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Original Article

Risk of Stroke Recurrence After Intravenous Thrombolysis in Patients with Symptomatic Carotid Stenosis

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ABSTRACT: ***Objective:*** To assess if intravenous thrombolysis (IVT) affects the risk of recurrent preoperative cerebrovascular events before carotid surgery or stenting in patients with symptomatic ≥ 50% carotid stenosis. ***Methods:*** Three cohorts of symptomatic ≥ 50% carotid stenosis patients were merged. To make the control group relevant, we excluded patients not presenting with stroke on the day of symptom onset. The risk of preoperative cerebrovascular events up to 30 days was compared between the IVT-treated and non-IVT-treated. ***Results:*** In total, 316 patients were included, 64 (20%) treated with IVT. Those treated with IVT had similar risk of recurrent ipsilateral ischemic stroke or retinal artery occlusion (12% at day 7, 12% at day 30) as those not treated (9% at day 7, 15% at day 30; adjusted HR 0.9, 95% CI 0.4–2.2). There was a tendency ($p = 0.09$) towards time-dependency in the data where the recurrence risk was higher in IVT-treated at day 0 (6% in IVT-treated, 1% in non-IVT-treated, OR 5.5, 95% CI 1.2–25.4, $p = 0.03$). This was not significant when adjusting for co-factors (adjusted OR 4.4, 95% CI 0.9–21.8, $p = 0.07$) and was offset by a later risk decrease, with no remaining risk difference between IVT-treated and non-IVT-treated at day 7. ***Conclusions:*** Intravenous thrombolysis treatment does not seem to affect the risk of recurrent ipsilateral ischemic stroke in patients with symptomatic ≥50% carotid stenosis: The risk is high in both IVT-treated and non-IVT-treated. However, there might be a risk increase on the day of IVT treatment that is offset by a risk decrease during the first week.

RÉSUMÉ : Risque de récidive d'accident vasculaire cérébral après une thrombolyse intraveineuse chez les patients porteurs d'une sténose carotidienne symptomatique. ***Objectif :*** L'étude visait à évaluer l'incidence de la thrombolyse intraveineuse (TIV) sur le risque de récidive d'accident vasculaire cérébral (AVC) avant une opération de la carotide ou la pose d'une endoprothèse chez les patients porteurs d'une sténose carotidienne symptomatique ≥ 50 %. ***Méthode :*** Trois cohortes de patients porteurs d'une sténose carotidienne symptomatique ≥ 50 % ont été fusionnées, et l'équipe de recherche a écarté les patients ne présentant pas d'AVC le jour de la manifestation des symptômes afin de rendre le groupe témoin approprié. Ensuite, il y a eu comparaison du risque de récidive d'AVC en phase préopératoire jusqu'à concurrence de 30 jours entre les patients traités et ceux non traités par TIV. ***Résultats :*** Au total, 316 patients ont été retenus dans l'étude, dont 64 (20 %) avaient été traités par TIV. Ces derniers connaissaient un risque de récidive d'AVC ischémique homolatéral ou d'occlusion de l'artère rétinienne (12 % au bout de 7 jours; 12 % au bout de 30 jours) comparable à celui des premiers (9 % au bout de 7 jours; 15 % au bout de 30 jours; rapport de risques instantanés [RRI] rajusté : 0,9; IC à 95 % : 0,4-2,2). Une tendance temporelle ($p = 0,09$) s'est dégagée de l'analyse des données, selon laquelle le risque de récidive était plus élevé chez les patients traités par TIV le jour même de l'apparition des symptômes (jour 0) que chez les patients de l'autre groupe (6 % chez les patients traités par TIV; 1 % chez les patients non traités par TIV; risque relatif approché [RRA] : 5,5; IC à 95 % : 1,2-25,4; p = 0,03). Toutefois, la tendance n'était pas significative après rajustement des valeurs pour tenir compte des cofacteurs (RRA rajusté : 4,4; IC à 95 % : 0,9-21,8; p = 0,07), et l'écart entre les patients traités et non traités par TIV s'estompait progressivement pour s'effacer au bout de 7 jours. ***Conclusion :*** Le traitement par TIV ne semble pas influer sur le risque de récidive d'AVC ischémique homolatéral chez les patients porteurs d'une sténose carotidienne symptomatique ≥ 50 %. Les deux groupes de patients connaissent un risque élevé de récidive, mais celui-ci pourrait s'accroître le jour du traitement par TIV, puis décroître au cours de la première semaine.

