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META-ANALYSIS

Editor's Choice – Risk of Stroke before Revascularisation in Patients with Symptomatic Carotid Stenosis: A Pooled Analysis of Randomised Controlled Trials

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WHAT THIS PAPER ADDS

Improvements in medical therapy over time may have lowered the risk of stroke in patients with symptomatic carotid stenosis. This study addressed this question by the first comparison of individual patient data from two historical series of large randomised controlled trials with very similar inclusion criteria. Its findings add to the current evidence that stroke risk has decreased over time. Thus, the added benefit of carotid revascularisation to modern medical care needs to be revisited in ongoing and future studies.

Objective: Current guidelines recommending rapid revascularisation of symptomatic carotid stenosis are largely based on data from clinical trials performed at a time when best medical therapy was potentially less effective than today. The risk of stroke and its predictors among patients with symptomatic carotid stenosis awaiting revascularisation in recent randomised controlled trials (RCTs) and in medical arms of earlier RCTs was assessed.

Methods: The pooled data of individual patients with symptomatic carotid stenosis randomised to stenting (CAS) or endarterectomy (CEA) in four recent RCTs, and of patients randomised to medical therapy in three earlier RCTs comparing CEA vs. medical therapy, were compared. The primary outcome event was any stroke occurring between randomisation and treatment by CAS or CEA, or within 120 days after randomisation.

Results: A total of 4 754 patients from recent trials and 1 227 from earlier trials were included. In recent trials, patients were randomised a median of 18 (IQR 7, 50) days after the qualifying event (QE). Twenty-three suffered a stroke while waiting for revascularisation (cumulative 120 day risk 1.97%, 95% confidence interval [CI] 0.75 — 3.17). Shorter time from QE until randomisation increased stroke risk after randomisation ($\chi^2 = 6.58$, $p = .011$). Sixty-one patients had a stroke within 120 days of randomisation in the medical arms of earlier trials (cumulative risk 5%, 95% CI 3.8 — 6.2).

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Stroke risk was lower in recent than earlier trials when adjusted for time between QE and randomisation, age, severity of QE, and degree of carotid stenosis (HR 0.47, 95% CI 0.25 — 0.88, $p = .019$).

Conclusion: Patients with symptomatic carotid stenosis enrolled in recent large RCTs had a lower risk of stroke after randomisation than historical controls. The added benefit of carotid revascularisation to modern medical care needs to be revisited in future studies. Until then, adhering to current recommendations for early revascularisation of patients with symptomatic carotid stenosis considered to require invasive treatment is advisable.

Keywords: Endarterectomy, Ischaemic stroke, Medical treatment, Revascularisation, Stenosis, Stent
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INTRODUCTION

Patients with recently symptomatic carotid artery stenosis are at high risk of stroke.[1,2] Earlier randomised controlled trials (RCTs), conducted in the 1980s and 1990s, demonstrated a reduction in stroke risk by revascularisation by carotid endarterectomy (CEA) when compared with medical therapy alone.[3—5] Pooled analysis of two of these trials suggested that the benefit of CEA was highest when performed early after the qualifying ischaemic event.[6] Current guidelines therefore recommend revascularisation within two weeks of initial symptoms.[7,8]

Medical therapy for secondary prevention of stroke has evolved since the completion of these trials with widespread use of statins and more aggressive control of vascular risk factors. Thus, the risk of stroke among patients with symptomatic carotid stenosis may have decreased over the years.

In this study, the risk of early stroke was studied in patients with symptomatic carotid stenosis recruited in four more recent RCTs,[9—12] which compared revascularisation by carotid artery stenting (CAS) *vs.* CEA. The aim was to assess the risk of stroke under medical therapy occurring between randomisation and revascularisation in these recent trials, to identify its predictors, and to compare this risk with the risk of early stroke among medically treated patients in earlier trials, which compared medical therapy *vs.* CEA.

