Early endarterectomy carries a lower procedural risk than early stenting in patients with symptomatic stenosis of the internal carotid artery – results from four randomized controlled trials

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Abstract (250 words)

Background

Patients undergoing carotid endarterectomy (CEA) for symptomatic stenosis of the internal carotid artery (ICA) benefit from early intervention. Heterogeneous data are available on the influence of timing of carotid artery stenting (CAS) on procedural risk.

Methods

We investigated the association between timing of treatment (0-7 days and >7 days after the qualifying neurological event) and the 30-day risk of stroke or death after CAS or CEA in a pooled analysis of individual patient data from four randomized trials by the Carotid Stenosis Trialists' Collaboration (CSTC). Analyses were done per protocol. To obtain combined estimates, logistic mixed models were applied.

Results

Among 4138 patients in both treatment groups, a minority received their allocated treatment within seven days after symptom onset (14% CAS versus 11% CEA). Among patients treated within one week of symptoms, those treated by CAS had a higher risk of stroke or death compared ~~to~~ with those treated with CEA: 8.3% vs 1.3%, risk ratio (RR) 6.7, 95% CI 2.1-21.9 (adjusted for age at treatment, sex and type of qualifying event). For interventions after one week, CAS was also more hazardous than CEA: 7.1% vs 3.6%, adjusted RR 2.0, 95% CI 1.5-2.7. The p value for interaction between timing of treatment and treatment technique was 0.06.

Interpretation

In randomized trials comparing stenting with carotid endarterectomy for symptomatic carotid artery stenosis, CAS was associated with a substantially higher periprocedural risk during the first seven days after the onset of symptoms. Early surgery is safer than stenting for preventing future stroke.

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Background

Carotid artery stenting (CAS) has evolved as an alternative treatment for carotid artery disease. Over the last 20 years, CAS has striven to prove its feasibility and efficacy in stroke prevention when compared with that of carotid endarterectomy (CEA) for patients with symptomatic internal carotid artery (ICA) stenosis. Because of the high risk of early stroke recurrence after plaque rupture, it is now accepted that intervention offers the greatest benefit when performed soon after the onset of neurological symptoms[1, 2]. The somewhat greater perioperative risk of rapid CEA is offset by a much lower risk of stroke recurrence[3].

Timing of treatment could also influence the results of carotid artery stenting. Unlike early surgery, CAS seems to be a higher risk procedure when performed soon after symptoms.

The 2012 analysis based on individual patient-level data from three randomized trials comparing CAS and CEA reported by the Carotid Stenosis Trialists' Collaboration (CSTC) suggested that timing of intervention influenced the occurrence of ~~endpoints~~outcomes. CAS between day 0 and 7 was associated with the highest number of procedural complications when compared with patients treated between 8 and 14 days, or thereafter. In contrast, surgery during each of these time intervals was safer[4].

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In this updated analysis, we added data from individual patients with symptomatic carotid stenosis from the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST). This provided the largest group yet studied of patients with symptomatic carotid stenosis randomized between CEA and CAS, and enabled us to investigate associations between periprocedural outcome and timing of treatment for both techniques.

Methods

Four randomized clinical trials with blinded adjudicated ~~endpoints~~ outcomes were included; EVA-3S (NCT 00190398), SPACE (ISRCTN 57874028), and ICSS (ISRCTN 25337470) and CREST (NCT 00004732). In the first 3 of these trials, patients with symptomatic moderate to severe carotid stenosis (≥50% stenosis measured according to NASCET criteria[5]), deemed suitable for both procedures, were randomly allocated to CAS or CEA [6-8]. Our pooled analysis of individual patient data was prospectively agreed at the design stage of the three European trials [9]. Data on symptomatic patients from CREST were added in 2015. CREST included patients with transient ischaemic attack (TIA), amaurosis fugax and minor non-disabling ischaemic stroke. To be eligible for CREST, patients had to have a carotid artery stenosis of at least 50% (on invasive angiography), of 70% or more (when detected by ultrasound or computed tomography angiography) or of 50-69% (on ultrasound or magnetic resonance angiography) [10].