Keywords: carotid stenosis; intravenous thrombolysis; risk; stroke

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Table 1: Cohort descriptions

Study work name	ANSYSCAP	TACNOS	UCC
Period	Aug 2007–Dec 2009	Jan 2010–Dec 2014	Feb 2018–May 2022
Site	Umeå, Sweden	Umeå, Sweden	Umeå, Sweden
Design	Prospective	Retrospective	Prospective
Consecutive series	Yes	Yes	Yes, but with 6-month COVID-19 break in 2020
Ethics	Waived need[a], need of informed consent waived	Approved[b], need of informed consent waived	Approved[b], informed consent required for inclusion
Main study aim	Prognosis of symptomatic ≥ 50% carotid stenosis	Prognosis of symptomatic carotid near-occlusion	Diagnostics, prognostics and pathophysiology of carotid near-occlusion
Ascertainment	Daily on-site	Search for consecutive CTAs	Daily on-site
Inclusion criteria	Symptomatic ≥ 50% carotid stenosis	50%–100% carotid stenosis[c]	50%–100% carotid stenosis[c]
n of cases in this analysis	63	136	117
TPA treatment[d]	6 (10%)	31 (23%)	27 (23%)
Modality for degree of stenosis	Mostly ultrasound, also CTA	Exclusively CTA	Both, systematically
Rationale for modality	Ultrasound was foremostly used in local clinical routine	Study emphasis on near-occlusion, requiring CTA	Both were done as part of the study when not done in clinical routine
Use of IVT	When clinically indicated	When clinically indicated	When clinically indicated
Data available about medical treatments	After adjustment based on presenting and recurrent events	At presentation	Both at presentation and after adjustments based on presenting and recurrent event

ANSYSCAP = additional neurological symptoms before surgery of symptomatic carotid stenosis, a prospective study; CTA = computed tomography angiography; IVT = intravenous thrombolysis; TACNOS = transatlantic carotid near-occlusion study; UCC = Umeå carotid cohort.
[a]The need for ethics approval was waived by the regional ethics board in Umeå. This was a standard practice at the time, but changed by revision of Swedish ethics laws in 2008.
[b]The study was approved by the regional ethics board in Umeå.
[c]Cases with carotid occlusion and asymptomatic stenosis was excluded from this analysis.
[d]$p = 0.06$, 2-sided χ^2-test.

Introduction

Carotid stenosis is a common cause of ischemic stroke.[1] The short-term risk of recurrent ipsilateral ischemic stroke is approximately 15% within 2 weeks of the presenting event.[2,3] Artery-to-artery embolism (thromboembolism) is considered the dominating mechanism of cerebrovascular events in these patients. One possible mechanism preceding these events is rupture of the atherosclerotic plaque that leads to carotid artery wall-attached thrombus formation, and the thrombus causes emboli.[1] The thrombus can sometimes be seen as an intraluminal clot, but could reasonably also exist without such imaging findings (as thrombus and plaque have similar appearance).[4]

Intravenous thrombolysis (IVT) is together with intracerebral thrombectomy routine treatments to reduce morbidity of acute ischemic stroke.[5] The thrombus dissolving effect (activating plasminogen to plasmin[6]) of IVT should reasonably affect both the wall-attached thrombus and the cerebral emboli. Hence, in addition to the established symptom-reducing effect, we hypothesize that IVT might reduce the risk of recurrent stroke. However, the wall-attached thrombus might also be dislodged by IVT, causing stroke recurrence within the first hours of treatment. Indeed, an association between IVT and early clinical worsening was recently shown for all-cause carotid occlusion (including embolic occlusion) within 3 hours of baseline imaging.[7] To date, a single study has been presented and showed a 5.5% risk of preoperative stroke recurrence,[8] lower than the ≈ 15% risk seen in other studies.[2,3] However, this study had no control group without IVT treatment and possible selection bias as only cases that subsequently underwent carotid endarterectomy (CEA) were included.[8] Also, IVT treatment possibly increases the risk of perioperative stroke/death with CEA or stenting (CAS) performed within 7 days of IVT treatment.[9] Therefore, to enable assessment of optimal timing of CEA/CAS in IVT-treated patients, additional assessments of preoperative risk of stroke in IVT-treated patients were called for in recent guidelines.[10]

Aim

The aim of this study was to assess the impact of IVT treatment on the short-term risk of recurrent ipsilateral ischemic stroke in patients with stroke caused by ≥ 50% symptomatic carotid stenosis.

