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Editor's Choice - Safety of Carotid Endarterectomy After Intravenous Thrombolysis for Acute Ischaemic Stroke: A Case-Controlled Multicentre Registry Study CME

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WHAT THIS PAPER ADDS

The literature on the safety of carotid endarterectomy (CEA) after intravenous thrombolysis (IVT) consists of relatively small series. This study presents the first very large registry based case controlled study on a consecutive series of patients having CEA with or without previous IVT for acute stroke. Equally low procedure related stroke and death rates were found in the two groups. Despite weaknesses in this study, including lack of data on the interval from symptoms to CEA in the control group, the results support the indication that CEA can also be performed within the recommended 2 weeks in patients having had IVT.

Objective: Few studies have been published on the safety of carotid endarterectomy (CEA) after intravenous thrombolysis (IVT). Registry reports have been recommended in order to gather large study groups.
Design: A retrospective, registry based, case controlled study on prospectively gathered data from Sweden, the capital region of Finland, and from Denmark, including 30 days of follow up.
Methods: The study group was a consecutive series of 5526 patients who had CEA for symptomatic carotid artery stenosis during a 4.5 year period. Among these, 202 (4%) had IVT prior to surgery, including 117 having CEA within 14 days, and 59 within 7 days of thrombolysis. IVT as well as CEA were performed following established guidelines. The median time from index symptom to CEA was 12 days (range 0–130, IQR 7–21).
Results: The 30 day combined stroke and death rate was 3.5% (95% CI 1.69–6.99) for those having IVT + CEA, 4.1% (95% CI 3.46–4.39) for those having CEA without previous IVT (odds ratio 0.84 [95% CI 0.39–1.81]), 3.4% (95% CI 1.33–8.39) for those having IVT + CEA within 14 days, and 5.1% (95% CI 1.74–13.91) for those having IVT + CEA within 7 days.
Conclusion: Data on the time from symptoms to CEA in patients not having IVT, Rankin score, degree of stenosis, and cerebral imaging were not available. Despite its weaknesses, this study reasserts that CEA can be performed within the recommended 2 weeks of the onset of symptoms and IVT without increasing the risk of peri-operative stroke or death. Centres and vascular registries are recommended to continue monitoring changes in patient characteristics, lead times, and major complications after CEA in general, with a special focus on those who have undergone a prior thrombolysis.

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INTRODUCTION

Intravenous thrombolysis (IVT) has proven effective in preventing permanent cerebral injury when applied to patients within the first few hours of onset of an acute ischaemic stroke: a thrombolytic agent, recombinant tissue plasminogen activator (rtPA), is injected into a peripheral vein with the purpose of resolving the suspected thrombosis of an intracerebral artery. The major complication to IVT is intracerebral haemorrhage, occurring in 2–8% of cases.[1,2] After uncomplicated IVT, patients with a significant

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internal carotid artery (ICA) stenosis may be candidates for carotid endarterectomy (CEA).

CEA is well established as secondary stroke prevention in patients with symptoms of cerebral or retinal ischemia (minor stroke, transient ischaemic attack [TIA], or amaurosis fugax) and a 50—99% stenosis (according to NASCET criteria) of the extracranial part of the ICA.[3,4] To prevent the highest possible number of strokes, CEA should be performed shortly after the index symptom.[5] The risk of stroke and death associated with CEA usually reaches 2—8%.[6] Whereas some studies indicate that performing CEA very early after the index symptom is safe, others indicate that there may be increased risk associated with CEA performed within 48 hours of the index symptom.[7]

There is limited knowledge about the effect of IVT on the rate of complications after subsequent CEA: the literature is scarce and consists of comparably small series (5—73 patients).[8—13] Collaborative registry reports have been recommended to recruit a sufficiently large study group.[14] Vascular registries are well established in Sweden, Denmark, and the capital province of Finland. Thus, a multinational population based study was initiated with the purpose of examining the rate of complications among patients undergoing CEA alone, and those undergoing CEA after successful IVT for acute ischaemic stroke in a large contemporary consecutive series of patients with a symptomatic ICA stenosis.