The primary outcome for the present analysis was the combination of any stroke or death occurring within 30 days after treatment. Secondary outcome events were any stroke and fatal or disabling stroke happening within the same time period. The analysis was done per-protocol: patients were only included in the analysis if the randomly allocated treatment was the first initiated revascularization procedure and if either the date of the qualifying event (the last ischaemic event ipsilateral to the carotid artery being randomized in the trial), or the interval between the qualifying event and treatment was known. Patients with missing data on delay between qualifying event and treatment were excluded from the analysis.

In three studies (EVA-3S, ICSS and CREST), the date of the qualifying event was entered at baseline. In the SPACE trial the date of the qualifying event was not prospectively assessed at study entry, however, the date of the qualifying event was retrospectively retrieved whenever possible for this pooled analysis. If the exact date was unknown, patients were included if information was available whether treatment had taken place within seven days of the qualifying event or thereafter.

Statistical Analysis

To obtain a combined estimate (risk ratio (RR) with 95% confidence intervals (CI)), logistic mixed models were applied with the study as random variable using a log-link. The first model was unadjusted whereas the second model accounted for age at treatment, sex, and type of qualifying event (retinal ischaemia, TIA, or stroke). Age at treatment was log-transformed based on the natural logarithm (ln) in the mixed model analysis. In contrast to our previous analysis, just two timing groups were created, because results of patients treated between 8-14 days or thereafter were similar, irrespective of the treatment technique[4]. Therefore the primary analysis compared patients treated within 7 days of neurological symptoms or thereafter. Secondly, an interaction between timing of treatment and treatment effect (CAS versus CEA) was tested by integrating a multiplicative interaction term in the logistic mixed model analyses. A p value of <0.10 for interaction terms was considered statistically significant, for all other statistical analyses a p-value of <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics

The pooled data set for all four trials included 4754 patients with symptomatic ICA stenosis. 2361 patients were randomized to CEA (49.7%) and 2393 patients to CAS. For both treatment groups a number of patients were excluded from data analysis due to missing information about their most recent neurological event, or the treatment date (n=290 patients in the CEA group and n=274 in the CAS group). Another 52 patients (26 in each treatment group) were excluded because they did not receive the initially allocated treatment. Figure 1 gives detailed information about included and excluded patients by source trial. In total, 4138 patients (n=2045 in the CEA and 2093 in the CAS group) remained for per protocol analysis. Table 1 summarizes the baseline characteristics of both treatment groups. The median delay between the most recent neurological event and treatment was 26 days [interquartile range: 11-61] for CAS and 29 days [interquartile range: 13-67] for CEA. Among 4138 patients, a

small but relevant group underwent CAS and CEA within a week of their symptoms (14% in CAS vs. 11% in CEA). Treatment groups did not differ for neurological parameters and comorbidities. Baseline characteristics were additionally provided for the two timing groups (Table 2).

Overall outcome in the study population for both treatment groups (CAS vs. CEA)

The risk of any stroke or death within 30 days after treatment was higher for the CAS compared with~~to~~ the CEA group for the entire study population: 7.3% vs. 3.3%, crude RR 2.29, 95% CI 1.71-3.08. This association remained significant when the model was additionally adjusted for age at treatment, sex and type of qualifying event (RR 1.92, 95% CI 1.50-2.47).

Outcome in both treatment groups by timing of treatment (0-7 days and > 7 days)

In the early period after the onset of neurological symptoms (0 to 7 days), CAS had the highest number and proportion of periprocedural strokes and deaths (n=24/287, 8.4%), compared with CEA (n=3/226, 1.3%). Patients in the CAS group had a higher risk of any stroke or death in the crude (RR 6.51, 95% CI 2.00-21.21) and adjusted models (RR 6.74, 95% CI 2.07-21.92) (Figure 2).

