Timing of procedural stroke and death in asymptomatic patients undergoing carotid endarterectomy: analysis of VACS, ACAS, ACST-1 and GALA RCTs

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Abstract

Background: The effectiveness of carotid endarterectomy (CEA) for stroke prevention depends on low procedural risks. We aimed to assess frequency and timing of procedural complications after CEA, which may clarify underlying mechanisms and help inform safe discharge policies.

Methods: Individual patient data (N=8752) were obtained from four large trials (VACS, ACAS, ACST-1, and GALA; 1983-2007). Patients undergoing CEA for asymptomatic carotid artery stenosis (N=3694) directly after randomization were used for the present analysis. We divided the timing of procedural death and stroke into intraoperative day 0, postoperative day 0, day 1-3, and days 4-30.

Results: In total, 103 (2.8%) patients had serious procedural complications (18 fatal strokes, 68 non-fatal strokes, 11 fatal myocardial infarctions, and 6 deaths from other causes). Of the 86 strokes, 67 (78%) were ipsilateral, 17 (20%) were contralateral, and two (2%) were vertebrobasilar. Forty-five strokes (52%) were ischaemic, 9 (10%) haemorrhagic and stroke subtype was not determined in 32 (37%) patients. Half the strokes happened on the day of CEA. Of all serious complications, 44 (43%) occurred on day 0 (20 intraoperative, 17 postoperative, and 7 with unclear timing), 23 (22%) occurred on days 1-3, and 36 (35%) on days 4-30.

Conclusions: At least half of the procedural strokes in this study are ischaemic and ipsilateral to the treated artery. Half of all procedural complications occurred on the day of surgery, but one third after day 3 when many patients have been discharged. Reported in-hospital stroke or death rates might underestimate true risks after CEA.

Introduction

Net benefit of carotid endarterectomy (CEA) for carotid artery stenosis is partly determined by the risk of procedural complications. Three randomized clinical trials (RCTs) in asymptomatic patients with high-grade carotid stenosis compared endarterectomy plus medical therapy with medical therapy alone: The Veterans Administration Cooperative Study (VACS);[1] The Asymptomatic Carotid Atherosclerosis Study Group (ACAS);[2] and the Asymptomatic Carotid Surgery Trial (ACST-1).[3,4] The 30-day death or stroke risk ranged from 2.3% to 4.6%, but this included strokes that occurred during diagnostic angiography, performed commonly in the early US trials.[1,2] More recently, the General Anaesthesia versus Local Anaesthesia (GALA) RCT compared general and local anaesthesia in patients undergoing CEA.[5] No differences were found in cardiovascular outcomes between groups up to 30 days after CEA.

Several risk prediction models for the procedural hazards of CEA have been published, but their predictive performance and clinical applicability are limited.[6] Although risk models might inform patients about their risks and benefits of CEA by applying predictors of adverse outcomes to individual patients, it remains unclear when and how procedural complications might be prevented.[7] A detailed analysis of the timing of procedural events and stroke subtype might help inform safe discharge policies and may critically review reporting of in-hospital complication rates after CEA.

We aimed to assess frequency and timing of procedural complications after CEA for asymptomatic carotid stenosis in order to inform future operative policies.

Material and methods

Data sources

Individual patient data from four RCTs were obtained: VACS,[1] ACAS,[2] ACST-1,[3,4] and GALA.[5] Details on the individual trials are published elsewhere.[8-11] In summary, the VACS, ACAS, and ACST-1 RCTs compared CEA plus medical treatment versus medical treatment alone. In the VACS, 444 male patients with ≥50% stenosis were randomized (1983-1987). ACAS randomized 1662 patients <80 years with ≥60% stenosis (1987-1993). ACST-1 randomized 3120 patients with ≥60% stenosis (1993-2003). GALA randomized 3526 (1362 asymptomatic and 2164 symptomatic) patients with carotid artery stenosis regardless of degree of stenosis between either loco-regional (LA) or general anaesthesia (GA) (1999-2007).