METHODS AND PATIENTS

In this a purely register based retrospective study of prospectively collected data, a consecutive series of patients who underwent CEA for symptomatic carotid artery stenosis during the period from May 2008 through November 2012 was reviewed. Data were collected from the national vascular registries in Sweden (SWEDVASC[15]), and Denmark (KARBASE[16]), and from the Finnish registry covering the Helsinki-Uusimaa region (HUSVASC[17]). Supplementary information on those patients having IVT was obtained, and data on any stroke or death after discharge from the vascular department was obtained by extracting data from The Swedish Stroke Registry,[18] the Finnish Thrombolysis registry,[19] and Cause of Death registry,[20] as well as from The Danish Stroke Register and The National Patient Register in Denmark.[21] The vascular registries have similar structures and data, including 30 day follow up. Data were merged into a predefined protocol for analysis. There were no missing data from the IVT + CEA group. The outcome data were crossmatched with the other registries.

Ethical approval was obtained from the ethical review boards of each nation.

Organisation

In Sweden (9.5 million inhabitants — 2012), management of patients with acute cerebral ischaemic events varies across the country depending on regional structures. In 2012, 72% were admitted to stroke units (departments with neurological expertise).[22] All regional, most county, and some district hospitals offer IVT at all hours. In 2012, approximately 12% of all patients with an acute ischaemic stroke were treated with IVT.[22] Carotid artery surgery is centralised to seven regional and 14 county hospitals. In the Helsinki-Uusimaa region of Finland (1.5 million inhabitants — 2012), all patients with suspected acute ischaemic stroke and eligible for IVT are transferred to the stroke unit at Helsinki University Central Hospital (HUCH) where IVT is available at all hours. In 2011, 31% were treated with IVT[23,24]. The department of vascular surgery is located at the same hospital. In Denmark (5.6 million inhabitants — 2012), 95% of all patients with symptoms of acute ischaemic stroke are admitted or transferred within the first 48 hours to the nearest stroke unit.[25] IVT is offered at all hours at selected centres in major cities. Twelve per cent of patients with acute ischaemic stroke are treated with IVT.[25] Vascular surgery is centralized to seven centres, not always located in the same hospital as the stroke unit.

Intravenous thrombolysis

IVT was given in accordance with internationally accepted guidelines: patients should present signs of acute stroke, cerebral imaging should exclude haemorrhage, IVT must be started within 4.5 hours of onset of symptoms, and the patient's previous level of function must have been good. A dose of 0.9 mg alteplase per kg bodyweight (concentration: 1 mg mL^{-1}) was injected in a peripheral vein (10% as a bolus during 1—2 min, and the rest during the following hour). All patients received antiplatelet therapy after 24 hours.[26,27]

Carotid endarterectomy

CEA was offered in accordance with internationally accepted guidelines to patients with symptomatic 50—99% stenosis (NASCET criteria) in all three countries.[5,6] Antiplatelet therapy was continued without interruption. Oral anticoagulants (warfarin) were discontinued if possible for 1—2 days prior to CEA to 1 day after CEA, and replaced with low-molecular-weight heparin (LMWH). Blood pressure was stabilised pre-operatively and monitored continuously per-operatively, and kept within ±20% of the pre-operative level depending on the degree of stenosis. CEA was performed under either local or general anaesthesia. Cerebral perfusion during CEA was monitored using locally preferred techniques: transcranial Doppler (TCD) or Near Infrared Spectroscopy (NIRS). Some preferred stump pressure for indirect evaluation of the cerebral perfusion during cross-clamping. A carotid shunt was used according to the centre/surgeon's algorithm. Patients were observed in post-operative recovery units with continuous intra-arterial blood pressure monitoring and neurological evaluation. When stable, patients were transferred to the vascular ward. To meet the risk of developing hyperperfusion, elevated blood pressure was lowered as was performed prior to the operation. If no complication was observed, patients were discharged after 1—2 days. Thirty days after

CEA, patients were examined by a neurologist, a stroke physician, a vascular surgeon, or (in Helsinki) a nurse.

As IVT is performed within few hours of the onset of symptoms, the time to CEA is calculated from the day at which IVT was initiated.

Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences, software version 21.0 (SPSS, Chicago, IL, USA). Dichotomic variables were expressed as number of cases and percentages and compared using chi-square test. Continuous variables are expressed as median values ± SD (range) and interquartile range (IQR) and were compared using the Student *t* test.

Any *p* values of <0.01 were considered significant, adjusting for multiple comparisons.