Compared with~~to~~ those treated within 7 days, patients treated after 7 days had fewer strokes and deaths in the CAS group (n=129/1806, 7.1%), while the risk of stroke and death in the CEA group slightly increased (n=65/1819, 3.6%). The risk ratio for CAS compared with CEA was still higher in this later treatment group: RR_{crude} 2.00, 95% CI 1.49-2.67; $RR_{adjusted}$ 2.00, 95% CI 1.50-2.68. Results were almost identical for the outcome analysis of any stroke: RR_{crude} for CAS in the early treatment group 6.27, 95% CI 1.92-20.44; RR_{crude} for CAS after 7 days 1.98, 95% CI 1.47-2.67 (Table 3). Adjustment did not importantly change results (Figure 2). The analysis of fatal or disabling stroke outcome at 30 days also showed that the crude risk ratio was higher for CAS than the CEA group within 7 days (RR 8.29, 95% CI 1.07-

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64.28) and after 7 days (RR 1.77, 95% CI 1.10-2.85) (Table 3). Results were virtually unchanged after adjustment (Figure 2).

Interaction between time and relative risks of CAS versus CEA

The test for interaction between timing of treatment and treatment effect (CAS versus CEA) revealed a p value of 0.07 in the crude and 0.06 in the adjusted model for the outcome any stroke or death. Comparable results were seen for the outcome any stroke at 30 days (p value for both models=0.07). There was no statistically significant interaction seen for fatal or disabling stroke (Figure 2).

Discussion

Carotid artery stenting is not as safe as carotid endarterectomy in the treatment of patients with symptomatic stenosis of the internal carotid artery irrespective of the timing of treatment. The difference in safety between CAS and CEA is particularly potent in patients treated within 7 days of symptom onset.

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There has been a heated debate as to whether early surgery in symptomatic patients is safe and meaningful. However, it is now widely accepted that early plaque removal effectively reduces stroke risk. Although early surgery may be associated with a slightly higher risk of perioperative complications, it still offers the best chance of a symptomatic patient avoiding future stroke[3, 11]. Recent literature suggests that the risk of early recurrent stroke from symptomatic ICA stenosis remains high[12-14]. In a very recently published series of 377 patients with symptomatic ICA stenosis stroke recurrence rate reached 2.7% within the first day, 5.3% within three days and 18.8% within 90 days after the qualifying event[14]. Only one retrospective Swedish study reported a lower overall number of second events in 397 patients with symptomatic stenosis of the ICA (for recurrent stroke 2.0%, 95% CI 0.6-3.4 by day 2, 2.4%, 95% CI 2.0-5.9 by day 7 and 7.5%, 95% CI 4.4-10.6 by day 30)[15].

The same group published results from the SWEDVASC registry where the outcome of CEA was analyzed depending on the timing of treatment. The authors found that rapid surgery

(between 0-2 days) was associated with a significantly higher frequency of perioperative complications (any stroke or death) when compared with patients treated between 3 and 7 days, 8 and 14 days and thereafter (11.5% vs. 3.6% vs. 4.0% vs. 5.4%, p<0.001, respectively)[16]. Only a small number of SWEDVASC patients were treated in the very early period (5.7%), which might limit the generalizability of these registry data. In contrast, their slight increase in perioperative complications was not replicated in two single center studies [17, 18]. Both studies reported comparable perioperative complication rates for the same four surgical timing groups. The analysis of more than 56.000 patients with symptomatic ICA stenosis from the German nationwide statutory quality assurance registry also revealed no outcome difference between patients treated early (within 48 hours) and thereafter (any stroke or death 3.0% for CEA between 0-2 days vs. 2.5% between 3-7 days vs. 2.6% between 8-14 days vs. 2.3% for CEA thereafter)[19]. Also results from the National Vascular Registry from the UK illustrated comparable results for the four timing groups among more than 23.000 symptomatic patients[20]. Complementary to this register data which only contained CEA patients very recently results from the National (Nationwide) Inpatient Sample (NIS) were published. In this analysis authors investigated the influence of ultra-early revascularizations (within 48 hours) on the outcome of CAS and CEA in more than 70.000 symptomatic patients. The comparison between CAS and CEA when performed within 48 hours after the onset of symptoms showed that CAS was associated with significantly more periprocedural complications, regardless of whether patients had a cerebral infarction on admission or not (OR 3.45, 95% CI 3.13-3.80, p>0.01 for CAS patients with infarct on admission compared with~~to~~ CEA under same conditions; OR 2.53, 95% CI 2.40-2.66, p<0.001 for CAS patients without infarct on admission compared with~~to~~ CEA again under same conditions)[21]. These authors did not find any outcome differences after later treatment for both CEA and CAS. Recently the influence of timing on the outcome of CAS and CEA was also analyzed in the CREST data. The authors used three timing groups (CAS or CEA <15 days, 15-60 days and thereafter) and did not see any time-dependence for periprocedural outcome for both treatment techniques (HR for stroke or death in the CAS