Assessment of carotid stenosis

All patients in VACS underwent intra-arterial angiography after randomization to determine the operability of the carotid stenosis,[8] and all patients in ACAS underwent duplex ultrasound (DUS), with additional intra-arterial angiography in patients allocated to CEA.[9] Though angiography was not required in ACST-1, some patients did have this.[4] In GALA, degree of stenosis was assessed by DUS in 1,259 (92.4%) of the 1,362 asymptomatic patients.[5]

Outcome measures

The primary outcome was timing of procedural (30-day) death and any non-fatal stroke after CEA among patients with asymptomatic carotid artery stenosis.

Data-collection

We collected baseline characteristics (age, sex, medical history, blood pressure), medication use (antihypertensive, lipid-lowering, antithrombotic medication, and anticoagulants at the

time of the CEA), disease characteristics (degree of ipsilateral and contralateral stenosis, cerebral infarct on imaging), CEA characteristics (type of anaesthesia, shunt use, patch use), and timing of the complication with respect to the CEA. For procedural strokes, we also collected the following data: type of stroke (ischaemic, haemorrhagic), severity (fatal, disabling, non-disabling), territory (carotid, vertebrobasilar), and side (ipsilateral, contralateral).

Definition of outcomes and ascertainment of timing of complications

Procedural stroke was defined as an acute deficit of focal neurological function which led to symptoms lasting >24 hours, resulting from intracranial vascular disturbance (ischaemia or haemorrhage) occurring within 30 days after CEA. We used the adjudicated procedural complications from the original RCTs.[8-11] For the current analysis, two authors (MHFP and DRM) independently analysed the collected data of patients with procedural complications that occurred on day 0 to determine whether the complication occurred during (intraoperative) or after the CEA (postoperative). Consistent with previous studies, 'intraoperative' was defined as any complication that occurred before the patient left the operation room in patients where CEA was performed under LA, or before the patient was fully awake, in patients where CEA was performed under GA.[12] 'Postoperative' was defined as any complication that occurred after the patient left the operation room in patients where CEA was performed under LA, or after the patient awoke, when the CEA was performed under GA.

For the timing of fatal procedural strokes, we used the date at which the stroke occurred to determine the timing of stroke, not the date of death. Timing was classified as: "timing unclear" if the complication occurred on day 0 but exact timing could not be determined. Uncertainties were discussed with a senior author (GJdB).

Statistical analyses

We included the first CEA of patients allocated immediate CEA from the VACS, ACAS and ACST-1 RCTs and all asymptomatic CEAs from GALA. We excluded patients who did not adhere to allocated treatment (8 patients in VACS, 97 ACAS, 134 in ACST-1, and 28 asymptomatic patients in GALA). Crossover patients from the medical therapy group (29 patients in VACS, 305 in ACAS, and 407 in ACST-1) were also excluded, since some characteristics at the time of deferred CEA and qualifying event for the deferred CEA were not systematically recorded in all RCTs. Angiography-related pre-procedural strokes were also excluded.

Patient, disease and procedural characteristics are reported with descriptive statistics. Categorical variables are reported as absolute number and percentage and continuous variables as mean and standard deviation (SD). The timing was divided into four intervals from CEA: intraoperative day 0, postoperative day 0, day 1-3 and day 4-30.

Results

The present study includes 3694 patients who underwent the allocated CEA for asymptomatic carotid artery stenosis (203 from VACS, 731 from ACAS, 1426 from ACST-1, and 1334 from GALA). (Figure 1).

A total of 103 (2.8%) patients had a stroke or died during the 30-day procedural period. Of these, 67 patients (65%) in VACS, ACAS and ACST-1 were randomized to immediate CEA; in GALA 19 (18%) patients were randomized to general anaesthesia and 17 (17%) to local anaesthesia. Patient, disease and procedural characteristics are provided in Table 1.

Of 103 procedural complications, 86 were strokes and 17 were non-stroke related deaths. Of 86 strokes, 18 (21%) were fatal, 23 (27%) were disabling, and 45 (52%) were non-disabling. Sixty-seven (78%) were ipsilateral to the operated artery, 17 (20%) contralateral and two (2%) were vertebrobasilar. Forty-five strokes (52%) were ischaemic, nine (11%) were haemorrhagic, and in 32 (37%) patients (6 patients from VA, 12 from ACAS, 5 from ACST-1 and 9 from GALA) stroke subtype could not be determined.