RESULTS

From May 2008 through November 2012 a consecutive series of 6630 patients with a symptomatic carotid stenosis was included in this investigation. To increase the comparability of groups, 1097 patients who had CEA following amaurosis fugax (which is not an indication for IVT) were excluded. Another seven patients from the Faroe Islands, having CEA in Denmark, were lost to follow-up, leaving 5526 patients available for study: 3064 from Sweden, 664 from Finland (Helsinki-Uusimaa region), and 1798 from Denmark. Among these, 202 patients (4%) had IVT prior to CEA (IVT + CEA) while 5324 patients (96%) had CEA without previous IVT (CEA alone). The percentage of patients having IVT + CEA was significantly higher in Helsinki (5.0%) and in Denmark (4.4%) compared with Sweden (2.0%) ($p < 0.001$).

The median time from IVT to CEA was 12 days (range 0–130, IQR 7–21), Sweden 10 days (range 1–130), Finland 7 days (range 0–89), and Denmark 15 days (range 2–85) (Sweden vs. Finland: $p = 0.26$; Sweden vs. Denmark: $p = 0.40$; Finland vs. Denmark: $p = 0.51$).

CEA was performed within 14 days of IVT in 177 patients (median 7 days [range 0–14]). Among these, 59 had CEA within 7 days of IVT (median 4 days [range 0–7]).

Information on the time from index symptom to CEA in those not having IVT was not available.

The stroke rate was 3.5% (95% CI 1.69–6.99) among patients having IVT + CEA, 3.4% (95% CI 1.33–8.39) among those having CEA within 14 days, and 5.1% (95% CI 1.74–13.91) among those having CEA within 7 days. No patients from these groups died within the first 30 days. Among the seven patients who suffered a stroke within 30 days of CEA, the time from IVT to CEA was the same as in the whole cohort: median 12 days (range 6–21, $p = 0.10$). The combined stroke and death rate was 4.1% (95% CI 3.59–0.46) among those having CEA without previous IVT. The odds ratio for the stroke and death rate for the IVT + CEA group compared with the CEA alone group was 0.84 (95% CI 0.39–1.81).

The distribution of age and sex between the countries, and for the two groups (IVT + CEA and CEA alone), are presented in Table 1. There was no difference in age and sex distribution between the patients who underwent IVT + CEA and those who underwent CEA alone ($p = 0.03$). Among those who underwent IVT + CEA, the proportion of females was higher in Finland (than in Denmark) (Finland vs. Sweden: $p = 0.03$; Finland vs. Denmark: $p = 0.002$). This was also true among those who underwent CEA alone, although the numerical difference was smaller (Finland vs. Sweden: $p < 0.0001$; Finland vs. Denmark: $p = 0.0003$).

Table 1. Age and gender of patients having and not having intravenous thrombolysis (IVT) prior to carotid endarterectomy (CEA) (number (per cent)).

CEA + IVT	*N*	Gender, *N* (%) Female	Male	Age, years Median (min–max)
Sweden	73	23 (32)	50 (68)	72 (38–84)
Finland	38	20 (53)	18 (47)	69 (50–88)
Denmark	91	22 (24)	69 (76)	71 (52–85)
Total	**202**	**65 (32)**	**137 (68)**	**71 (38–88)**
CEA alone	*N*	Gender, *N* (%) Female	Male	Age, years Median (min–max)
Sweden	2990	981 (33)	2009 (67)	74 (41–93)
Finland	626	259 (41)	367 (59)	71 (34–90)
Denmark	1708	567 (33)	1141 (67)	69 (35–93)
Total	**5324**	**1807 (34)**	**3517 (66)**	**72 (34–93)**

Further characteristics including comorbidity (diabetes, hypertension, heart disease, and smoking habits) are listed in Table 2. There was no difference in the prevalence of comorbidity between the total group of IVT + CEA patients and the CEA alone patients.

Among the IVT + CEA patients, the prevalence of diabetes was lower in Denmark (Denmark vs. Sweden: $p = 0.001$; Denmark vs. Finland: $p = 0.005$). There were no differences between the three nations regarding the prevalence of heart disease or smoking habits. Among the CEA alone patients, the prevalence of diabetes and heart disease, as well as the proportion of current smokers was significantly lower in Denmark than in Sweden ($p = 0.006$, $p < 0.0001$, and $p < 0.0001$, respectively).

