The risk of carotid artery stenting compared with carotid endarterectomy is greatest in patients treated within 7 days of symptoms

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Objective: **Among patients with symptomatic carotid artery stenosis, carotid artery stenting (CAS) is associated with a higher risk of periprocedural stroke or death than carotid endarterectomy (CEA). Uncertainty remains whether the balance of risk changes with time since the most recent ischemic event.**
Methods: **We investigated the association of time between the qualifying ischemic event and treatment (0-7 days, 8-14 days, and >14 days) with the risk of stroke or death within 30 days after CAS or CEA in a pooled analysis of data from individual patients randomized in the Endarterectomy vs Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, and the International Carotid Stenting Study (ICSS). Data were analyzed with a fixed-effect binomial regression model adjusted for source trial.**
Results: **Information on time of qualifying event was available for 2839 patients. In the first 30 days after intervention, any stroke or death occurred significantly more often in the CAS group (110/1434 [7.7%]) compared with the CEA group (54/1405 [3.8%]; crude risk ratio, 2.0; 95% confidence interval, 1.5-2.7). Patients undergoing CEA within the first 7 days of the qualifying event had the lowest periprocedural stroke or death rate (3/106 [2.8%]). Patients treated with CAS in the same period had a 9.4% risk of periprocedural stroke or death (13/138; risk ratio CAS vs CEA: 3.4; 95% confidence interval, 1.01-11.8; adjusted for age, sex, and type of qualifying event). Patients treated between 8 and 14 days showed a periprocedural stroke or death rate of 3.4% (7/208) and 8.1% (19/234), respectively, for CEA and CAS. The latest treatment group had 4% complications in the CEA group (44/1091) and 7.3% in the CAS group (78/1062).**
Conclusions: **The increase in risk of CAS compared with CEA appears to be greatest in patients treated within 7 days of symptoms. Early surgery might remain most effective in stroke prevention in patients with symptomatic carotid artery stenosis. (J Vasc Surg 2013;57:619-26.)**

The timing of revascularization of symptomatic internal carotid artery stenosis has changed over the last decade. Contrary to the recommendations from the 1960s and 1970s, carotid endarterectomy (CEA) is now performed as soon as possible after the index symptom. The rapidly declining benefit of surgery with the delay of treatment results from the high percentage of recurrent ischemic events in the first 7 to 14 days after the qualifying event.[1-5] The benefit of early treatment in surgery overcomes the slightly increased perioperative risk in this period.[3] There are few data on the optimal timing of carotid artery stenting (CAS) in symptomatic patients, however. Single-center studies on the safety of early CAS have yielded controversial results.[6,7] A higher percentage of periprocedural complications after rapid CAS treatment might result from the fact that the recently symptomatic plaque is vulnerable to dislodging of thrombus or plaque debris during catheter passage.[6] Time for plaque stabilization under optimal medical treatment

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might be necessary to minimize periprocedural complications in CAS. However, any delay in treatment must be balanced against the risk of a recurrent ischemic event.

The study at hand investigated the association between outcome and timing of treatment in a pooled analysis of individual patient data from the Symptomatic Severe Carotid Stenosis trial (EVA-3S), the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, and the International Carotid Stenting Study (ICSS).

METHODS

EVA-3S (NCT 00190398), SPACE (ISRCTN 57874028), and ICSS (ISRCTN 25337470) were randomized clinical trials with blinded outcome adjudication. In all three trials, patients with recently symptomatic moderate or severe carotid stenosis (≥50% reduction of the lumen diameter according to the method used in the North American Symptomatic Carotid Endarterectomy Trial [NASCET][8]), who were considered equally suited for either procedure, were randomly allocated to undergo treatment by stenting or endarterectomy.[9-11] The pooled analysis of individual patient data was prospectively agreed on at the design stage of these trials.[12] The primary outcome event for the present analysis of the pooled data was the combination of any stroke or death occurring within 30 days after treatment. Secondary outcome events were disabling stroke or death and any stroke occurring during this period. The analysis was done per protocol, including only those patients who received the randomly allocated treatment as the first initiated revascularization procedure after randomization and in whom the date of the qualifying event (defined as the last ischemic event ipsilateral to the relevant carotid artery prior to randomization: retinal ischemia, hemispheric transient ischemic attack [TIA], or hemispheric stroke) or the interval between the qualifying event and treatment was known.

The date of the qualifying event was ascertained at baseline in EVA-3S and ICSS. The date of the qualifying event was not prospectively collected in the SPACE trial at baseline; for the pooled analysis, the date of the qualifying event (or, if the exact date was unknown, whether or not randomization and treatment took place within 7 days or within 14 days of the qualifying event) was retrieved where possible. Patients with missing data concerning delay between qualifying event and treatment were excluded from the analysis.