MATERIALS AND METHODS

In the Carotid Stenosis Trialists' Collaboration (CSTC), the data of individual patients with symptomatic carotid stenosis, who were recruited between 2000 and 2008 into four RCTs comparing CAS *vs.* CEA were pooled: Endarterectomy *vs.* Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S), Stent-Supported Percutaneous Angioplasty of the Carotid Artery *vs.* Endarterectomy (SPACE), International Carotid Stenting Study (ICSS), and Carotid Revascularisation Endarterectomy *vs.* Stenting Trial (CREST), from here on referred to as recent trials.[9—12] These trials recruited patients with moderate (50% — 69% reduction of the lumen diameter according to the NASCET method[4]) and severe (70% — 99%) stenosis of the internal carotid artery, presenting with recent associated symptoms of retinal ischaemia, hemispheric transient ischaemic attack (TIA), or non-disabling stroke. Patients were thought to require revascularisation by CAS or CEA and were considered suitable for both. In the present analysis, symptomatic patients from CREST were included only if they had received the allocated treatment. Ethics approval for the contributing trials was obtained at the competent institutional review boards, and all patients provided written informed consent.

In addition, individual patient data were extracted from a pooled analysis[13] of three earlier RCTs: European Carotid Surgery Trial (ECST), North American Symptomatic Carotid Endarterectomy Trial (NASCET), and Veterans Affairs Cooperative Studies Program 309 (VA309).[3,5,14] These trials recruited patients from 1981 until 1996 and compared CEA plus medical treatment *vs.* medical treatment alone. For the study, patients were included with moderate or severe symptomatic carotid stenosis from the medical arms of those earlier trials which served as a historical comparison group (from here on referred to as medical arm of earlier trials). In NASCET, randomisation was delayed until it was clear that surgery could be rapidly delivered if the patient was to be allocated to CEA. For this reason, only patients randomised to the medical arms in the earlier trials were included. Medical treatment in these trials consisted mainly of different doses of aspirin, and antihypertensive and antidiabetic treatment. Statins were not used at the beginning of these trials but were gradually introduced during the recruitment period. Selected inclusion criteria, recommended medical therapy, and medication at baseline of earlier and recent trials are shown in Table S1.[15]

Definitions of patient baseline characteristics at the time of randomisation, outcome events, subgroup variables, and statistical methods were specified before the data were analysed. Baseline characteristics available for all trials were sex, age, history of hypertension, diabetes, smoking (current or past), coronary heart disease (i.e., angina pectoris or myocardial infarction in the medical arm of earlier trials), degree of ipsilateral carotid stenosis (according to NASCET criteria[4]), contralateral severe carotid stenosis or occlusion, time between qualifying event and randomisation, and type of the qualifying event. Additional baseline characteristics for recent trials were history of hyperlipidaemia or lipid lowering drugs, and modified Rankin scale (mRS). The qualifying event was the most recent (not necessarily the first) ischaemic event before randomisation in the territory of the relevant carotid artery, categorised as retinal ischaemia including amaurosis fugax or retinal infarction, hemispheric TIA, or hemispheric ischaemic stroke.

The primary outcome event was stroke in any territory occurring within the first 120 days after randomisation and

before revascularisation by CEA or CAS. Patients were censored at 120 days after randomisation or at the time of revascularisation, which ever came first. The period of 120 days was chosen because nearly all patients undergoing revascularisation in the recent trials were treated within that period. Stroke was defined as an acute deficit of focal neurological function with symptoms lasting more than 24 hours with ischaemic or haemorrhagic origin. Retinal infarction, defined as visual loss lasting more than 24 hours resulting from retinal ischaemia, was also considered as stroke. Fatal stroke was defined as any stroke leading to death within 30 days after onset, and disabling stroke resulting in new or increased disability with a mRS $\geq$ 3; all other strokes were classified as non-disabling.