group comparing 15-60d days to <15 days 1.15, 95% CI 0.48-2.75 and 1.12, 95% CI 0.53-2.40 comparing >60days to <15 days, both p=0.93). For the CEA group comparing 15-60d days to <15 days the HR was 0.74, 95% CI 0.22-2.49 and 0.91, 95% CI 0.25-3.33, respectively, comparing >60days to <15 days, both p=0.89)[22]. Differences in outcome analysis between CREST only and CSTC plus CREST data might be due to different time strata, making results more difficult to compare.

In the present report we found that the CAS group had the highest periprocedural stroke or death risk in the period of 0-7 days after the onset of symptoms compared with~~to~~ patients treated with CEA. CAS was also associated with a significantly higher risk in the later treatment period (> 7 days). Early surgery had the lowest absolute number of periprocedural complications for all three ~~endpoints~~outcomes. CAS complications slightly decreased with time (for primary outcome any stroke or death from 8.4% to 7.1%). This result is consistent with the hypothesis that the plaque surface of a recently symptomatic plaque is fragile and vulnerable for catheter passage. The clinical decision to perform either CAS or CEA early is likely influenced by characteristics of the patient and the symptomatic event. We saw in both treatment groups that the percentage of patients treated following a hemispheric stroke was about 10% higher in the later treatment group compared with~~to~~ early treated patients (Table 2). Patients within the timing groups did not differ for neurological parameters. Since timing of treatment was not of note when the four randomized trials were conducted in the early years of the new millennium the slight increase in the procedural risk for CEA over time (any stroke or death 1.3% for 0-7 days vs. 3.6% for CEA after 7 days) might be by chance.

In another analysis of the NIS, the authors focused on patients with symptomatic ICA stenosis and recent cerebral infarction. Analyses were done in four timing groups: CEA or CAS within 48 hours after the onset of symptoms, between 48 hours and 4 days, between 5 and 7 days and between 8 and 14 days. Amongst the 27839 patients with recent cerebral infarction, patients treated between five and seven days after symptoms had the lowest probability of periprocedural complications (OR 0.64, 95% CI 0.56-0.74, p<0.001) and mortality (OR 0.63, 95% CI 0.45-0.89, p<0.001), irrespective of the treatment technique[23].

Without having details about cerebral lesions we found in the CSTC population that CEA was most beneficial when performed between 0 and 7 days, whereas CAS was most harmful during the first week after the onset of symptoms. Due to small numbers of patients who were treated early after the onset of symptoms and relatively small numbers of periprocedural complications in both treatment groups we could not build further time groups to determine an ideal time point for CAS and CEA amongst our study population.

Limitations of our analysis

Timing of treatment has to date never been a randomization criterion in larger trials. All information on the influence of timing of treatment is driven from post hoc analysis from randomized controlled trials comparing two treatment techniques (best medical treatment vs. CEA or CEA vs. CAS). Therefore, detailed information on patient selection and disease severity is lacking. This significantly limits the value of timing analysis so far. A randomized trial on timing of treatment would be mandatory in the near future.

Recent ischaemic infarction on neuroimaging is reported to be a relevant risk factor for periprocedural complications after CAS as well as after CEA. Unfortunately, detailed findings from baseline CT or MRI were not available for the present analysis.

Conclusion

Carotid endarterectomy is very effective at preventing stroke. Early plaque removal can be performed without relevantly increasing perioperative complications. In contrast, carotid artery stenting during the early period after plaque rupture is associated with an increased risk of periprocedural complications. We could clearly demonstrate in this randomized and large population of symptomatic patients that risk differences between CAS and CEA were greatest in the early days after the index symptom. Early CEA was associated with the lowest risk of periprocedural complications. We therefore conclude that early carotid endarterectomy after an initial neurological event offers the highest stroke prevention benefit for the patient at risk.