Statistical analysis. The pooled data were first analyzed with a fixed-effect binomial regression model including only source trial terms as covariables, to obtain crude estimates of risk ratio (RR) with 95% confidence interval (CI) of major outcome events between CAS and CEA, depending on the interval between the qualifying event and treatment (0-7, 8-14, and >14 days). For adjusted risk calculation, age, sex, and type of qualifying event (retinal ischemia, TIA, or stroke) were additionally included in the regression model. The interaction between delay from qualifying event and treatment effect (CAS vs CEA) was formally tested by including a multiplicative interaction term in the model. Furthermore, we calculated the RRs between each time stratum in both treatment arms and early CEA (within 7 days of the qualifying event), which was defined as referenced standard procedure.

RESULTS

The pooled Carotid Stenting Trialists' Collaboration (CSTC) analysis included 3433 patients (1725 in the CAS group and 1708 in the CEA group) who were randomized and followed up in the three contributing trials. In total, 1679 patients underwent stenting and 1645 patients received endarterectomy as their randomly allocated revascularization procedure. Information on delay of treatment from qualifying event was not available for 483 patients from the SPACE study (245 patients received CAS and 238 patients were treated by surgery) and for two patients from ICSS (both treated by CEA). Therefore, a total of 2839 patients (n = 1434 in the CAS group and n = 1405 in the CEA group) remained for per-protocol data analysis concerning outcome under the influence of timing of treatment (Figure).

The median delay between the most recent ipsilateral event and treatment was 29 days in the stent group (interquartile range [IQR], 14-65) and 32 days in the endarterectomy group (IQR, 15-71). Patient characteristics at baseline were comparable in the two treatment groups (Table I). A total of 244 patients (8.6%) received treatment within 7 days after the index event (n = 138 in the CAS group and n = 106 in the CEA group), 442 patients (15.6%) had treatment between 8 and 14 days after the qualifying event (CAS: n = 234; CEA: n = 208), whereas the majority of patients (CAS: n = 1062; CEA: n = 1091) were treated more than 14 days after the qualifying ischemic event. Supplementary Table I, online only, shows that demographic data of the patients, vascular risk factors, preexisting vascular disease, degree of stenosis, and severity of neurologic deficit (measured by the modified Rankin score) did not change in a relevant way with time until treatment. The proportion of patients with hemispheric stroke as the qualifying event was lower among patients treated within 7 days (CAS: 31%; CEA: 32%) than in the groups treated for 8 to 14 days (CAS: 53%; CEA 47%) and >14 days (CAS: 48%, CEA: 49%) after the qualifying event, but there were no significant differences between treatment groups across the three time strata. In the first 30 days after intervention, any stroke or death occurred significantly more often in the CAS group (110/1434 [7·7%]) compared with the CEA group (54/1405 [3.8%]; crude RR, 2.0; 95% CI, 1.5-2.7; $p_{\chi^2} < .001$). Type and number of major outcome events, as well as information on stroke severity and territory in the three time strata, are given in Supplementary Table II, online only.

Table II lists the RRs and number of major outcome events in the three strata of time between qualifying event and treatment adjusted only for source trial. The risk of any stroke or death within 30 days of treatment (the primary outcome event) was lowest in the early CEA (0-7 days) group (3/106 [2.8%]). Early CAS had a stroke or death