Statistical analysis

All analyses were conducted using R (Version 3.4.4, R Core Team, 2017). All data were treated as non-normally distributed. R package mice[16] were used (multiple imputation by chained equations) to create m = 20 imputations per missing value across all covariates (details in the Supplementary material). For the recent trials, the association between baseline characteristics and time to stroke after randomisation or time from qualifying event until randomisation individually was analysed using Cox proportional hazards models. The qualifying event type was analysed both as three single degree of freedom contrast and as a continuous variable for severity (retinal ischaemia < TIA < stroke). The four recent RCTs were fitted as three single degree of freedom contrasts. The models were fitted to each of the imputed data sets. For each combination of model and data set, the Akaike information criterion (AIC), the likelihood ratio χ^2, and the corresponding *p* value were extracted and averaged for each model (across all imputed data sets). The best single predictor was chosen based on the AIC. To select the best model with two predictors a forward variable selection approach was used based on the AIC. The selected models were then applied to all imputed data sets and the results were pooled to one final result using Rubin's rules.[17,18]

The risk of stroke after randomisation was compared between recent trials and the medical arm of earlier trials using Kaplan–Meier curves and log rank tests for patients with moderate stenosis, patients with severe stenosis, and patients with moderate or severe stenosis combined. Cox proportional hazards models of the original dataset were used with recent trials *vs.* the medical arm of earlier trials as the explanatory factor. To analyse patients with moderate or severe stenosis, the stenosis degree was used as an additional explanatory factor. Cox proportional hazards models of all imputed data sets were adjusted for time (weeks) from the qualifying event until randomisation, and for other potential confounders: age, carotid stenosis degree (moderate *vs*. severe), qualifying event severity. The Cox proportional hazards assumption was assessed graphically by plotting the scaled Schoenfeld residuals *vs.* the transformed survival times and using a χ^2 test to detect significant correlations (per variable test and global). A *p* value < .05 was considered to be statistically significant.

Table 1. Baseline characteristics of patients included in trials on treatment of symptomatic carotid stenosis

Baseline characteristics	Recent trials (*n* = 4 754)	Medical arm of earlier trials (*n* = 1 227)
Age – y	69.3 ± 9.3	64.8 ± 8.5
Men	3 317 (69.8)	881 (71.8)
History of hypertension	3 574 (75.5)	558 (49.4)
History of diabetes	1 193 (25.1)	242 (19.7)
History of smoking	3 063 (65.0)	620 (50.5)
History of coronary heart disease	1 293 (27.8)	416 (33.9)
Ipsilateral carotid stenosis		
Moderate	919 (19.3)	721 (58.8)
Severe	3 835 (80.7)	506 (41.2)
Contralateral carotid stenosis or occlusion	626 (14.7)	84 (6.8)
Qualifying event type		
Retinal ischaemia	808 (17.1)	396 (32.3)
Transient ischaemic attack	1 741 (36.9)	355 (29.0)
Ischaemic stroke	2 173 (46.0)	474 (38.7)
Time qualifying event until randomisation – d	18 (7–50)	37 (14–75)

Data of known values are presented as *n* (%), mean ± standard deviation, or median (interquartile range).

RESULTS

In the recent trials comparing CAS *vs.* CEA, 4 754 patients with symptomatic carotid stenosis were enrolled (CAS 2 393, CEA 2 361). In the earlier trials comparing CEA *vs.* medical therapy alone, 1 227 patients were assigned to the medical therapy arm.

Baseline characteristics of patients included in recent trials and the medical arm of earlier trials are listed in Table 1. Recent trials included a larger proportion of patients with severe stenosis than the medical arm of earlier trials. Patients in the recent trials were older, had a more frequent history of cardiovascular risk factors, contralateral carotid stenosis, or occlusion, and presented less frequently with retinal ischaemia. There were 797 patients with an unknown date of the qualifying event in recent trials, most of whom originated from one trial where this information was not systematically collected.[10] Time from the qualifying event until randomisation was shorter in recent trials (median 18 days, interquartile range [IQR] 7, 50) than in the medical arm of earlier trials (median 37 days, IQR 14, 75) (Fig. 1).