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Table 1 Baseline data of the combined trial population according to treatment group (CAS and CEA)			
	CAS n=2093	**CEA** n=2045	**p value**
Age at treatment (years)	69.4±9.2 [63,70,76]	69.5±9.3 [63,70,77]	0.49
Male, n (%)	1449 (69)	1442 (71)	0.37
History of diabetes, n (%)	519 (25)	507 (25)	0.997
History of hypertension, n (%)	1570 (75)	1552 (76)	0.56
History of hypercholesterolemia, n (%)[a]	1142 [a,] (55)	1172 [a] (57)	0.06
Any smoking history (current/past), n (%)	1317 (63)	1310 (64)	0.44
History of coronary heart disease, n (%)	572 (27)	576 (28)	0.49
History of peripheral artery disease, n (%)[b]	173 [a] (8)	161 [a] (8)	0.52
Degree of ipsilateral carotid stenosis, n (%)[c]			
Moderate (50-69%)	366 [b] (17)	369[b] (18)	0.64
Severe (70-99%)	1727 [b] (83)	1676 [b] (82)	
Contralateral severe carotid stenosis (≥70%) or occlusion, n (%)[c]	208 [b] (10)	204 [b] (10)	0.94
Type of most recent ipsilateral ischaemic event before randomization, n (%)			
TIA	774 (37)	761 (37)	0.95
Retinal ischaemia	363 (17)	347 (17)	
Hemispheric stroke	942 (45)	923 (45)	
modified Rankin Score (mRS) at baseline[d]			
mRS=0 , n (%)	1033 (49)	994 (49)	0.79
mRS=1 , n (%)	564 (27)	539 (26)	
mRS=2 , n (%)	334 (16)	342 (17)	
mRS=3 , n (%)	114 (5)	124 (6)	

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mRS=4 , n (%)	26 (1)	24 (1)	
mRS=5 , n (%)	1 (0.05)	3 (0.1)	
History of stroke before most recent event, n (%)[b]	371 [a] (18)	365 [a] (18)	0.93
Days elapsed between most recent ipsilateral ischaemic event and treatment[e]	45.5±50.6 [11,26,61]	49.8±59.1 [13,29,67]	0.004
Treatment within 7 days of most recent event [e]	287 (14)	226 (11)	0.009

Mean ± standard deviation (SD) and [25th, 50th, 75th percentile] in case of non-normal distribution; interquartile range (IQR): 25th - 75th percentile] or number (%) (=percent excluding missing values)
CAS: carotid artery stenting, CEA: carotid endarterectomy; TIA: transient ischemic attack

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

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

[c] Degree of stenosis measured by NASCET method or equivalent non-invasive method.

[d] Modified Rankin Scores at baseline may reflect non-stroke impairments; protocols of contributing trials excluded patients with disabling strokes.

[e] The date of the most recent ipsilateral ischaemic 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 7 days of the qualifying event), were retrieved where available.

	0-7 days		>7 days	
	CAS n=287	**CEA** n=226	**CAS** n=1806	**CEA** n=1819
Age at randomization (years)	68.3±9.0 [62,69,75]	69.2± 8.9 [63,70,76]	69.6±9.2 [63,70,77]	69.6±9.4 [63,70,77]
Male, n (%)	198 (69)	157 (69)	1251 (69)	1285 (71)
History of diabetes, n (%)	82 (29)	55 (24)	437 (24)	452 (25)
History of hypertension, n (%)	220 (77)	189 (84)	1350 (75)	1363 (75)
History of hypercholesterolemia, n (%)[a]	164 (57)	123 (54)	978 (54)	1049 (58)
Any smoking history (current/past), n (%)	191 (67)	146 (65)	1126 (62)	1164 (64)
History of coronary heart disease, n (%)	89 (31)	77 (34)	483 (27)	499 (27)
History of peripheral artery disease, n (%)[a]	12 (4)	11 (5)	161 (9)	150 (8)
Degree of ipsilateral carotid stenosis, n (%)[b]				
Moderate (50-69%)	54 (19)	38 (17)	312 (17)	331 (18)
Severe (70-99%)	233 (81)	188 (83)	1494 (83)	1488 (82)
Contralateral severe carotid stenosis (≥70%) or occlusion, n (%)[b]	16 (5.6)	14 (6.2)	192 (11)	190 (10)
Type of most recent ipsilateral ischaemic event before randomization, n (%)				
TIA	146 (51)	112 (50)	628 (35)	649 (36)
Retinal ischaemia	37 (13)	30 (13)	326 (18)	317 (17)
Hemispheric stroke	101 (35)	83 (37)	841 (47)	840 (46)
modified Rankin Score (mRS) at baseline[c]				
mRS=0 , n (%)	138 (48)	119 (53)	895 (50)	875 (48)
mRS=1 , n (%)	91 (32)	68 (30)	473 (26)	471 (26)
mRS=2 , n (%)	38 (13)	32 (14)	296 (16)	310 (17)
mRS=3 , n (%)	13 (5)	4 (2)	101 (6)	120 (7)
mRS=4 , n (%)	4 (1)	1 (0.4)	22 (1)	23 (1)
mRS=5 , n (%)	0 (0)	0 (0)	1 (0.06)	3 (0.2)