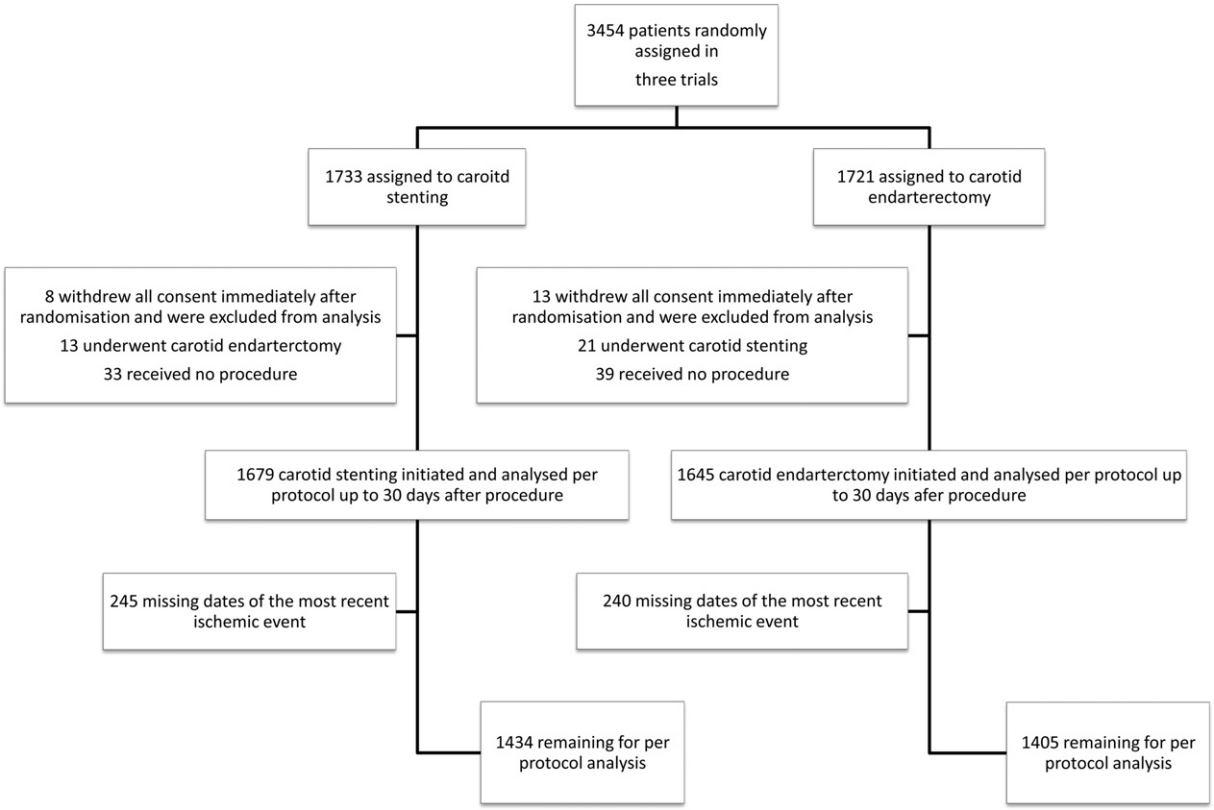


Fig. Flow diagram of patients included in the meta-analysis.

rate of 9.4% (13/138), which corresponds to an RR of 3.79 (95% CI, 1.1-13.1; $P = .03$). With a delay of 8 to 14 days, CEA had a stroke or death rate of 3.4% (7/208) compared with 8.1% (19/234) in the CAS group (RR, 2.42; 95% CI, 1.0-5.7; $P = .04$). The latest CEA group (>14 days) showed a perioperative stroke or death rate of 4.0% (44/1091) compared with 7.3% (78/1062) in the stenting group (RR, 1.82; (95% CI, 1.3-2.6; $P = .001$) Results were similar with any stroke within 30 days of treatment as the outcome event. There was no significant difference in the two treatment groups in the occurrence of periprocedural disabling stroke or death. The test for interaction between delay from qualifying event and the treatment effect of CAS vs CEA was not significant for any of the three outcome measures.

Additional adjustment for age, sex, and type of qualifying event for time strata analysis did not influence the RRs in a relevant way (Supplementary Table III, online only).

Proposing that early CEA (0-7 days) might be the treatment of choice because of the lowest periprocedural rate of complications, we created a multivariate model, adjusted for age, sex, source trial, and type of qualifying event, with early CEA as the reference procedure. Here we saw that the 9.4% risk of stroke or death in the early CAS group corresponds to an RR of 3.4 (95% CI, 1.01-11.8) compared with early CEA. The adjusted RR declined to 2.68 (95% CI, 0.8-8.9) for carotid stenting between 8 to 14 days and to 2.58 (95% CI, 0.8-8.0) for CAS after 14 days. Later CEA had a higher risk for perioperative stroke or death compared with early surgery, without reaching statistical significance, however (8-14 days: adjusted RR, 1.16; 95% CI, 0.3-4.4; >14 days: adjusted RR, 1.38; 95% CI, 0.4-4.4). Table III summarizes the adjusted RRs for all three end points.

DISCUSSION

Timing of surgery significantly influences the benefit in patients with symptomatic internal carotid artery stenosis. Analysis from the pooled data from NASCET and the European Carotid Surgery Trial (ECST) showed that surgery was most effective when performed within the first 2 weeks after a qualifying ischemic event.[13] Recent literature even supports CEA in the very early stage after neurologic symptoms.[14-18] Over the last decade, it became apparent that the early days after cerebral ischemia were most hazardous for the patient. The percentage of recurrent ischemic events is notably high in the first 2 weeks with 12% to 15%.[3,5,18] Therefore, carotid revascularization should be carried out as soon as possible to prevent a recurrent stroke.