In the recent trials, the median time from randomisation until revascularisation was six days (IQR 3, 12 days), and from the qualifying event until revascularisation 28 days (IQR 12, 65), with considerable variation between the individual trials (Fig. 2A). A total of 1 133 patients (23.8%) in the recent trials were treated within the recommended 14 days after the qualifying event. A total of 108 patients were censored at 120 days after randomisation because they did not undergo revascularisation until then. Patients

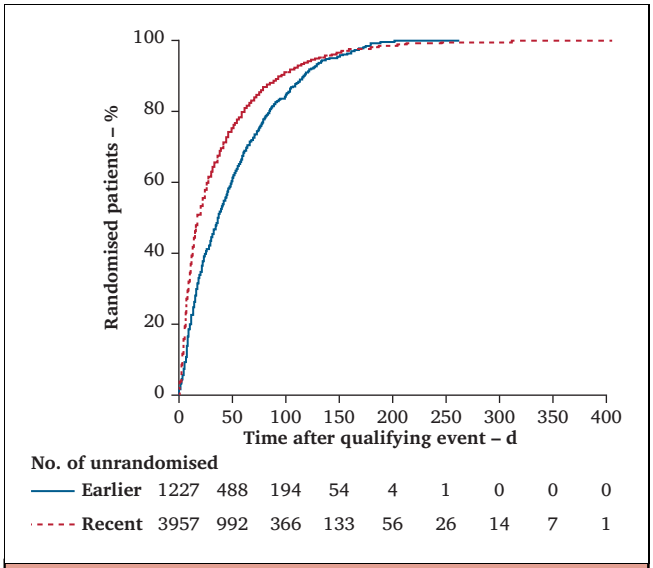

Figure 1. Cumulative Kaplan–Meier estimate for randomisation after the qualifying event in patients with symptomatic moderate or severe carotid stenosis in recent and the medical arm of earlier trials ($n = 5\,184$ patients). Time between the qualifying event and randomisation for the recent trials was median 18 days (interquartile range [IQR] 7, 50), and for the earlier trials median 37 days (14, 75).

randomised to CAS were treated earlier (median 26 days, IQR 11, 61) after the qualifying event than those randomised to CEA (median 29 days, IQR 13, 67) (Fig. 2B).

In the recent trials, a total of 23 (15 CEA, 8 CAS) patients suffered a stroke after randomisation while waiting for revascularisation, resulting in a cumulative 120 day risk of 1.97% (95% CI 0.75 — 3.17). Of these 23 patients, 17 were men and 22 had a severe carotid stenosis. The qualifying event was TIA in 13 patients, hemispheric stroke in 9 and retinal ischaemia in one. These patients were randomised between 0 and 133 days after the qualifying event with a median of 10.5 days (IQR 3.75, 42.5, one qualifying event date missing). The mRS at randomisation was 2 or less in 19 patients. Eight patients received treatment as randomised despite their stroke, one patient died from his stroke, and the remaining 14 patients did not receive any revascularisation within 120 days. The severity of the 23 strokes was fatal in one, disabling in 13 and non-disabling in eight patients, with 20 strokes occurring ipsilateral to the symptomatic carotid stenosis. All strokes occurred within the first 31 days after randomisation.

In the recent trials, the strongest single predictor of stroke was time from the qualifying event until randomisation with a hazard ratio (HR) of 0.88 (95% CI 0.78 — 1.0, $\chi^2 = 6.58$, $p = .011$, AIC = 321.25), indicating that the risk was highest in patients randomised early after the qualifying event. The model with the two strongest predictors included time from qualifying event until randomisation (HR 0.98, 95% CI 0.97 — 1.0) and TIA as the qualifying event (HR 2.72, 95% CI 1.13 — 6.57, $\chi^2 = 11.73$, $p = .003$, average AIC = 318.10). Severity of carotid stenosis as a single predictor was not statistically significant (HR 4.13, 95% CI 0.55 — 30.88, $\chi^2 = 2.99$, $p = .084$, AIC = 324.84).

In the medical arm of earlier trials, 61 patients had a stroke within 120 days after randomisation with a cumulative risk of 5% (95% CI 3.8 — 6.2). The risk of stroke within 120 days after randomisation in recent trials was not different to the risk in the medical arm of earlier trials in the unadjusted comparison for patients with moderate stenosis (log rank $\chi^2 = 1.68$, $p = .19$; Fig. 3A), severe stenosis ($\chi^2 = 1.43$, $p = .23$; Fig. 3B), and moderate or severe stenosis combined ($\chi^2 = 1.11$, $p = .29$; Fig. 3C, Fig. S1). However, after adjustment for time between the qualifying event and randomisation, age, severity of qualifying event and degree of stenosis, hazards for stroke were significantly lower in the recent trials than in the earlier trials among patients with moderate or severe stenosis combined (HR 0.47, 95% CI 0.25 — 0.88, $p = .019$).