History of stroke before most recent event, n (%)[a]	43 (15)	28 (12)	328 (33)	337 (33)

Mean ± standard deviation (SD) and [25th, 50th, 75th percentile] in case of non-normal distribution; interquartile range (IQR): 25th - 75th percentile] or number (%) (=percent excluding missing values)
CAS: carotid artery stenting, CEA: carotid endarterectomy; TIA: transient ischaemic attack

Table 3: Logistic mixed models of two treatment groups (CAS vs. CEA) depending on timing of treatment (0-7 days and >7 days) on three different outcomes within 30 days after treatment (any stroke or death, any stroke and fatal or disabling stroke).

	CEA n event/ n total (%)	**CAS** n event/ n total (%)	**Crude RR (95% CI)** *	**p-value**
Any stroke or death				
0-7 days	3/226 (1.3)	24/287 (8.4)	6.51 (2.00-21.21)	0.002
>7 days	65/1819 (3.6)	129/1806 (7.1)	2.00 (1.49-2.67)	<0.0001
Any stroke				
0-7 days	3/226 (1.3)	23/287 (8.0)	6.27 (1.92-20.44)	0.002
>7 days	62/1819 (3.4)	122/1806 (6.8)	1.98 (1.47-2.67)	<0.0001
Fatal or disabling stroke				
0-7 days	1/226 (0.4)	9/287 (3.1)	8.29 (1.07-64.28)	0.04
>7 days	26/1819 (1.4)	46/1806 (2.5)	1.77 (1.10-2.85)	0.02

* CEA represents reference group.

CAS: carotid artery stenting, CEA: carotid endarterectomy, CI: confidence interval

Commented [AA8]: Also these p-values may be deleted as they are redundant when presenting the effect estimate and 95% CI.

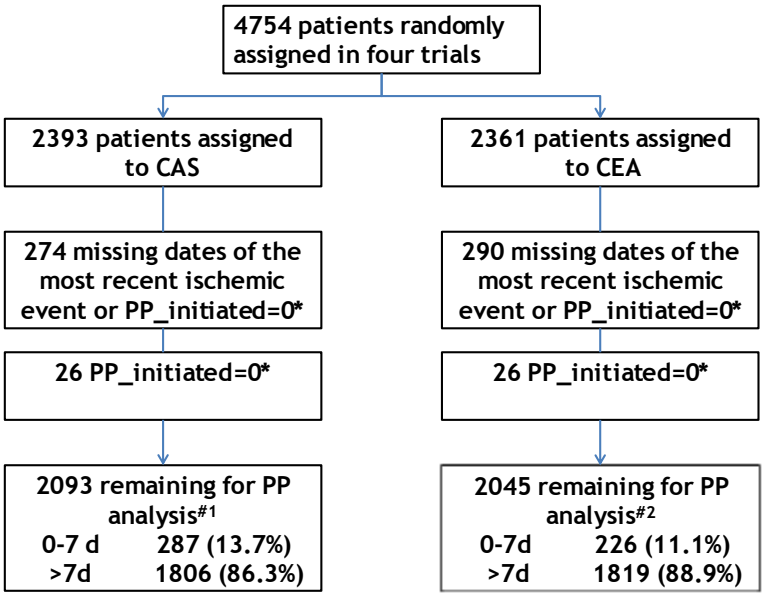

Figure 1: Flow diagram of patients included in the meta analysis referring to source trial