Outcome of CAS and CEA depending on the timing of treatment after the most recent ischemic event. Several trials focused on the safety and efficacy of CAS compared with CEA as gold standard in the treatment of symptomatic stenosis in the internal carotid artery.[19-24]

Table I. Baseline data of the combined trial population

	CAS (n = 1434)	*CEA (n = 1405)*
Age at randomization, mean (SD), years	70.2 (9.0)	70.2 (9.2)
Male, No. (%)	1032 (72%)	1012 (72%)
History of diabetes, No. (%)	335 (23.4%)	331 (23.6%)
History of hypertension, No. (%)	1025 (71.5%)	1012 (72.0%)
History of hypercholesterolemia, No. (%)[a]	661[a] (46.1%)	681[a] (48.5%)
Any smoking history (current or past), No. (%)	887 (61.9%)	876 (62.3%)
History of coronary heart disease, No. (%)	347 (24.2%)	351 (25.0%)
History of peripheral artery disease, No. (%)[a]	173[a] (12.1%)	161[a] (11.5%)
Degree of ipsilateral carotid stenosis, No. (%)[b]		
Moderate (50%-69%)	245[b] (17.1%)	230[b] (16.4%)
Severe (70%-99%)	1189[b] (82.9%)	1175[b] (83.6%)
Contralateral severe carotid stenosis (≥70%) or occlusion, No. (%)[b]	205[b] (14.3%)	202[b] (14.4%)
Transient ischemic attack	491 (34.2%)	486 (34.6%)
Retinal ischemia	261 (18.2%)	243 (17.3%)
Hemispheric stroke	670 (46.7%)	664 (47.3%)
History of stroke before most recent event, No. (%)[a]	184[a] (12.8%)	176[a] (12.5%)
Days elapsed between most recent ipsilateral ischemic event and treatment, median (IQR)[c]	29 (14-65)	32 (15-71)
Treatment within 7 days of most recent event[c]	138 (9.6%)	106 (7.5%)
Treatment within 14 days of most recent event[c]	372 (25.9%)	314 (22.3%)

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *EVA-3S,* Endarterectomy vs Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; *ICSS,* International Carotid Stenting Study; *IQR,* interquartile range; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial; *SPACE,* Stent-Protected Angioplasty versus Carotid Endarterectomy; *SD,* standard deviation.

Percentages exclude missing data. *P* values are not included because there is no statistically significant difference between time groups.

[a]Data collected in EVA-3S and ICSS only.

[b]Degree of stenosis measured by NASCET method or equivalent noninvasive method.

[c]The date of the most recent ipsilateral ischemic event before randomization was not collected in the SPACE trial initially, but for the meta-analysis, these dates (or if the exact date was unknown, whether or not randomization and treatment took place within 14 days of the qualifying event) were retrieved where available.

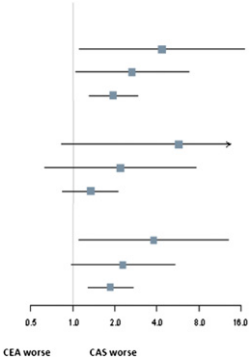
However, little effort has been given to the study of ideal time management in CAS. Topakian et al[6] investigated the outcome of 77 consecutive patients who underwent CAS for ≥60% symptomatic carotid stenosis within 180 days of TIA or moderate stroke (modified Rankin scale score ≤3). The 30-day composite end point for stroke (7.8%) and death of any cause (1.3%) was 9.1%. The authors saw that patients suffering from periprocedural complications underwent stenting significantly earlier compared with patients with uneventful treatment (median delay, 1.5 weeks vs 3.2 weeks; $P = .004$). In multivariate logistic regression analyses, delay of treatment <2 weeks (odds ratio, 22.4; 95% CI, 2.2-223.4; $P = .008$) remained predictive for the 30-day outcome.[6] However, in a series of 320 patients undergoing CAS for symptomatic stenosis, Gröschel et al[7] saw that timing was not significantly associated with periprocedural complications, regardless of whether this variable was dichotomized (<14 days and ≥14 days), separated into IQRs, or analyzed as a continuous variable. The pooled data from SPACE, EVA-3S, and ICSS represent the largest series of patients receiving either CAS or CEA for symptomatic carotid artery stenosis in trial conditions. We found that CEA within 1 week of the latest ischemic event was the treatment with the lowest number of periprocedural complications. Stenting, however, was most hazardous when performed early. This supports the findings of Topakian et al.[6] The fact that the risk of CAS declines with delay to the ischemic event is also apparent in our study population, with the *P* value showing a clear trend, without reaching statistical significance. Surgery, on the other hand, was more harmful in the later period after the ischemic event but also without reaching statistical significance.

