

# Carotid Endarterectomy after Intravenous Thrombolysis for Acute Cerebral Ischaemic Attack: Is It Safe?

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## WHAT THIS PAPER ADDS

A small series of patients who presented with acute cerebral ischaemic attacks had intravenous thrombolysis (IVT) followed up within 2 weeks after their first symptoms by carotid endarterectomy (CEA) for >50% stenosis. Our results suggest that following established guidelines, IVT followed by CEA seems safe. However, other vascular centres should validate their practice.

**Objectives:** Intravenous thrombolysis (IVT) has proven effective in the treatment of acute cerebral ischaemic attack in selected cases. In the presence of a carotid artery stenosis, such patients may be candidates for carotid endarterectomy (CEA). Few studies have been made on the safety of CEA performed after IVT.

**Design:** This was a retrospective study. Data including 30 days' follow-up were obtained from medical records and from a vascular registry.

**Materials:** A consecutive series of 306 patients were operated on for symptomatic carotid artery stenosis during a 5-year period. Among these, 22 (7%) patients had been treated with IVT for an acute cerebral ischaemic attack prior to CEA and 284 (93%) patients had CEA only.

**Methods:** IVT as well as CEA was performed following established guidelines. CEA was performed in median 11 days (25 and 75% percentiles: 7–13 days) after the neurological index event in patients having undergone IVT and 12 days (25 and 75% percentiles: 8–21 days) in patients undergoing CEA only.

**Results:** The 30 days' stroke and death rate was 0% (95% confidence interval (CI): 0–15%) in patients who had IVT before CEA and 2.4% (95% CI: 0.9–4.7%) in patients who underwent CEA only.

**Conclusion:** Our experience indicates that CEA performed after IVT for acute cerebral ischaemic attack is safe, confirming existing but sparse publications. However, our series is small and our study possesses a number of limitations. Thus, our results cannot necessarily be transferred to other units, who instead should perform similar studies, preferably together.

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Intravenous thrombolysis (IVT) has proven effective in the treatment of acute cerebral ischaemic attack in selected cases and has become standard care in many centres following national and international guidelines.<sup>1–3</sup> IVT is so far not offered any patient later than 4.5 h after the onset of symptoms. The major complication to IVT is symptomatic intracerebral haemorrhage, which occurs in 2–8% of patients.<sup>2</sup> Symptoms may very well resolve within 24 h after onset, which by definition separates a transient ischaemic attack (TIA) from a stroke. We have therefore used the term 'cerebral ischaemic attack'.

Following successful IVT, such patients may be candidates for carotid endarterectomy (CEA), unless IVT increases the risk of complications.

In general, patients with a symptomatic 50–99% internal carotid artery stenosis should have CEA as soon as possible to reduce the risk of future stroke.<sup>4,5</sup> The combined rate of stroke and death within 30 days after CEA for symptomatic stenosis is around 5%.<sup>6</sup> CEA performed within the first 14 days after the index symptom may increase the procedural risk.<sup>7</sup> As the risk of a recurrent ischaemic attack is highest within the weeks following the first attack, the sooner CEA is performed, the higher the preventive value.<sup>8,9</sup>

Considering CEA after IVT, only smaller case series have been published recommending that the patients are very carefully selected and that particularly the blood pressure is carefully monitored prior to, during and immediately after CEA.<sup>10–12</sup>

In our region, IVT was by 2007 part of the routine treatment in suitable cases at hospitals receiving patients

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with signs of acute cerebral ischaemic attack. A fast track had been established at our vascular clinic allowing us to offer CEA within few days after referral. As we follow the same guidelines with regard to selection and monitoring whether the patients have had IVT or not, we wanted to evaluate whether in our hands, recent treatment with IVT affects the rate of complications associated with CEA.

## METHODS AND PATIENTS

We reviewed a consecutive series of patients who underwent CEA during a 5-year period from January 2007 through December 2011 and patients who had undergone IVT before CEA were identified. Data were collected from their medical records and from the Danish Vascular Registry.<sup>13</sup>

### Intravenous thrombolysis

Eligibility for IVT was based on The National Guidelines for Intravenous Thrombolysis in Acute Ischemic Stroke: the patient should present signs of acute stroke, IVT must be started within 4.5 h after the onset of symptoms and the patient's previous level of function must be high. Patients with suspected higher than normal risk of bleeding and patients with a high and not readily reducible blood pressure are excluded.<sup>3</sup>

The IVT was performed at one of two neuro-interventional units. A dose of 0.9 mg Actilyse® (alteplase) per kg bodyweight in saline (concentration: 1 mg ml<sup>-1</sup>) was injected in a peripheral vein (10% as a bolus during 1–2 min and the rest during the following hour). All patients were put on anti-platelet therapy after 24 h.