Timing and severity of procedural stroke or death

Forty-three (50%) procedural strokes occurred on the day of the procedure, 18 (21%) between day 1 and 3, and 25 (29%) between day 4 and 30. Of the procedural strokes on the day of the procedure, 19 (44%) were intraoperative and 17 (40%) were postoperative. Forty-four (43%) procedural deaths and strokes occurred on the day of procedure, 23 (22%) between day 1 and 3, and 36 (35%) between day 4 and 30. Six (54.5%) of the 11 fatal myocardial infarctions occurred between day 4 and 30. (Table 2 & Figure 2). The severity of procedural strokes by timing after CEA is provided in Figure 3.

Discussion

In this individual patient data analysis from four randomized clinical trials, half of procedural complications occurred after the day of operation and one third of the complications occurred between day 4 and 30. At least half of the procedural strokes were ischaemic and ipsilateral to the treated artery. Half the strokes occurred after the day of the procedure.

Our findings are consistent with a previous study in symptomatic patients who reported that about half of the events also occurred on the day of the CEA.[13] This study also found that patients who underwent carotid artery stenting were at greater risk of complications at the day of the procedure compared to CEA, but not for complications beyond the day of the operation.

Previous studies showed that the pathogenesis of stroke may vary with the time interval from intervention.[7,12,14-17] It was concluded thatearly strokes could be due to thrombosis or thrombotic occlusion of the carotid artery sometimes associated with hypotension, while later strokes could be due to hyperperfusion. Data from ACST-1 revealed the same results with most post procedural events being related to hyperperfusion.[12] Understanding the patho-physiological mechanism of procedural stroke informs the surgeon about specific technical aspects (in, for example, cases of residual stenosis) and the application of additional protective measures, such as use of dual antiplatelet therapy to prevent increased thrombo-embolisation, or additional postoperative TCD monitoring to prevent hyperperfusion might results in lower procedural stroke risk.

Procedural complication rates after CEA in asymptomatic patients have decreased since recruitment of the included RCTs .[20] Reasons for this decrease may include improvements in medical treatment, better patient selection, and possibly the increased understanding of the mechanisms of procedural strokes and increased attention to postoperative blood pressure

control. There is also a trend towards centralization of CEA in high volume centres with high volume surgeons.[21]

Stroke risk factors include age, smoking, diabetes mellitus, ischaemic heart disease, heart and renal failure.[22] Contralateral stenosis or occlusion and use of patch angioplasty have been implicated.[23,24] Hyperperfusion syndrome (HPS)can lead to intracerebral haemorrhage and intra-arterial blood pressure monitoring for the first 3-6 hours postoperatively, followed by hourly non-invasive blood pressure monitoring for the first 24 hours, may help prevent HPS and enable early intervention.[25-27] Furthermore, transcranial doppler (TCD) monitoring during and after CEA identifies patients at high risk of developing cerebral hyperperfusion.[27,28] Intra-operative monitoring might also include measuring stump pressure, near-infrared spectroscopy, assessment of backflow in the internal carotid artery following clamping. Residual thrombus and large intimal flaps might be identified before blood flow restoration by angioscopy or, after blood flow restoration, by angiography or DUS. Residual stenosis might also be discovered by angiography or DUS. Despite, the evidence for these monitoring options is low, and therefore the recent ESVS guidelines leave to the operator to decide whether to use of either of these intra-or post procedural measures.[18]

Our study has some limitations. Procedural stroke and death were included but not non-fatal myocardial infarctions, retinal infarctions, hematomas, and cranial nerve injury. Recruitment of patients in the four RCTs stopped more than a decade ago. The inclusion of patients who underwent CEA for mild stenosis. Data on management of procedural strokes was not systematically collected. The high number of procedural strokes in which the stroke subtype was not reported. Stroke severity was not assessed with the same standardized outcome scale, but reporting of strokes in the included RCTs allowed to determine strokes severity, in terms of non-disabling, disabling or fatal. We were not able to identify risk factors for early and late procedural complications due to small number of outcomes. Minor deficits may have been

missed in the operation room, but noticed later when a neurologist examined the patient, leading to an underestimation of intraoperative strokes.

