantly influenced by the use of either iFR or FFR, even when the individual components of MACE were analyzed separately. Numerically, we observed higher rates of MACE in the ACS compared with SAP cohort among patients deferred with FFR. This difference in rates was less pronounced in patients deferred with iFR.

STUDY LIMITATIONS. This was a nonrandomized subset of 2 prospective randomized trials, but the results have been fully adjusted for baseline clinical characteristics. Both iFR and FFR are continuous variables, which were reported and acted in a dichotomous manner (i.e., treat or do not treat if below or above a threshold), and therefore relevant clinical information is omitted from the decision-making process. In DEFINE-FLAIR, both the patients and the treating physicians remained blinded to group assignments, whereas in iFR-SWEDEHEART, both were aware of the group assignment.

CONCLUSIONS

Overall, deferral of revascularization is equally safe with both iFR and FFR, with a low MACE rate of approximately 4%. Lesions were more frequently deferred when iFR was used to assess physiological stenosis significance. Deferral of patients with ACS is associated with a significant increase in event rates at 1 year compared with patients with SAP.

ADDRESS FOR CORRESPONDENCE: Dr. Justin E. Davies, Hammersmith Hospital, Imperial College NHS Trust, Du Cane Road, London, W12 0HS, United Kingdom. E-mail: justindavies@heart123.com.

PERSPECTIVES

WHAT IS KNOWN? DEFINE-FLAIR and iFR-SWEDEHEART are the largest coronary physiology clinical outcome trials ever conducted. Within the trials, overall MACE rates at 1 year were similar for both iFR- and FFR-guided populations. However, the clinical outcomes of patients who had coronary revascularization deferred on the basis of iFR or FFR measurements, and the influence of clinical presentation (SAP and ACS) on outcomes, are unknown.

WHAT IS NEW? Despite a higher rate of deferral with iFR, clinical outcomes for both iFR- and FFR-deferred populations were similar at 1 year. This indicates that deferral of coronary revascularization by either iFR or FFR methods is equally safe. However, deferral of patients with ACS was associated with a significant increase in event rates at 1 year compared with patients with SAP.

WHAT IS NEXT? Reporting of longer term clinical outcomes from the DEFINE-FLAIR and iFR-SWEDEHEART trials are awaited. Furthermore, analyses of key substudy populations of clinical interest are ongoing.

REFERENCES

1. Windecker S, Kohl P, Alfonso S, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2014;35:2541-619.
2. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.
3. Bech GJ, De Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation* 2001;103:2928-34.
4. Zimmermann FM, Ferrara A, Johnson NP, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J* 2015;36:3182-8.
5. Arbab-Zadeh A. Fractional flow reserve-guided percutaneous coronary intervention is not a valid concept. *Circulation* 2014;129:1871-8.
6. Davies JE, Sen S, Dehbi H-M, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med* 2017;376:1824-34.
7. Götzberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med* 2017;376:1813-23.
8. Escaned J, Echavarría-Pinto M, García-García HM, et al. Prospective assessment of the diagnostic accuracy of instantaneous wave-free ratio to assess coronary stenosis relevance: results of ADVISE II international, multicenter study (Adenosine Vasodilator Independent Stenosis Evaluation II). *J Am Coll Cardiol Intv* 2015;8:824-33.
9. Van Belle E, Rioufol G, Pouillot C, et al. Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: insights from a large French multicenter fractional flow reserve registry. *Circulation* 2014;129:173-85.
10. Petraco R, Al-Lamee R, Gotberg M, et al. Real-time use of instantaneous wave-free ratio: results of the ADVISE in-practice: an international, multicenter evaluation of instantaneous wave-free ratio in clinical practice. *Am Heart J* 2014;168:739-48.
11. Smits PC, Abdel-Wahab M, Neumann F-J, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med* 2017;376:1234-44.
12. Engström T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label,

randomised controlled trial. *Lancet* 2015;386:665-71.

13. Masrani Mehta S, Depta JP, Novak E, et al. Association of lower fractional flow reserve values with higher risk of adverse cardiac events for lesions deferred revascularization among patients with acute coronary syndrome. *J Am Heart Assoc* 2015;4:e002172.

14. Hakeem A, Edupuganti MM, Almomani A, et al. Long-term prognosis of deferred acute coronary syndrome lesions based on nonischemic fractional flow reserve. *J Am Coll Cardiol* 2016;68:1181-91.

15. Lee JM, Choi KH, Koo B-K, et al. Prognosis of deferred non-culprit lesions according to fractional flow reserve in patients with acute coronary syndrome. *EuroIntervention* 2017;13:e1112-9.

16. De Bruyne B, Fearon WF, Pijls NHJ, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014;371:1208-17.

17. Toth G, Hamilos M, Pyxaras S, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J* 2014;35:2831-8.

18. Bhatt DL. Assessment of stable coronary lesions. *N Engl J Med* 2017;376:1879-81.

19. Pijls NHJ, Fearon WF, Tonino PAL, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol* 2010;56:177-84.

20. Ahn J-M, Park D-W, Shin E-S, et al. Fractional flow reserve and cardiac events in coronary artery disease: data from a prospective IRIS-FFR registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation* 2017;135:2241-51.

21. Sels J-WEM, Tonino PAL, Siebert U, et al. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol Intv* 2011;4:1183-9.

22. Belle EV, Baptista S-B, Raposo L, et al. Impact of routine fractional flow reserve on management decision and 1-year clinical outcome of patients with acute coronary syndromes. *Circ Cardiovasc Interv* 2017;10:e004296.

23. Hess CN, Clare RM, Neely ML, et al. Differential occurrence, profile, and impact of first recurrent cardiovascular events after an acute coronary syndrome. *Am Heart J* 2017;187:194-203.

24. Libby P, Tabas I, Fredman G, Fisher EA. Inflammation and its resolution as determinants of acute coronary syndromes. *Circ Res* 2014;114:1867-79.

25. Cuculi F, De Maria GL, Meier P, et al. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after. *J Am Coll Cardiol* 2014;64:1894-904.

KEY WORDS ACS, coronary physiology, deferral of revascularization, FFR, iFR, SAP

APPENDIX For inclusion and exclusion criteria, supplemental tables, and a supplemental figure, please see the online version of this paper.



Go to <http://www.acc.org/jacc-journals-cme> to take the CME/MOC quiz for this article.