According to the National Guidelines, a duplex scan of the extracranial part of the carotid arteries was performed within 48 h after the onset of symptoms. Trained clinical physiologists or radiologists at the hospital housing the neuro-interventional unit performed these scans. During the period of our study, pre- and post-IVT perfusion computed tomography (CT) scans were performed. Cerebrovascular CT angiography (CTA) was not performed routinely. Potential candidates for CEA were referred by the neurologists at the above-mentioned hospitals to our vascular service located in a different hospital.

### Carotid endarterectomy

CEA was offered only in patients with a SYMPTOMATIC 50–99% internal carotid artery stenosis in accordance with the national guidelines of the Danish Vascular Society<sup>14</sup> and the European Society for Vascular Surgery (ESVS).<sup>15</sup> CEA was not offered to patients who present with major neurological deficits. The CEAs were all performed by one of four experienced vascular surgeons on the basis of duplex scans, the latter being performed by experienced sonographers at our Department of Vascular Surgery. Here, duplex scans have been performed for more than 20 years during which period it has been repeatedly validated.<sup>16,17</sup>

In four patients (neither having had IVT), the duplex scan failed to visualise the distal limit of the ICA stenosis. In those cases, a CTA was performed. Anti-platelet therapy

(dipyridamole, acetylsalicylic acid and/or clopidogrel) was continued without interruption. Oral anticoagulants (warfarin) were discontinued for 1–2 days prior to CEA to 1 day after CEA and replaced with low-molecular-weight heparin (LMWH). With a few exceptions CEA was performed during local anaesthesia: general anaesthesia was used in one patient who suffered severe claustrophobia and local anaesthesia was converted to general anaesthesia in four patients due to uneasiness of the patient or due to insufficient local anaesthesia. In these patients, a stump pressure in excess of 40 mmHg was regarded acceptable leaving none of the patients in need of a shunt.

Shunt was used in 12 patients as their mental or neurological status changed upon cross clamping. In these patients, conventional CEA was performed. In all other patients, the eversion technique was used. Blood pressure was continuously monitored and lowered if exceeding 160 mmHg, preferably using labetalol. Patients were observed in a postoperative recovery unit with intra-arterial blood-pressure monitoring. Signs of bleeding requiring re-operation and neurological status were monitored closely. After 4 h, stable patients were transferred to the vascular ward where the blood pressure was measured every hour. If no complication was observed, patients were discharged on the first postoperative day.

At 30 days postoperatively, the surgeons at the outpatient clinic performed a neurological examination.

A total of 306 symptomatic patients underwent CEA in the 5-year time span. Twenty-two (7%) patients had undergone IVT prior to CEA while 284 (93%), underwent CEA only. Patient characteristics are listed in Table 1. Of the 22 patients who underwent IVT prior to CEA, the neurological deficits had resolved in 14 patients before CEA, while 5 had minor and 3 moderate residual neurological deficits. The IVT patients were categorised according to their neurological status just prior to CEA using the Rankin scale (Table 1). Pre-IVT CT scan precluded intracranial haemorrhage in all cases. Signs of infarction were evident at the pre-IVT CT in eight patients. At the post-IVT CT, these signs had disappeared in three patients. Another six patients revealed signs of ischaemic infarction at the post-IVT CT scan.

### Statistics

Samples, for example timing of CEA, were characterised by the median value and interquartile range. For proportions, for example complication rates, we calculated 95% binominal confidence intervals. Proportions are compared using the chi-squared test and *p* values of <0.05 were considered significant.

## RESULTS

During the period in question 308 patients underwent CEA for symptomatic internal carotid artery stenosis. Two patients were lost for follow-up, leaving 306 patients under study. Among these, 22 patients had undergone IVT for acute cerebral ischaemic attack.

**Table 1.** Characteristics of 306 patients who underwent carotid endarterectomy for symptomatic stenosis (CEA) within 21 days after onset of symptoms. Twenty-two patients were operated on after intravenous thrombolysis (IVT) while 284 had CEA without proceeding IVT (ICA: *internal carotid artery*).