PP_initiated=0 reflects patients who did not receive the primarily allocated treatment technique. Those patients were excluded for per protocol analysis

#1 2093 CAS patients: 260 (12.4%) EVA-3S, 381 (18.2%) SPACE, 828 (39.6%) ICSS, 624 (29.8%) CREST;

#2 2045 CEA patients: 257 (12.6%) EVA-3S, 365 (17.8%) SPACE, 819 (40.0%) ICSS, 604 (29.5%) CREST

PP: per protocol, CAS: carotid artery stenting, CEA: carotid endarterectomy

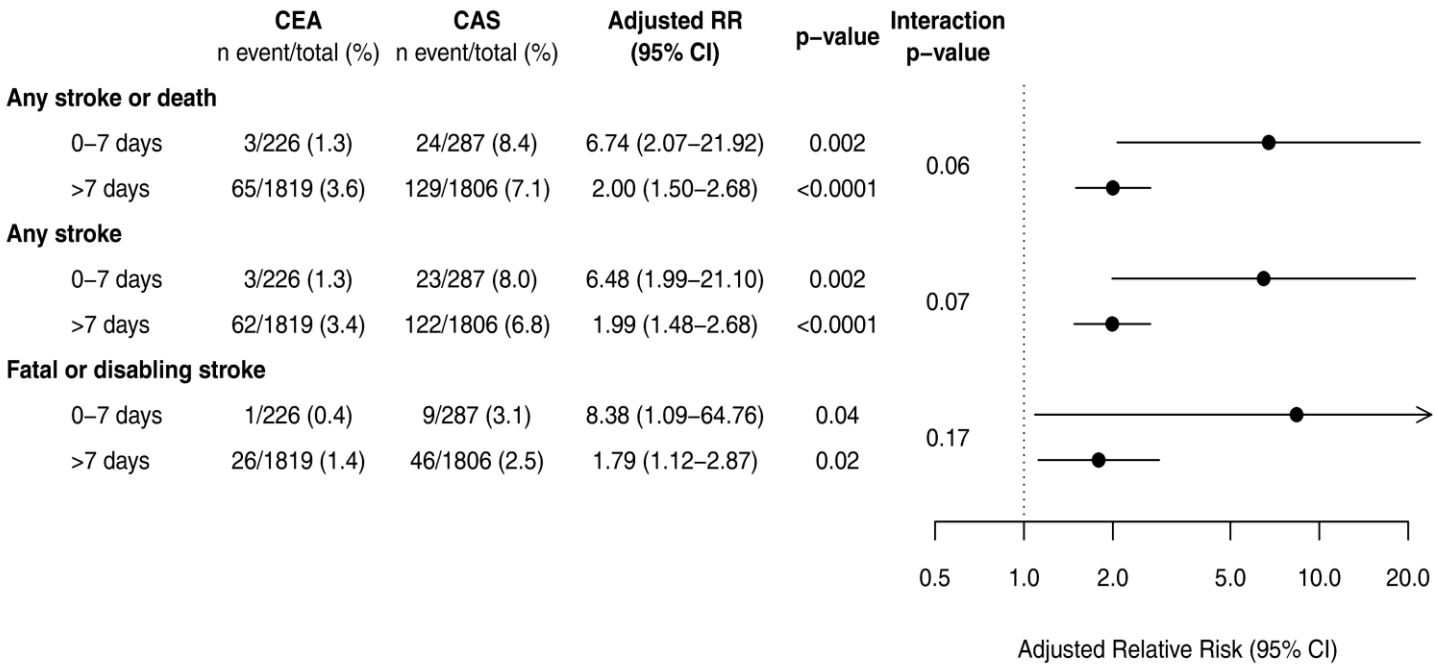

Figure 2: Forest plot illustrating the adjusted relative risk of two treatment groups (CAS vs. CEA) in two timing groups (0-7 days and >7 days) on three different outcomes within 30 days after treatment (any stroke or death, any stroke and fatal or disabling stroke). Model adjusted for age at treatment, sex, and type of qualifying event (retinal ischaemia, TIA, or stroke).