Methods

This study is a pooled analysis of three observational studies conducted at a single tertiary center, two previously published (Table 1).[2,11] All of the underlying studies were cohort studies of risk factors for recurrent stroke in consecutive patients with ≥ 50% symptomatic carotid stenosis (two cohorts also included occlusions) before carotid interventions. The studies' inclusion periods were 2.4 years, 5.0 years, and 3.8 years during a 15-year period. All studies were approved by the appropriate ethical review board (Table 1).

Population

For this analysis, the inclusion criterion was ≥50% symptomatic carotid stenosis (excluding occlusions) potentially eligible for CEA/CAS. Cases presenting with transient ischemic attack (TIA), amaurosis fugax, or retinal artery occlusion were excluded.[2,11] Patients treated with thrombectomy for their presenting event ($n = 5$) were not excluded, but acute stenting resulted in very short

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observation time (between presentation and procedure). We also excluded cases that did not seek health care on the same day as their presenting event. Data on medical treatment were collected at presentation in one cohort, after adjustment in one cohort and both in cohort, why no coherent data on medical treatments can be presented. However, the policy of antiplatelet treatment was the same in all cohorts: Foremost aspirin alone or aspirin and dipyridamole, avoiding clopidogrel (not modern dual antiplatelet therapy). Statin was recommended during all studies. In cases treated with IVT, antiplatelet therapy was started after 24 hours. Both CEA and CAS were used, but CAS was often chosen in cases with high risk of perioperative complications.

Degree of stenosis

Degree of stenosis was assessed with computed tomography angiography (CTA) and ultrasound, in general days after presentation. For CTA, the exams were reassessed by study personnel and graded according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) methodology. All CTAs were assessed by one observer (EJ) and large subset (73%, 191/263) was also assessed by another observer (either AH or AJF). Emphasis on CTA assessments was on grading near-occlusion with systematic interpretive approach, as presented elsewhere.[2] In short, near-occlusion was diagnosed when the distal ICA was reduced in distal diameter and a severe proximal stenosis was the most reasonable cause.[2] Full collapse was defined as distal ICA diameter of ≤ 2.0 mm and/or ICA side-to-side diameter ratio of ≤ 0.42 – a definition derived from two of the cohorts.[12] Ultrasound was performed by several experienced sonographers as previously reported with≥50% stenosis threshold at peak systolic velocity of ≥ 145 cm/s, emulating NASCET-style stenosis grading.[13] Only CTA was used to differentiate between near-occlusion and conventional stenosis.[13,14]

IVT treatment

Decision to perform IVT treatment was based on clinical routine at the time and in line with what is still recommended practice:[5] Relevant symptoms with treatment started within<4.5 hours of onset and no relevant contraindications such as recent surgery, recent stroke, or use of anticoagulants. Exception was the first year of the first cohort, before ECASS III results extended the time window from 3.0 to 4.5 hours.[15] A vast majority of treatments were with Actilyse, a few with Metalyse (data not available).

Definitions

Definitions were the same in all cohorts.[2,11] In short, stroke and retinal artery occlusion were clinically defined with symptoms lasting > 24 hours (<24 hours for TIA and Amaurosis fugax) regardless of radiological ischemia. In this analysis, cases treated with IVT with complete symptom resolution within 24 hours were considered as stroke (not TIA), and hence included. Symptomatic intracerebral hemorrhage (sICH) was defined as in ECASS III (in short, relevant bleeding with>4 NIH points increase).[15] Co-existent atrial fibrillation did not rule out symptomatic stenosis, but cases with events obviously attributed to another source than the stenosis were excluded. Presenting event was defined as the last event before the patient sought health care. Free-floating thrombus was assessed on CTA in the second transatlantic carotid near-occlusion study (TACNOS) and third Umeå carotid cohort (UCC) study by one observer (EJ, blinded to clinical events and tPA treatment), defined as a low-attenuating structure attached to the stenosis, visible in at least 2 projections and surrounded by contrast (donut-appearance) in at least 1 projection.