The CSTC recently reported that age had a relevant influence on the outcome after CAS. In patients younger than 70 years, the estimated 120-day risk of stroke or death was 50 (5.8%) of 869 patients in the carotid stenting group and 48 (5.7%) of 843 in the CEA group (RR, 1.00; 95% CI, 0.68-1.47). In patients 70 years or older, the estimated risk with carotid stenting was twice that with CEA (103/856 [12.0%] vs 51/865 [5.9%]; 2.04; 95% CI, 1.48-2·82; interaction $P = .0053$; $P = .0014$ for trend).[21]

Outcome in the adjusted model. The crude comparison between CAS and CEA in the three timing strata showed, as has already reported elsewhere, that surgery had better results in the treatment of symptomatic internal carotid artery stenosis.[25] The analysis at hand shows that this is true independent from timing of treatment. However, we see in our study population that the risk of CAS is especially high in the early days after the qualifying ischemic event. The outcome was worst in patients treated by CAS within 7 days after the latest cerebral ischemia. Patients who underwent early surgery, however, had the best periprocedural outcome, independent from age, sex, type of qualifying neurologic event, and source trial. From this, we conclude that rapid surgery still remains the gold standard for treatment of symptomatic internal carotid artery stenosis.

Table II. Risks for different end points depending on the timing of treatment (0-7 days, 8-14 days, and thereafter) and treatment modality

	CEA, No. (%)	*CAS, No. (%)*	*Crude RR (95% CI)*	P *value*
Stroke or death				
0-7 days	3 (2.8%)	13 (9.4%)	3.79 (1.1-13.1)	.03
8-14 days	7 (3.4%)	19 (8.1%)	2.42 (1.0-5.7)	.04
>14 days	44 (4.0%)	78 (7.3%)	1.82 (1.3-2.6)	.001
Disabling stroke or death				
0-7 days	1 (0.9%)	7 (5.1%)	6.40 (0.8-51.0)	.08
8-14 days	3 (1.4%)	7 (3.0%)	2.28 (0.6-8.7)	.23
>14 days	28 (2.6%)	34 (3.5%)	1.35 (0.8-2.2)	.22
Any stroke				
0-7 days	3 (2.8%)	13 (9.4%)	3.79 (1.1-13.1)	.03
8-14 days	7 (3.4%)	18 (7.7%)	2.27 (1.0-5.4)	.06
>14 days	41 (3.8%)	74 (7.0%)	1.86 (1.3-2.7)	.001



CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *CI,* confidence interval; *RR,* risk ratio.
RRs are calculated within the time strata only adjusted for source trial. The CEA group represents the reference group.

Limitations of data analysis. The three trials—SPACE, ICSS, and EVA-3S—randomized patients between 2001 and 2009, at a time when the concept of early surgery was not fully implemented worldwide. This might be the explanation for the small number of patients who received treatment close to the qualifying event (only 9.6% of CAS patients and 7.5% of CEA patients within 1 week and 16.3% and 14.8% in the CAS and CEA group within 2 weeks of last symptoms). Therefore, statistical power to show a significant interaction between timing of treatment and relative risks of stroke or death between CAS and CEA was low. Incorporating data from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), which is foreseen in the future, may help to answer this question.[26]

Importantly, the timing of treatment was not subject to randomization in any of the three contributing trials. Therefore, we needed to exclude a treatment bias in the way that neurologically stable patients were treated earlier and those with severe impairment were treated in a later period of time. Supplementary Table I, online only, summarizes type and severity of the qualifying neurologic event in the three timing groups. The type of qualifying event differed significantly between patients treated within the first week of the event and those treated later, with a lower proportion of patients with hemispheric stroke treated in the early period. On the other hand, the severity of neurologic impairment, measured by the modified Rankin scale, was comparable in the treatment groups and both treatment techniques. Adjustment for the type of the qualifying event in the multivariate model did not change our results in a relevant way.

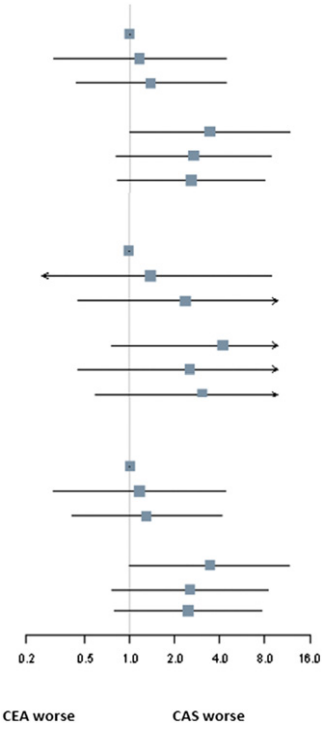
Timing of treatment was not a primary focus at baseline examination in the SPACE trial. As a consequence, timing data for 483 patients at baseline are missing in this trial. These patients had to be excluded for the analysis at hand. To allow a timing analysis, a retrospective data collection in the SPACE trial was performed in time intervals (treatment within 7 days after the most recent ischemic event, treatment between 8 and 14 days, and treatment thereafter). This consecutively influenced timing analysis in the whole study population. Receiver-operating characteristic curves with timing as continuous parameter did not allow the identification of a cutoff value because we had a broad CI due to the small number of complications.