			Number of patients having CEA without IVT	Number of patients having CEA after IVT
Gender	Female		91 (32%)	4 (18%)
	Male		193 (68%)	18 (82%)
Age (median years (range))			70 (62–77)	71 (66–77)
Degree of stenosis of the extracranial part of ICA	Operated ICA ( <i>n</i> = 302)	50–69%	121 (43%)	12 (55%)
		70–99%	159 (57%)	10 (45%)
	Contralateral ICA ( <i>n</i> = 290)	<50%	173 (65%)	15 (68%)
		70–99%	23 (9%)	1 (5%)
		Occlusion	15 (5%)	2 (9%)
Index symptom	Amaurosis fugax		33 (12%)	
	Transient ischaemic attack		146 (51%)	
	Stroke		105 (37%)	
Rankin <sup>a</sup> score	0			14
	1			4
	2			1
	3			3
Days between symptom and CEA (median (interquartile range))			12 (8–21)	11 (7–13)

<sup>a</sup> *The modified Rankin scale*: 0: No symptoms. 1: No significant disability. Able to carry out all usual activities, despite some symptoms. 2: Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities. 3: Moderate disability. Requires some help, but able to walk unassisted. 4: Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted. 5: Severe disability. Requires constant nursing care and attention, bedridden, incontinent 6: Dead.

Overall, seven patients (2.3%) suffered a stroke and/or died within 30 days after CEA. Five patients (1.6%) suffered a perioperative stroke ipsilateral to the CEA, two of which were haemorrhagic and three embolic, verified by CT scans, and two patients suffered a fatal myocardial infarction. None of the patients had had IVT. Thus, the combined stroke and death rate in patients who had IVT first was 0% (95% confidence interval (CI): 0–15%) and in those patients who underwent CEA without preceding IVT: 2.4% (95% CI: 0.9–4.7%).

Complications in terms of cervical bleeding occurred in two IVT patients (9% (95% CI: 1–29%)) and in 17 of the patients having CEA only (6% (95% CI: 4–10%)) ( $p = 0.6$ ). By the time of CEA, 12 of these patients received dipyridole and aspirin, 6 had clopidogrel and one had LMWH. Among those not developing cervical bleeding, information on anti-thrombotic treatment was available in 279 patients. Among these, 159 received dipyridole, 102 clopidogrel and 18 had LMWH. Cervical bleeding as a consequence of anti-thrombotic agents or of hypertension could not be addressed properly as more specific data on the medication of the patients were not available.

The median elapsed time from onset of symptoms to CEA was 11 days (25 and 75% percentiles: 7–13 days) in patients who had IVT before CEA versus 12 days (25 and

75% percentiles: 8–21 days) in patients having CEA only ( $p = 0.15$ ). The length of postoperative stay at the vascular ward was 1 day (25 and 75% percentiles: 1–2 days). Seven patients were kept in hospital for up to 4 days post-CEA to achieve a stable blood pressure. Among these patients, two were temporarily transferred to the intensive care unit for continuous (intra-arterial) blood-pressure monitoring. One of these patients had developed a haemorrhagic (ipsilateral) stroke on the first postoperative day.

## DISCUSSION

The main finding of our study was that the 30 days' rate of stroke and death among patients who underwent CEA after successful IVT was low. The combined stroke and death rate was 0% (95% CI: 0–15%) in this subgroup, with no instances of intracerebral haemorrhage. In patients who underwent CEA without preceding IVT, the combined rate of stroke and death was 2.4% (95% CI: 0.9–4.7%).

We present a series of 22 patients who during a 5-year period underwent CEA after IVT.

The annual number of patients suffering stroke in Denmark (5.5 million inhabitants) reaches approximately 13,000, among whom an estimated 5% presently are supposed to benefit from IVT.<sup>3</sup> A significant carotid artery stenosis is found in 12–15%.<sup>18</sup> As our catchment

**Table 2.** Stroke and death rates in series of patients undergoing carotid endarterectomy (CEA) after intravenous thrombolysis (IVT).