The symptom leading to IVT was defined as stroke in all patients even though symptoms may resolve within 24 hours – similar to the definition of a transient ischaemic attack (TIA). The index symptoms among patients having CEA alone are listed in Table 3.

Specific information on the degree of stenosis, disability before and after CEA (e.g. modified Rankin score), and on the nature of antiplatelet therapy in each patient was not available for this study.

DISCUSSION

The main finding of this multinational registry study was that there was no difference regarding the 30 days combined stroke and death rate following carotid endarterectomy comparing patients who underwent IVT prior to CEA with those who underwent CEA alone. Among the 117 patients having CEA within 14 days of IVT, and in those

Table 2. Comorbidity among patients having and not having intravenous thrombolysis (IVT) prior to carotid endarterectomy (CEA) (number (per cent)).

	DM[a]	Hypertension[b]	Heart disease[c]	Active smoking
IVT + CEA				
Sweden	18 (27) ($N = 66$)	56 (84) ($N = 67$)	18 (28) ($N = 64$)	13 (25) ($N = 52$)
Finland	9 (29) ($N = 31$)	28 (88) ($N = 32$)	12 (29) ($N = 31$)	13 (42) ($N = 31$)
Denmark	8 (9) ($N = 91$)	61 (68) ($N = 90$)	27 (30) ($N = 90$)	25 (28) ($N = 28$)
Total	**35 (19) ($N = 188$)**	**145 (77) ($N = 77$)**	**57 (31) ($N = 185$)**	**51 (30) ($N = 171$)**
CEA alone				
Sweden	583 (21) ($N = 2792$)	1756 (61) ($N = 2868$)	834 (30) ($N = 2756$)	565 (24) ($N = 2354$)
Finland	175 (29) ($N = 599$)	486 (84) ($N = 578$)	564 (44) ($N = 597$)	194 (31) ($N = 630$)
Denmark	285 (17) ($N = 1701$)	1234 (73) ($N = 1698$)	442 (26) ($N = 1695$)	668 (40) ($N = 1686$)
Total	**1043 (20) ($N = 5094$)**	**3972 (77) ($N = 5129$)**	**1537 (30) ($N = 5051$)**	**1427 (31) ($N = 4583$)**

[a] Medically treated diabetes (type I or II).
[b] Medically treated hypertension in any form.
[c] Coronary artery and/or congestive heart disease (medically or surgically treated including endovascular treatment).

having CEA within 7 days of IVT, rates of complications were similarly low. The rate of complications for the IVT + CEA group in the present study is similar to the pooled outcome from previously reported series (3.1%) (Table 4).[8–13]

It could be argued that patients with TIAs should be excluded from the control group. However, it has been shown that, despite full remission within 24 hours, signs of cerebral infarction on cerebral magnetic resonance imaging (MRI) can be seen in 30–50% of TIA patients, and revision of the time dependent definition of TIA was suggested by the American Heart Association in 2009.[28] In the present study, the "old" definition of TIA (symptoms lasting less than 24 hours) was used, and information on the duration of symptoms was not available nor was data on cerebral imaging. Therefore, all patients with cerebral ischaemic symptoms were included in the control group.

The characteristics in terms of age, gender, smoking habits, and comorbidity of the patients in the two groups, IVT + CEA and CEA alone, were comparable. There were some differences in basic characteristics between the countries: firstly, there was a larger proportion of female patients in Finland. This may be associated with a somewhat shorter interval from symptom to CEA among the Finnish patients: because the benefit of CEA has been shown to decrease more rapidly with time in women than men, the longer the delay, the fewer women benefit from CEA, and thus fewer are offered surgery.[5] Secondly, the proportion of patients with diabetes was significantly lower in Denmark and the proportions of smokers, diabetics, and patients with heart disease were significantly lower in Denmark compared with Sweden. Most likely, these differences reflect difficulties in gathering true risk factor/comorbidity data in registries. Contrary to data on stroke and deaths, where crosschecking of data is possible, it was not possible to validate data on comorbidity in the same way, and therefore these data are less robust.

The organisation of, and guidelines for, treatment with IVT, as well as CEA, were more or less the same within the three nations. The time from IVT to CEA was less than 20 days in 75% of patients. During the studied period, initiatives were taken in all three countries to minimize the interval. In consequence, the overall interval from the index symptom to CEA reached a median of 7 days in Sweden in 2012 (IQR 4–13).[15] In Helsinki, the interval decreased

Table 3. Index symptom (number (per cent)) among 5324 patients having carotid endarterectomy without previous intravenous thrombolysis.