Outcomes

Outcome events were assessed by one observer (EJ) in the first and third studies, and by two observers (EJ, TG) in the second (TACNOS). Blinding to IVT treatment was not possible. In all studies, the main source was medical records from both local and referring hospitals, in the two prospective studies (Additional Neurological SYmptoms before Surgery of the Carotid Arteries, a Prospective study (ANSYSCAP) and UCC). This was augmented by contact with the patient for clarifications when needed (rarely used). In all studies, the access to medical records at our and referring institutions was excellent, and all assessed cases were well documented by a specialist in neurology and often also a specialist in internal medicine. For this analysis, all outcome events were rechecked (by EJ) for consistency, discarding one as insufficiently certain. The main outcome was ipsilateral ischemic stroke or ipsilateral retinal artery occlusion in all cohorts, as in the pooled analysis of NASCET and European Carotid Surgery Trial (ECST).[2,11] Secondary outcomes were ipsilateral ischemic events (stroke, retinal artery occlusion, TIA, and amaurosis fugax), sICH, any stroke, and all death. Except for postoperative outcomes, outcomes were assessed for 30 days after the presenting event, and only preoperative events were assessed.

Analyses and statistics

The risk of the outcomes was compared between cases treated and not treated with IVT for their presenting event. Cases treated with IVT only for recurring events were not considered as treated.

Data is presented with percent, 95% confidence intervals (95% CI), mean with standard deviation, and median with inter-quartile range. Mean values (t-test) were preferred (law of large numbers), but median (Mann-Whitney) was used for delay to CEA/CAS as this variable was not normally distributed (Skewness 4.0; Kurtosis 18.3). We used 2-sided χ^2-test for categorical variables. Survival analysis was used for time to recurrent events as in previous similar studies:[2,11] Censoring at CEA/CAS, death, and 30 days. The first event was counted in cases with multiple events. There were no cases with data lost to follow-up. In Kaplan-Meier analyses, log-rank test was used to compare groups. For bivariate and multivariable analyses, Cox regression was used. The proportional hazard assumption was checked by time-varying interaction assessment[16] and was found to be valid ($p = 0.09$ for IVT and $p \geq 0.25$ for co-variates). Cases associated ($p < 0.10$) with either IVT treatment and/or outcome were included in the multivariable models as possible confounders. Variables with > 10 cases missing data (i.e. blood lipid level data) were not included in multivariable models nor was data on medications as these had different definitions in the different cohorts. When assessing risk for the period day 1–30, day 1 was used as index time, and cases with outcome or censoring at day 0 were excluded. When assessing the risk at day 0, binary logistic regression was used. $p < 0.05$ was considered statistically significant. IBM SPSS 28.0 was used in the analyses.

Results

The three cohorts included 935 patients with symptomatic ≥ 50% carotid stenosis. After excluding 295 cases seeking health care≥1

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day after presenting event (presenting event stroke $n = 132$, TIA $n = 64$, retinal artery occlusion $n = 19$, amaurosis fugax $n = 80$) and 324 non-stroke cases on the day of the presenting event (TIA $n = 237$, retinal artery occlusion $n = 25$, amaurosis fugax $n = 62$), 316 patients were included in the analysis. Of 619 excluded cases, 1 (0.2%) underwent IVT (retinal artery occlusion as presenting event). Of included cases, 64 (20%) were treated with IVT for the presenting event, see Table 2 for baseline comparisons. In total, 200 patients underwent CEA or CAS, and 5 patients underwent thrombectomy, all with acute CAS as part of the procedure.

Preoperative main outcome Within 30 Days of presenting event

Forty patients suffered a preoperative recurrent ipsilateral ischemic stroke or retinal artery occlusion. None of the outcomes were retinal artery occlusion. Treatment with IVT had no impact on the risk of recurrent ipsilateral ischemic stroke, HR 1.0 (95% CI 0.4–2.2, $p = 0.93$; Figure 1a, Table 3). Multivariable adjustment made no relevant impact on the association between IVT and stroke risk (adjusted HR 0.9; 95% CI 0.4–2.2; Table 4). Limiting the analysis to patients without atrial fibrillation had no relevant impact either (HR for IVT 0.9, 95% CI 0.4–2.5, $p = 0.90$).