	Number of patients	Interval from IVT to CEA	Follow up	Stroke and death
McPherson et al.	5	<48 h	5–22 months	0
Bartoli et al.	12	8 (1–16) days	90 days	1 stroke (8%)
Crozier et al.	10	8 (2–23) days	6 weeks	0
Rathenborg et al.	22	10 (7–13) days	30 days	0
Total	49		30 days	1 (2%)

population covers approximately 1 million inhabitants, the estimated number of patients undergoing CEA after IVT should reach 14–18 per year. The reason why we did only 22 during a 5-year period remains unclear: there may be some patients who for several reasons are not being offered IVT. Some patients are perhaps not being referred to the vascular department after IVT. Further, surgeons may be too restrictive in the selection of CEA candidates.

Publications hitherto have though been on even smaller caseloads: McPherson et al. reported uncomplicated CEAs in five patients after IVT.<sup>10</sup> In a study on 12 patients, Bartoli et al. reported one non-fatal haemorrhagic stroke related to a very early CEA after IVT.<sup>11</sup> In the most recent publication on the subject, Crozier et al. report of 10 patients who underwent CEA after IVT without any stroke or death.<sup>12</sup> Including our series, a total of 49 cases have been published for a total incidence of 30 days' stroke and or death of 2% (95% CI: 0–11%) (Table 2).

The most recent available report from The Danish Vascular Registry reveals a combined 30 days' stroke and death rate of 3.0% (2.2–3.7%) in 2057 patients operated on in 2007 through 2011 in Denmark.<sup>12</sup> Surgeons tend to report a lower stroke rate than neurologists.<sup>6</sup> As we discharge our patients shortly after CEA and perform the neurological assessment ourselves, we may have underestimated the number of minor strokes.

The risk of stroke and death related to a recent symptomatic carotid stenosis is well described in the large, but older multicentre trials.<sup>5</sup> As best medical therapy has continued to improve, the comparative benefits of CEA may be less than when these trials were completed. The present study does not attempt to assess the benefit from CEA after IVT. To do so, a randomised trial of patients having IVT plus CEA versus IVT without CEA should be established — addressing also the need for renewal of the knowledge regarding these groups of patients in general.

An association between the rate of cervical bleeding and the rate of (haemorrhagic) strokes cannot be excluded. Baracchini et al. found a rate of 5% needing re-exploration.<sup>17</sup> The half-life of the thrombolytic agents in use for IVT is very short (approximately 5 min). Increased risk of bleeding in relation to the subsequent CEA is therefore not likely to be seen, corroborated also by our data. Antiplatelet therapy could potentially be associated with an increased risk of postoperative cervical bleeding.<sup>19</sup> However, the main concern regarding the risk of intracranial haemorrhage is related to the arterial hypertension postoperatively and the possibility of a hyper-perfusion syndrome. Demirel et al. have shown that eversion CEA is associated with a significantly higher post-procedural blood pressure than conventional endarterectomy.<sup>20</sup> It could be argued that instead of postponing the CEA until the blood pressure is stable, these patients should be offered early conventional CEA. As, however, Demirel et al. did not demonstrate any significant difference in the perioperative complication rate, we recommend that future studies on the subject should be awaited. In our study, moderate hypertension may have contributed to the developing of

one perioperative stroke and some patients required a prolonged stay in order to achieve a stable, sufficiently low blood pressure. However, most of our patients were discharged on the first postoperative day and hypertension did not, in any patient, lead to severe complications after discharge. We acknowledge that this retrospective case series has some weaknesses, which limit the general applicability. First the series was small; second the regional organisation disconnected IVT and CEA; third we did not have detailed information on anti-thrombotic medication; and last post-CEA neurological examinations were performed by vascular surgeons. Before accepting that CEA after IVT is safe, other centres should collect data like this. Further, collaborative, standardised data collection across multiple sites could give a clearer indication of risks much quicker.

In conclusion: IVT followed — within 2 weeks from first onset of the cerebral ischaemic attack — by CEA for a >50% stenosis seems safe in this small, selected series. Before being applied generally, other vascular centres should validate their practice.

#### CONFLICT OF INTEREST/FUNDING

None.