DISCUSSION

In this study, the early risk of stroke under medical therapy was analysed in patients with symptomatic carotid stenosis awaiting revascularisation in recent RCTs.[9–12] The cumulative stroke risk was 2% at 120 days and was higher among patients that were randomised shortly after the qualifying event. The risk of stroke was lower in these recent trials than it was among patients treated medically in earlier trials[3–5] when the comparison was adjusted for important patient characteristics differing between trials.

In the recent trials, all strokes occurred within the first 31 days after randomisation. This finding is in line with previous studies showing that the risk of stroke is highest early after an athero-embolic event.[1,2,19] However, observational studies of patients with symptomatic carotid stenosis reported a much higher cumulative risk. A pooled analysis of three prospective cohort studies showed a risk of ipsilateral stroke or retinal infarction of 11.4% at 14 days and 18.9% at 90 days after the qualifying event.[20] Other studies demonstrated similar findings with risks of 7.5% within 30 days,[21] 3.2% within three days,[22] or 21% at 14 days and 32% at 90 days.[23] In the study, the majority of patients were randomised more than 14 days after the qualifying event which probably explains the lower stroke risk compared with observational data. In the trials included in the present analysis, the qualifying event was defined as the last ischaemic event before randomisation but the timing of previous events was not uniformly assessed. Therefore, the risk of stroke after the first event could not be estimated. In one study, 11% of patients presenting with ischaemic stroke for CEA reported one or more previous episodes of TIA or amaurosis fugax.[24] Furthermore, patients recruited for the RCTs were subjected to a selection bias since patients with significant stroke related disability were not eligible for these trials. In observational studies, patients with any level of disability were included and it is known that higher disability at baseline is associated with greater risk of recurrent events.[20] Thus, the RCTs analysed here included a patient population which was at a lower risk of stroke compared with observational cohorts.