Operator experience and its influence on the outcome is still a matter of controversial discussion. Many authors suggest that the inexperience of interventional centers participating in the large trials was responsible for the high complication rate in the stenting arms. This fear was diluted for the EVA-3S data. In this trial, patients who were treated by the most experienced interventionalists (>50 carotid procedures) had the highest risk for stroke or death at 12.2%. Interventionalists who had done 50 or fewer procedures reached a periprocedural stroke or death rate of 11.0%. Best results were achieved by physicians who were still in procedural training at 7.1%. The differences did not reach statistical significance ($P = .49$).[27] In contrast, in the latest update of a Cochrane Systematic Review of randomized trials, the odds ratio for periprocedural stroke or death in CAS vs CEA was higher in trials requiring lower numbers of pretrial procedures than in trials requiring a higher level of experience, but not significantly so.[28] A detailed analysis on the role of experience in the risk of complications with CAS in all three contributing trials is ongoing.

Our data suggest that CEA remains treatment of first choice and can be performed safely within the first week of ischemic symptoms in neurologically stable patients. In contrast, the risk of CAS appears to be especially high in this early phase and declines thereafter. Because we do know that these early days after the initial ischemic event carry the highest risk for a recurrent ischemia, a delay in

Table III. Risks for different end points depending on timing of treatment (0-7 days, 8-14 days, and thereafter) and treatment modality adjusted for age, sex, source trial, and type of qualifying event

	No. (%)	*RR (95% CI)*
Stroke or death		
CEA		
0-7 days (ref)	3 (2.8%)	1
8-14 days	7 (3.4%)	1.16 (0.3-4.4)
>14 days	44 (4.0%)	1.38 (0.4-4.4)
CAS		
0-7 days	13 (9.4%)	3.44 (1.0-11.8)
8-14 days	19 (8.1%)	2.68 (0.8-8.9)
>14 days	78 (7.3%)	2.58 (0.8-8.0)
Disabling stroke or death		
CEA		
0-7 days (ref)	1 (0.9%)	1
8-14 days	3 (1.4%)	1.49 (0.2-14.1)
>14 days	28 (2.6%)	2.86 (0.4-20.9)
CAS		
0-7 days	7 (5.1%)	5.73 (0.7-45.8)
8-14 days	7 (3.0%)	3.11 (0.4-25.0)
>14 days	34 (3.5%)	3.93 (0.5-28.4)
Any stroke		
CEA		
0-7 days (ref)	3 (2.8%)	1
8-14 days	7 (3.4%)	1.16 (0.3-4.4)
>14 days	41 (3.8%)	1.29 (0.4-4.1)
CAS		
0-7 days	13 (9.4%)	3.43 (1.0-11.7)
8-14 days	18(7.7%)	2.54 (0.8-8.5)
>14 days	74 (7.0%)	2.45 (0.8-7.7)



CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *CI,* confidence interval; *RR,* risk ratio.
Early surgery (0-7days) was defined as reference procedure.

treatment seems unreasonable because it might be harmful for the patients at risk. CEA remains most effective in stroke prevention.

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DISCUSSION

Dr Eva Rzucidlo (*Lebanon, NH*). Dr Cambria had mentioned in his presidential address that maybe it's how we're treating patients with carotid stents that's leading to the high stroke rate. I wonder if you could just comment about the embolic protection, if we should be using more flow reversal and whether stent grafting would decrease the risk of stroke for those patients when we want to treat them early.

Dr Gustav Fraedrich. As you know, in the three European trials, there were different regimens regarding the use of protection

devices. We analyzed these parameters and couldn't identify an influence on the results.

Dr Wesley Moore (*Los Angeles, Calif*). I'd like to congratulate you on an excellent presentation and bringing to our attention an extremely important observation with regard to the early differential complication rate between CAS and CEA.

In your table, you listed not only the comparative complication rates within the first 7 days but also in several time intervals after that. You went through that rather quickly and I couldn't see the exact numbers, but as I looked at it, that differential complication rate favoring carotid endarterectomy also persisted in 7 to 14, 14 to 28, and so forth. Could you comment and perhaps elaborate on that a little bit? Again, these are extremely important data.

Dr Fraedrich. As I showed at the beginning, we published the whole data in 2010 in *The Lancet*, and there was a significant difference in favor of endarterectomy that of course still persists in the subgroups. But what we could show is that this difference is significantly most pronounced in the first 7 days. It continues to exist in the 14-day group and later on, but it's more pronounced in the first week.