#### REFERENCES

- 1 Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in stroke-monitoring study (SITS-MOST): an observational study. *Lancet* 2007;**27**: 275–82.
- 2 Wechsler LR. Intravenous thrombolytic therapy for acute ischemic stroke. *N Engl J Med* 2011;**22**:2138–46.
- 3 Sorensen L, Andersen G, Iversen HK; On behalf of the Danish Neurological Society. <http://www.sst.dk/%7E/media/Planlaegning%20og%20kvalitet/Specialeplanlaegning/Udmeldinger/trombolysbehandling/Trombolys%20-%20nationaleretningslinierfortrombolysbehandling22-01-09.ashx>.
- 4 Ricotta JJ, AbuRahma A, Ascher E, Eskandari M, Faries P, Brajesh KL. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg* 2011;**54**(3):e1–31. Erratum in *J Vasc Surg* 2012;**55**(3):894.
- 5 Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett H, Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;**363**:915–24.
- 6 Rerkasem K, Rothwell PM. Temporal trends in the risk of stroke and death due to endarterectomy for symptomatic carotid stenosis: an updated systematic review. *Eur J Vasc Endovasc Surg* 2009;**37**(5):504–11.
- 7 Naylor AR. Delay may reduce procedural risk, but at what price to the patient? *Eur J Vasc Endovasc Surg* 2008;**35**(4):383–91.
- 8 Salem MK, Sayers RD, Bown MJ, Eveson DJ, Robinson TG, Naylor AR. Rapid access carotid endarterectomy can be performed in the hyperacute period without a significant increase in procedural risks. *Eur J Vasc Endovasc Surg* 2011;**41**(2):222–8.
- 9 Rantner B, Kollerts B, Schmidauer C, Willeit J, Thauerer M, Rieger M, et al. Carotid endarterectomy within seven days

- after the neurological index event is safe and effective in stroke prevention. *Eur J Vasc Endovasc Surg* 2011;**42**:732–9.
- 10 McPherson CM, Woo D, Cohen PL, Pancioli AM, Kissela BM, Carrozzella JA, et al. Early carotid endarterectomy for critical carotid artery stenosis after thrombolysis in acute stroke in the middle cerebral artery. *Stroke* 2001;**31**:2075–80.
  - 11 Bartoli MA, Squarcioni C, Nicoli F, Magnaa PE, Malikov S, Berger L, et al. Early carotid endarterectomy after intravenous thrombolysis for acute stroke. *Eur J Vasc Endovasc Surg* 2009;**37**:512–8.
  - 12 Crozier CEM, Reid J, Welch GH, Muir KW, Stuart WP. Early carotid endarterectomy following thrombolysis in the hyper-acute treatment of stroke. *Br J Surg* 2011;**98**:235–8.
  - 13 The Danish Vascular Registry. *Annual report*. [www.karbase.dk](http://www.karbase.dk); 2011. 2013-02-01.
  - 14 Vestersgaard-Andersen T, Baudier F, Eldrup N, Groenholdt ML, Schroeder TV, Rathenborg LK; on behalf of Danish Society for Vascular Surgery. *Guidelines for vascular surgical treatment of patients with carotid artery stenosis*. [http://www.karkirurgi.dk/filer/landsdaekkende\\_retningslinjer\\_carotis.pdf](http://www.karkirurgi.dk/filer/landsdaekkende_retningslinjer_carotis.pdf). 2012-08-23.
  - 15 Liapis CD, Bell PRF, Mikhailidis D, Sivenius J, Nicolaidis A, Fernandes e Fernandes J, et al. On behalf of the ESVS Guidelines Collaborators. ESVS guidelines, invasive treatment for carotid stenosis: indications, techniques. *Eur J Vasc Endovasc Surg* 2009;**37**:1–19.
  - 16 Sillesen HH, Henriksen BM, Schroeder TV. Carotid stenosis — is arteriography necessary in investigation and treatment. *Ugeskr Laeger* 1996;**158**(46):6617–9.
  - 17 Sillesen HH, Kofoed SC, Ammundsen PO, Schroeder TV. Variation of Doppler ultrasonography of carotid arteries. *Ugeskr Laeger* 2000;**162**(10):1379–82.
  - 18 Flaherty ML, Kissela B, Khoury JC, Alwell K, Moomaw CJ, Woo D, et al. Carotid artery stenosis as a cause of stroke. *Neuroepidemiology* 2013;**40**:36–41.
  - 19 Baracchini C, Grupo M, Mazzalai F, Lorenzetti R, Meneghetti G, Ballotta E. Predictors of neck bleeding after eversion carotid endarterectomy. *J Vasc Surg* 2011;**54**(3):699–705.
  - 20 Demirel S, Bruiknen H, Attigah N, Hakimi M, Böckler D. The effect of eversion and conventional-patch technique in carotid surgery on postoperative hypertension. *J Vasc Surg* 2011;**54**(1): 80–6.