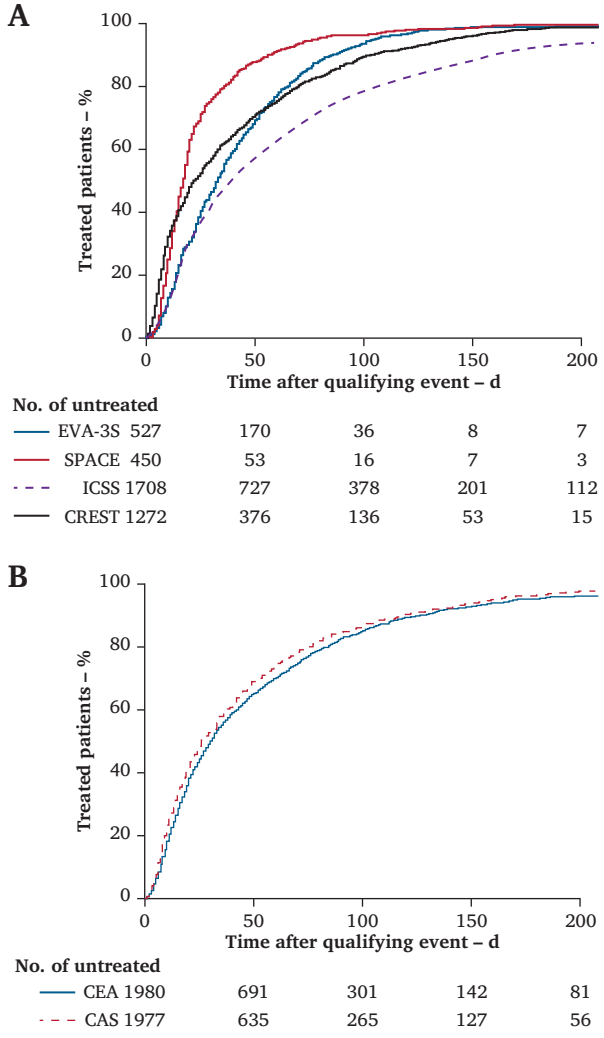

Figure 2. Cumulative Kaplan–Meier estimate for revascularisation treatment within 200 days after the qualifying event in recent trials according to (A) individual trials and (B) revascularisation treatment ($n = 3\,957$ patients; 797 with unknown qualifying event date not shown) for symptomatic carotid stenosis. Time between the qualifying event and treatment was a median 24 days (interquartile range [IQR] 12, 47) in EVA-3S, 12 (6, 24) in SPACE, 22 (8, 62) in ICSS, and 15 (5, 47) in CREST. In all recent trials combined, patients randomised to carotid artery stenting (CAS) were treated at a median 26 days (11, 61) and those randomised to carotid endarterectomy (CEA) at 29 (13, 67) after the qualifying event.

Guidelines recommend revascularisation of symptomatic carotid stenosis within 14 days after a cerebrovascular event, but the optimal timing is under debate.[25–27] In the recent trials, only a quarter of patients were treated within the recommended time. Of note, patients randomised to CAS were treated at median of three days earlier than those randomised to CEA, probably reflecting differences in availability of staff and infrastructure.

In the second part of the study, the risk of early stroke was compared among patients with symptomatic carotid stenosis waiting for CAS or CEA in recent trials and patients randomised to the medical arms of earlier trials comparing CEA with medical therapy. A lower risk was found in recent trials than in earlier trials, when adjusting the comparison for factors that had been shown to affect the risk of ischaemic events.[6,20] It is possible that improvements in medical therapy and greater awareness for risk factor control and lifestyle modification contributed to this risk reduction. Medical therapy had changed between the completion of the earlier trials and beginning of the recent trials, including the widespread prescription of statins. In an observational study among patients presenting with TIA due to a symptomatic carotid stenosis, the early stroke risk within 90 days was 8.9% among patients with statin pretreatment and 20.8% among those without statins.[28] Reported statin use at randomisation was notably lower in some of the earlier trials (13% — 16%) than in the recent trials (49% — 63%).[4,10,11] Antithrombotic therapy at randomisation varied greatly among all trials and exact dosages were rarely reported (Table S1). The finding of a lower risk of stroke over time is supported by large prospective observational studies. Prospective registries from 2004 and 2007 reported an approximate 20% risk of recurrent stroke within 90 days after stroke or TIA due to large artery atherosclerosis, whereas a registry published in 2016 reported a mere 6%.[19]

The main strength of this analysis is the inclusion of data at individual patient level from two series of clinical trials with very similar inclusion criteria. However, there are also limitations. First, despite the large study population, the number of strokes in recent trials was low, which limited statistical power. However, there are no other comparable data that would allow a similar comparison of two series of large RCTs of patients with symptomatic carotid stenosis. Second, although the comparison of stroke risk between recent and earlier trials was adjusted for important patient characteristics, the trial populations may have differed in factors that were not accounted for. Third, patients enrolled in RCTs are selected and not necessarily representative of the population of all patients with symptomatic carotid stenosis: patients with a persisting major stroke as the presenting event were excluded from both recent and earlier trials; patients with progressive or fluctuating symptoms may have been excluded; and patients perceived to be at very high risk of stroke may have undergone immediate revascularisation outside a trial. Therefore, no statement can be made about stroke risk in these specific patient groups. Fourth, the risk of stroke after the first presenting event could not be estimated. It is likely that some patients suffered from repeated ischaemic events occurring before the qualifying event, as defined in the trials. Therefore, the findings probably underestimate the true risk of early stroke in symptomatic carotid stenosis. Contemporary prospective registries are better suited to provide evidence on early stroke risk in patients with symptomatic carotid stenosis than the more selected population of patients included in clinical trials. Fifth, as far as conservative management is concerned, changes of medical therapy over time, such as the gradual introduction of statins into management during the recruitment period of