	TIA, *n* (%)	Stroke, *n* (%)	Total, *n* (%)
Sweden	1635 (55)	1356 (45)	2991 (100)
Finland	345 (55)	281 (45)	626 (100)
Denmark	900 (53)	807 (47)	1347 (100)
Total	**2880 (54)**	**2444 (46)**	**5324 (100)**

Table 4. Stroke and death rates after IVT and CEA reported from the earlier case series.

	Number of patients	30-day stroke and death (%)
McPherson[9]	5	0
Bartoli[10]	12	8.3
Crozier[13]	10	0
Rathenborg[8]	22	14
Yong[11]	7	2.7
Koraen-Smith[12]	73	3.1
Total	**129**	**3.1**

similarly.[24] In Denmark in 2012, 61% of all CEAs were performed within 14 days (from admission to a hospital with symptoms of cerebral ischemia); in the capital region the proportion reached 89%.[25] Presuming that a similar pattern is seen in Sweden and Finland, it is not surprising that, in this study, the IVT to CEA interval was a little shorter among the Finnish patients compared with the Swedish and Danish patients, reflecting that the Finnish catchment area was restricted to the capital area. The differences in timing of CEA, however, were not significant. Nevertheless, this is a potential confounder when comparing the three countries.

Unfortunately, data on the length of the interval from the index symptom to CEA in the group of patients having CEA alone were not available from all registries. In a previous study, Rathenborg et al.[8] reported a median delay for IVT + CEA patients of 11 days and 12 days for CEA alone patients. Koraen-Smith et al.[12] reported an interval from index symptom to either CEA or carotid artery stenting (CAS) of 10 days for the IVT + CEA/CAS group and 9 days for the CEA/CAS alone group among a similar cohort of Swedvasc patients to those in this study. The authors of the present study have no reason to believe that the timing of CEA without IVT should be any different from the timing of CEA after IVT in our study. Although the lack of a uniform definition of the term "index symptom", as indicated by den Hartog et al.[29] may weaken the validity of results, it is acknowledged that the incomplete data on timing of CEA among those patients not having IVT is a limitation in the present study.

As indicated by Fassbender et al.,[30] even though the half life of the thrombolytic agent reaches only 3–5 minutes, IVT has been shown to induce a widespread response of markers of coagulation activation and fibrin formation, persisting up to 72 hours. In addition, Vivien et al.[31] indicated that rtPA may exacerbate a hyperperfusion injury by facilitating the opening of the blood–brain barrier, promoting kainite induced neurotoxicity, and activating several inflammatory mediators and metalloproteinases that play a central role in the development of parenchymal haemorrhages. On the other hand, the beneficial effects of IVT on restoring perfusion and salvaging ischaemic brain tissue outweigh the potential drawbacks if given within the accepted 4.5 hour window. Among others, Rha et al.[32] have emphasized, that after an acute stroke, the strongest predictor of good clinical outcome is early recanalization. Thus, IVT may restore perfusion and therefore actually reduce the risk of complications following subsequent CEA.

The previous literature on this subject consists of studies on small series and registry reports have recommended larger series. Although this study presents a large consecutive series of patients all having carotid endarterectomy for symptomatic carotid stenoses, the percentage of patients having had IVT prior to surgery was only 4%. An increasing proportion of patients undergoing pre-operative IVT may be expected in the future, as it is becoming routine treatment in an increasing number of stroke units. Furthermore, the interval from index symptom to initiation of IVT is expanding, and the exclusion criteria are becoming fewer. If, as recommended, more patients with symptomatic ICA stenoses are offered CEA, the number of patients having both procedures will increase over time.

In conclusion, given the limitations presented above, the present study supports the indication that carotid endarterectomy can be performed within the recommended 2 weeks of onset of symptoms and thrombolysis without increasing the risk of peri-operative stroke or death. Centres performing CEA and vascular registries are recommended to continue monitoring changes in patient characteristics, lead times, and major complications after carotid endarterectomy in general, with special focus on those who have undergone a prior thrombolysis.

CONFLICT OF INTEREST

None.

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None.

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