In conclusion, at least half of the procedural strokes in this study were ischaemic and most were ipsilateral to the treated artery. Half of all procedural complications occurred on the day of surgery, but one third of complications occurred after day 3 when many patients have been discharged. Reported in-hospital stroke or death rates might underestimate true risks after CEA. Intensive medical therapies, particularly antihypertensive and antithrombotic regimes, should be used for optimal procedural stroke prevention. In addition, patients should be informed about signs and symptoms of stroke and should receive clear instructions about seeking emergent medical help lest stroke occurs after discharge.

Contributions

MP, RB, DM, GdB, and AH designed the study plan. MP, DM and HP cleaned the data. MP performed the statistical analysis. MP wrote the first version of the article. All authors contributed to data interpretation, critical revision of the article, and approved the final version. All authors gave final approval to submit for publication.

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CSTC collaboration

Involvement of the authors in the CSTC Steering Committee is as follows: Ale Algra, Jacoba Greving (coordinator); EVA-3S: Jean-Pierre Becquemin, David Calvet, Jean-Louis Mas; ICSS: Leo Bonati (chair), Martin Brown, Jeroen Hendrikse; SPACE and SPACE-2: Hans-Henning Eckstein, Gustav Fraedrich, Olav Jansen, Peter Ringleb; CREST and CREST-2: Thomas Brott, George Howard, Gary Roubin; ACST-1 and ACST-2: Richard Bulbulia, Alison Halliday; trial statistician: John Gregson. The members of the Steering Committees and a list of Investigators contributing data to the trials including those in this pooled analysis can be found in earlier publications.

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Table 1. Patient and disease characteristics

	Patients with a procedural stroke or death (N = 103)	Patients without a procedural stroke or death (N = 3591)
Patient characteristics		
Age at CEA, y	68.9 ± 7.9	68.3 ± 7.8
Male sex	65 (63.1%)	2496 (69.5%)
Systolic blood pressure, mmHg	148 ± 19.5	147 ± 20.2
Diastolic blood pressure, mmHg	83 ± 11.2	81 ± 10.4
Diabetes mellitus	34 (33.0%)	899 (25.0%)
Ischaemic heart disease	41 (39.8%)	1346 (37.8%)
Prior contralateral symptoms	32 (31.1%)	782 (21.8%)
Medical therapy		
Anti-platelet therapy	73 (77.7%)	2725 (77.8%)
Anticoagulant	3 (3.2%)	91 (2.6%)
Antihypertensive therapy	55 (68.8%)	2086 (69.8%)
Lipid-lowering therapy	30 (38.0%)	972 (32.5%)
Disease characteristics		
Ipsilateral stenosis >80%	39 (42.9%)	1435 (42.2%)
Contralateral stenosis >60%	35 (38.5%)	974 (28.7%)
Contralateral occlusion	16 (17.6%)	353 (10.4%)
Brain infarct on imaging	27 (33.8%)	947 (33.4%)
Intra-operative care		
General anaesthesia	30 (61.2%)	1294 (64.3%)
Intraoperative shunt	31 (51.7%)	837 (38.0%)
Patch angioplasty	22 (36.7%)	844 (38.3%)

Categorical variables are reported as absolute number and percentage and continuous variables as mean and standard deviation (SD).
CEA, carotid endarterectomy.

Table 2. Procedural deaths and strokes by timing after CEA

	Total	Day of the procedure				Day 1-3	Day 4-30
		Intraoperative	Postoperative	Unclear timing	Total day 0		
Death / stroke per RCT (%)							
VACS	12	-	-	3 (25)	3 (25)	5 (42)	4 (33)
ACAS	13	2 (15)	2 (15)	1 (8)	5 (38)	3 (23)	5 (38)
ACST-1	42	12 (29)	10 (24)	-	22 (52)	7 (17)	13 (31)
GALA	36	6 (17)	5 (14)	3 (8)	14 (39)	8 (22)	14 (39)
Procedural outcome in all RCTs combined (%)							
Stroke or death (%)	103	20 (19)	17 (17)	7 (7)	44 (43)	23 (22)	36 (35)
Stroke (%)	86	19 (22)	17 (20)	7 (8)	43 (50)	18 (21)	25 (29)
Fatal MI (%)	11	1 (9)	-	-	1 (9)	4 (36)	6 (55)
Any death (%)	35	4 (11)	4 (11)	-	8 (23)	8 (23)	19 (54)

MI, myocardial infarction. RCT, randomized clinical trial.