The stroke risk was consistent between the three cohorts ($p = 0.75$, log rank). In bivariate and multivariable analyses, atrial fibrillation and near-occlusion with full collapse were associated with an increased risk of recurrent ipsilateral ischemic stroke (Table 4). When limiting the analysis to only IVT-treated, near-occlusion with full collapse, compared to all other degrees of stenosis, increased the risk of recurrent ipsilateral ischemic stroke (HR 5.7, 95% CI 1.3–25.8, $p = 0.02$), but atrial fibrillation did not (HR 2.7, 95% CI 0.5–14.1, $p = 0.23$). Free-floating thrombus was not significantly associated with risk of stroke, either in the whole cohort (HR 1.9, 95% CI 0.8–4.6, $p = 0.15$) or when limiting the analysis to only IVT-treated (HR 3.0, 95% CI 0.6–16.6, $p = 0.20$).

On the same day as the presenting event (day 0), there was a higher risk of ipsilateral ischemic stroke recurrence in the IVT group, odds ratio 5.5 (95% CI 1.2–25.4; $p = 0.03$, Table 3). This association was also seen for near-occlusion with full collapse ($n = 3$; 8%) compared to other degrees of stenosis ($n = 4$; 1%, $p = 0.02$); but not for any other variable. When adjusting for near-occlusion with full collapse, IVT was no longer statistically significantly associated with stroke recurrence on the day of presenting event (adjusted odds ratio 4.4; 95% CI 0.9–21.8; $p = 0.07$). During days 1–30, there was no statistically significant risk difference between IVT-treated and non-IVT-treated ($p = 0.20$); but numerically, the risk difference seen on day 0 was no longer present at day 14 (Fig. 1a, Table 3).

Of the 200 cases subsequently treated with CEA or CAS, 18 (9%) suffered a preoperative ipsilateral ischemic stroke, compared to 22 (19%) among the 116 cases not treated with CEA/CAS ($p = 0.01$). In 10 patients (3.2%), a severe stroke recurrence (i.e. an outcome in the main analysis) was the reason for not undergoing CEA/CAS.

Preoperative secondary outcomes Within 30 Days of presenting event

In total, 65 patients suffered preoperative recurrent ipsilateral ischemic events: 34 strokes, 28 TIAs. IVT treatment had no clear impact on the risk of recurrent ipsilateral ischemic events ($p = 0.17$, Fig. 1b, Table 3).

There were two hemorrhagic strokes, both were sICH in the IVT group within 48 hours of IVT treatment (3% risk of sICH in the IVT group). There are two ischemic strokes that are not in main outcome: One fatal ischemic stroke on unclear side on day 14 (died on day 31) in the non-IVT group and a contralateral stroke on day 2 in the IVT group (bilateral severe stenosis, presumed hypoperfusion mechanism). Beyond the non-IVT-treated fatal stroke (died on day 31), no patient died within 30 days.

Discussion

The main findings in this study were that IVT does not clearly affect the risk of recurrent ipsilateral ischemic stroke in patients with symptomatic ≥ 50% carotid stenoses, the risk was high in both IVT-treated and non-IVT-treated patients. The risk of very early recurrent ipsilateral ischemic stroke might be increased with IVT treatment, but if so, this was also offset by a lower risk the next few days.

Despite IVT being in routine use for more than 20 years, as far as we know, this is the first study with a control group that assesses the impact of IVT treatment in cases with symptomatic carotid stenosis. Gathering high-quality data on stroke recurrence in consecutive symptomatic carotid stenosis is labor intensive (usually neurology-based single-center studies) and most such cases do not undergo IVT. Thus, our combined cohort, much larger than any previous similar cohort, was reasonably required to enable this analysis. To enable a good control group, we excluded many cases not clearly eligible for IVT treatment (TIA, retinal events, and long delay), limiting statistical power. However, the study was still powered to find several positive subgroup findings. Intravenous thrombolysis might be associated with an increased risk of stroke recurrence during the day of IVT treatment. But it seems like this could be explained, at least in part, by confounding by association with near-occlusion with full collapse: Near-occlusion with full collapse was common in the IVT group, caused a higher risk of stroke and when adjusted for, the risk of stroke was no longer statistically significant for IVT. The emphasis on detailed near-occlusion assessments in the underlying cohorts made this novel finding possible. If IVT treatment increases the risk of very early stroke recurrence, it could be caused by thrombus fragmentation and/or delaying antiplatelet treatment. However, at 7 days and beyond, the stroke risk had become similar for both IVT-treated and non-IVT-treated, albeit formal analysis of stroke risk during days 1–30 was not significant. Also, formal analysis of time-dependency was not significant ($p = 0.09$) – why it is not clearly established that there is an initial risk increase followed by a risk decrease. Also, there was a weak tendency for lower risk of recurrent ipsilateral ischemic events in the IVT group – but this is of limited clinical importance. Thus, although unclear, it does not seem that IVT treatment causes excessive risk or benefit with regards to stroke recurrence in patients with symptomatic carotid stenoses. As our data were observational (non-randomized), certain conclusions were not possible. However, our findings give no indications that IVT treatment should be withheld or given extra aggressively to affect recurrent events in cases with symptomatic carotid stenosis; the well-established indication (to reduce morbidity of the stroke underway) stands.