It is our policy, as in the majority of large vascular centers, to treat symptomatic patients as early as possible. In our institution, they are treated within 1 or 2 days after onset of symptoms. I believe that this is the group that really profits from revascularization. So, the risk of treatment within the first 7 days is of special importance.

Dr John Ricotta (*Washington, DC*). I just wanted to follow up on that a little bit. This is great data and congratulations on a good analysis.

I understand that the Rankin score for CAS and CEA are the same, but I want to ask a little different question regarding these data and whether you could look at them to see whether the severity of the stroke that the patient had before surgery impacted the postprocedure intervention stroke rate. One of the things we're being pushed to do is to try to determine in these patients how severe a stroke are you willing to operate on within a few days. I know that you didn't analyze it in this situation, but I just wonder if you could comment on that and whether you think your data set could help give us some information about that.

Dr Fraedrich. Our policy today is on patients with stroke with a Rankin score below 2 to 3, in particular when the neurological situation improves after the initial stroke. If the neurological situation becomes worse, we perform a CT scan with regard to the blood-brain barrier, and we tend not to operate on the patient.

Dr Ricotta. I think that's what we all do. I'm wondering whether with the database that you have, you can give us some better guidelines.

Dr Fraedrich. We were looking at that, but the data do not allow to answer this question.

Supplementary Table I (online only). Baseline characteristics of patients according to the timing of treatment in three groups (0-7 days, 8-14 days, and >14 days)

	0-7 days		*8-14 days*		*>14 days*	
	CAS (n = 138)	*CEA (n = 106)*	*CAS (n = 234)*	*CEA (n = 208)*	*CAS (n = 1062)*	*CEA (n = 1091)*
Age at randomization, mean (SD), years	68.9 (8.3)	69.3 (9.1)	70.3 (9.4)	69.9 (9.9)	69.7 (9.0)	69.8 (9.2)
Male, No. (%)	103 (74.6%)	80 (75.5%)	179 (76.5%)	160 (76.9%)	741 (69.8%)	781 (71.6%)
History of diabetes, No. (%)	38 (27.5%)	20 (18.9%)	58 (24.8%)	43 (20.7%)	239 (22.5%)	268 (24.6%)
History of hypertension, No. (%)	98 (71.0%)	85 (80.2%)	166 (70.9%)	145 (69.7%)	761 (71.7%)	782 (71.7%)
History of hypercholesterolemia, No. (%)[a]	52 (37.7%)	34 (32.1%)	103 (44.0%)	87 (41.8%)	506 (47.6%)	560 (51.3%)
Any smoking history (current/past), No. (%)	96 (69.6%)	65 (61.3%)	147 (62.8%)	130 (62.5%)	644 (60.6%)	681 (62.4%)
History of coronary heart disease, No. (%)	39 (28.3%)	36 (34.0%)	53 (22.6%)	57 (27.4%)	255 (24.0%)	258 (23.6%)
History of peripheral artery disease, No. (%)[a]	12 (8.7%)	11 (10.4%)	31 (13.2%)	25 (12.0%)	130 (12.2%)	125 (11.5%)
Degree of ipsilateral carotid stenosis, No. (%)[b]						
Moderate (50%-69%)	27 (19.6%)	16 (15.1%)	50 (21.4%)	47 (22.6%)	168 (15.8%)	167 (15.3%)
Severe (70%-99%)	111 (80.4%)	90 (84.9%)	184 (78.6%)	161 (77.4%)	894 (84.2%)	924 (84.7%)
Contralateral severe carotid stenosis (≥70%) or occlusion, No. (%)[b]	17 (12.3%)	14 (13.2%)	27 (11.5%)	33 (15.9%)	161 (15.2%)	155 (14.2%)
Type of most recent ipsilateral ischemic event before randomization, No. (%)						
Transient ischemic attack	75 (54.3%)	53 (50.0%)	81 (34.6%)	79 (38.0%)	337 (31.7%)	352 (32.3%)
Retinal ischemia	18 (13.0%)	18 (17.0%)	31 (13.2%)	26 (12.5%)	212 (20.0%)	199 (18.2%)
Hemispheric stroke	43 (31.2%)	34 (32.1%)	123 (52.6%)	98 (47.1%)	504 (47.5%)	532 (48.8%)
Modified Rankin score at baseline, No. (%)[c]						
0	63 (45.7%)	49 (46.2%)	103 (44.0%)	81 (38.9%)	506 (47.6%)	470 (43.1%)
1	43 (31.2%)	32 (30.2%)	64 (27.4%)	57 (27.4%)	274 (25.8%)	285 (26.1%)
2	24 (17.4%)	22 (20.8%)	45 (19.2%)	44 (21.2%)	192 (18.1%)	228 (20.9%)
3	7 (5.1%)	3 (2.8%)	17 (7.3%)	19 (9.1%)	62 (5.8%)	81 (7.4%)
4	1 (0.7%)	0	4 (1.7%)	2 (1.0%)	12 (1.1%)	15 (1.4%)
5	0	0	0	0	1 (0.1%)	3 (0.3%)
History of stroke before most recent event, No. (%)[a]	13 (9.4%)	0 (9.4%)	35 (15.0%)	25 (12.0%)	136 (12.8%)	141 (12.9%)