Figure 1. Study flow chart

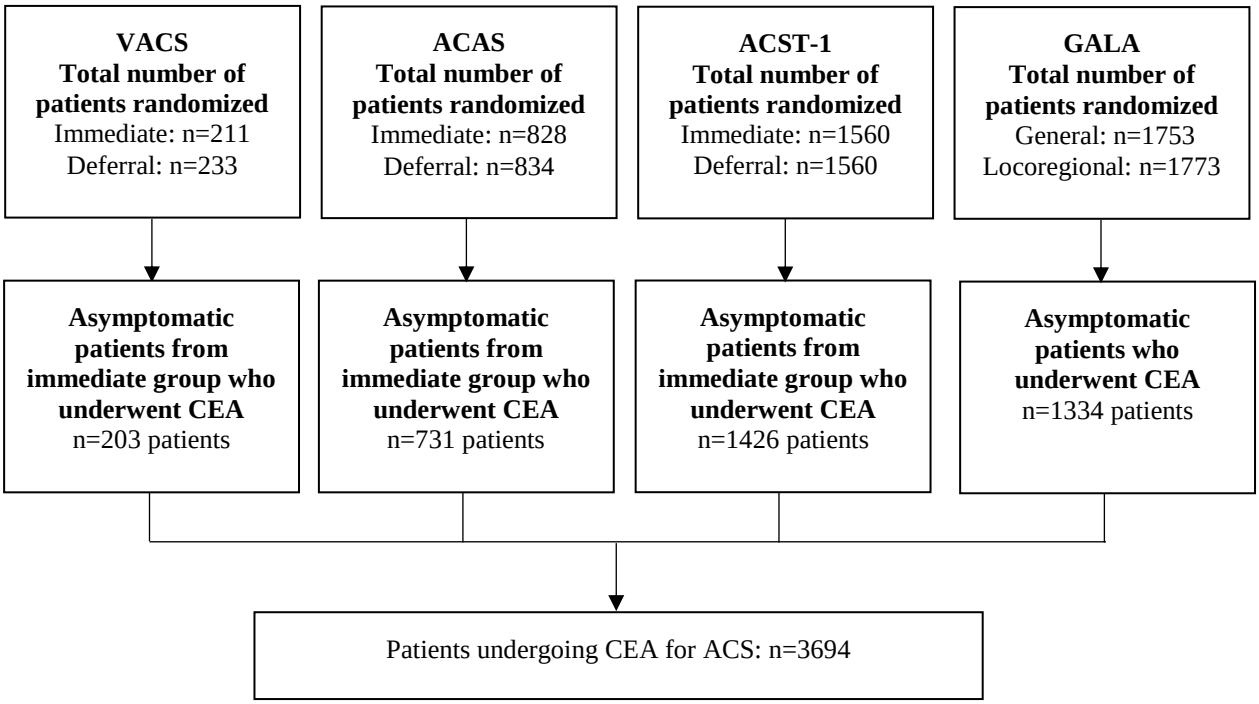
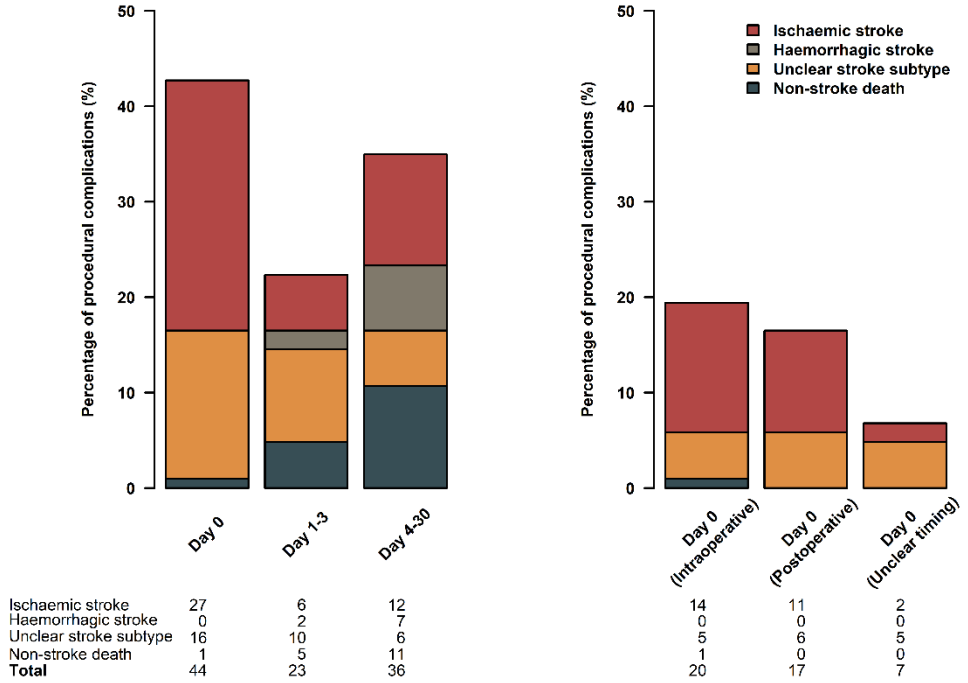
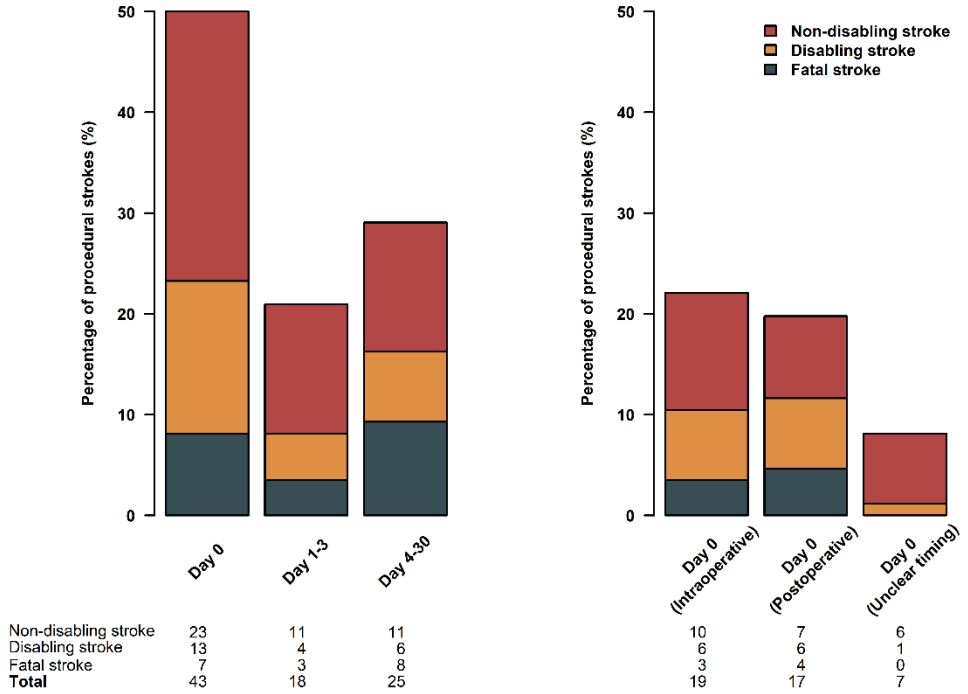


Figure 2. Timing of procedural strokes and deaths



Ischaemic stroke	27	6	12	14	11	2
Haemorrhagic stroke	0	2	7	0	0	0
Unclear stroke subtype	16	10	6	5	6	5
Non-stroke death	1	5	11	1	0	0
Total	44	23	36	20	17	7

Figure 3. Severity of procedural strokes, by timing after CEA



Non-disabling stroke	23	11	11
Disabling stroke	13	4	6
Fatal stroke	7	3	8
Total	43	18	25

10	7	6
6	6	1
3	4	0
19	17	7