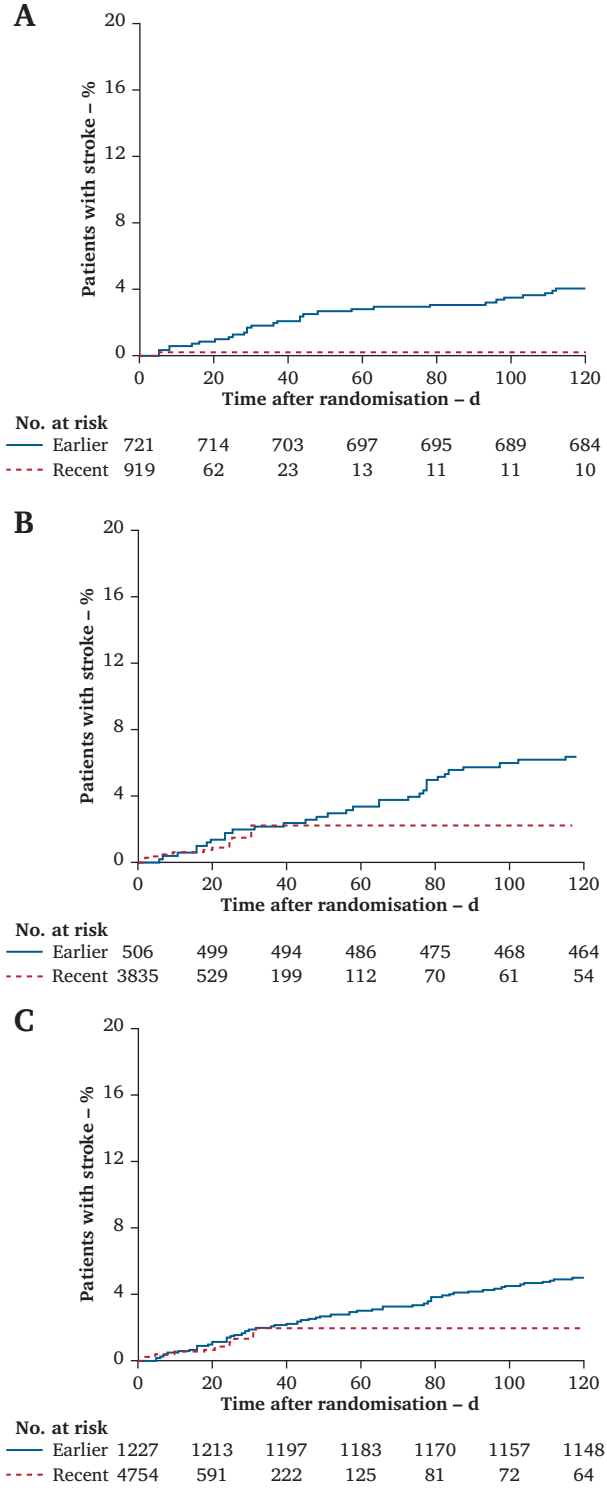

Figure 3. Cumulative Kaplan–Meier estimate for stroke within 120 days after randomisation for patients in recent and the medical arm of earlier trials with symptomatic (A) moderate ($n = 1$ 640), (B) severe ($n = 4$ 341), and (C) moderate or severe carotid stenosis combined ($n = 5$ 981 patients). Note the adapted scale for y-axes.

the early trials, could not be accounted for. In addition, the latest advances in medical treatment such as early dual antiplatelet therapy that were introduced after completion of the recent trials were not considered in this analysis.[29] Finally, information on behavioural and lifestyle factors was generally lacking. For all these reasons, the applicability of the findings to current carotid disease management is limited and the results should not deflect from the current practice of early treatment of patients considered for revascularisation.

Despite these limitations, the study adds to the current evidence that the risk of stroke associated with symptomatic carotid stenosis has decreased over time, potentially attributable to improved medical care and risk factor control. The added benefit of carotid revascularisation to modern medical care needs to be revisited in ongoing and future studies. However, at present the data should not deflect from current recommendations for early revascularisation of patients with symptomatic carotid stenosis considered to require invasive treatment.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.02.024.

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