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *EVA-3S,* Endarterectomy vs Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; *ICSS,* International Carotid Stenting Study; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial; *SD,* standard deviation.
Percentages exclude missing data. *P* values are not included because there is no statistically significant difference between time groups.
[a]Data collected in EVA-3S trial and ICSS only.
[b]Degree of stenosis measured by NASCET method or equivalent noninvasive method.
[c]Modified Rankin scores at baseline may reflect nonstroke impairments; protocols of contributing trials excluded patients with disabling strokes.

Supplementary Table II (online only). Type and number of outcome events in the three time strata and treatment groups

	0-7 days		*8-14 days*		*>14 days*	
	CAS (n = 138)	*CEA (n = 106)*	*CAS (n = 234)*	*CEA (n = 208)*	*CAS (n = 1062)*	*CEA (n = 1091)*
Any stroke or death	13 (9.4%)	3 (2.8%)	19 (8.1%)	7 (3.4%)	78 (7.3%)	44 (4%)
Disabling stroke or death	7 (5.1%)	1 (0.9%)	7 (3%)	3 (1.4%)	37 (3.5%)	28 (2.6%)
All-cause death	2 (1.4%)	0	3 (1.3%)	0	13 (1.2%)	8 (0.7%)
Any stroke	13 (9.4%)	3 (2.8%)	18 (7.7%)	7 (3.4%)	74 (7%)	41 (3.8%)
Stroke severity						
Fatal stroke	0	0	2 (9.9%)	0	9 (0.8%)	5 (0.5%)
Disabling stroke	7 (5.1%)	1 (0.9%)	4 (1.7%)	3 (1.4%)	23 (2.2%)	20 (1.8%)
Nondisabling stroke	6 (4.3%)	2 (1.9%)	12 (5.1%)	4 (1.9%)	42 (4%)	17 (1.6%)
Stroke pathology						
Ischemic stroke	13 (9.4%)	3 (2.8%)	16 (6.8%)	1 (2.9%)	69 (6.5%)	33 (3%)
Hemorrhagic stroke	0	0	2 (0.9%)	1 (0.5%)	5 (0.5%)	7 (0.6%)
Unknown pathology	0	0	0	0	0	1 (0.1%)
Stroke territory						
Ipsilateral carotid	12 (8.7%)	3 (2.8%)	16 (6.8%)	6 (2.9%)	67 (6.3%)	38 (3.5%)
Contralateral carotid or vertebrobasilar	1 (0.7%)	0	1 (0.4%)	1 (0.5%)	6 (0.6%)	4 (0.4%)
Unknown territory	0	0	1 (0.4%)	0	1 (0.1%)	0

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy.

Supplementary Table III (online only). Risks for different endpoints depending on the timing of treatment (0-7 days, 8-14 days, and thereafter) and treatment modality

	Carotid endarterectomy, No. (%)	*Carotid stenting, No. (%)*	*Adjusted risk ratio (95% CI)*	P *value*
Stroke or death				
0-7 days	3 (2.8%)	13 (9.4%)	4.00 (1.2-13.8)	.03
8-14 days	7 (3.4%)	19 (8.1%)	2.27 (1.0-5.3)	.06
>14 days	44 (4.0%)	78 (7.3%)	1.87 (1.3-2.7)	.001
Disabling stroke				
0-7days	1 (0.9%)	7 (5.1%)	6.41 (0.8-50.1)	.08
8-14 days	3 (1.4%)	7 (3.0%)	2.30 (0.6–8.4)	.25
>14 days	28 (2.6%)	34 (3.5%)	1.39 (0.9-2.3)	.18
Any stroke				
0-7days	3 (2.8%)	13 (9.4%)	4.00 (1.2–13.8)	.03
8-14 days	7 (3.4%)	18 (7.7%)	2.12 (0.9-5.0)	.09
>14 days	41 (3.8%)	74 (7.0%)	1.90 (1.3-2.8)	.001

CI, Confidence interval.

Risk ratios are calculated within the time strata adjusted for age, sex, source trial, and type of qualifying event. The carotid endarterectomy group represents the reference group.