Compared to the previous similar study that found a 5.5% risk of preoperative stroke in IVT-treated,[8] our risk was slightly more than double (12%). By our Kaplan-Meier approach, we took the variable timing to CEA/CAS into account, the previous study did not.[8] But if we do not, the stroke risk in the present study was still twice as high (7/64 = 10.9%). As patients in the present study had similar delay to surgery (median ≈ 9–10 days), this comparison is

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Table 2: Baseline comparisons

		Not treated with IVT n = 252	Treated with IVT n = 64	p[a]
Age mean (SD)		73.4 (7.7)	72.4 (8.1)	0.36
Women n (%)		79 (31)	18 (28)	0.65
Previous myocardial infarction n (%)		57 (23)	13 (20)	0.74
Current angina[b] n (%)		34 (14)	7 (11)	0.68
Current heart failure n (%)		16 (6)	5 (8)	0.78
Previous arterial revascularization[b] n (%)		66 (26)	12 (19)	0.26
Previous stroke[c] n (%)		40 (16)	7 (11)	0.34
Atrial fibrillation[b] n (%)		26 (10)	8 (13)	0.65
Diabetes[b] n (%)		73 (29)	12 (19)	0.12
Current smoker[b] n (%)		42 (17)	15 (23)	0.27
Hypertension[d] n (%)		234 (93)	50 (78)	0.001
Total cholesterol[e] mmol/l mean (SD)		4.5 (1.2)	4.6 (1.8)	0.60
LDL cholesterol[e] mmol/l mean (SD)		2.5 (1.1)	2.6 (1.2)	0.85
HDL cholesterol[e] mmol/l mean (SD)		1.2 (0.4)	1.2 (0.3)	0.60
On presentation[f]: Any AP/AC[g] medication n (%)		96 (51)	16 (31)	0.02
On presentation[f]: Any blood pressure reducing medication n (%)		143 (75)	37 (69)	0.38
On presentation[f]: Any blood lipid lowering medication n (%)		99 (52)	22 (42)	0.21
After adjustments[h]: Any AP/AC[g] medication n (%)		146 (99)	31 (97)	0.33
After adjustments[h]: Any blood pressure reducing medication n (%)		134 (92)	26 (79)	0.053
After adjustments[h]: Any blood lipid lowering medication n (%)		135 (93)	26 (81)	0.045
Referred n (%)		50 (20)	15 (23)	0.60
Days between presenting event and first recorded carotid exam[i] median (IQR)		2 (0–5)	0 (0–3)	<0.001
Degree of ipsilateral stenosis[j]	50%–69% n (%)	100 (40)	20 (32)	0.002
	≥70% n (%)	102 (41)	16 (26)	
	Near-occlusion without full collapse n (%)	26 (10)	12 (19)	
	Near-occlusion with full collapse n (%)	23 (9)	14 (23)	
Contralateral 50-100% stenosis n (%)		68 (27)	16 (25)	0.76
Contralateral occlusion n (%)		7 (3)	1 (2)	0.70
Free-floating thrombus n (%)[j]		20 (10)	9 (16)	0.35
Underwent CEA/CAS n (%)		154 (61)	46 (72)	0.15
CEA n (%)		147 (95)	39 (85)	0.02
CAS n (%)		7 (5)	7 (15)	
Days between presenting event and CEA/CAS[k] median (IQR)		10 (6–22)	9 (5–14)	0.12
CEA/CAS within 7 days of presenting event n (%)		53 (21)	19 (30)	0.18
Postoperative stroke or death within 30 days of CEA/CAS[l] n (%)		11 (7)	1 (2)	0.30

ANSYSCAP = additional neurological symptoms before surgery of symptomatic carotid stenosis, a prospective study; AP/AC = anti-platelet or anticoagulant; CAS = carotid stenting; CEA = carotid endarterectomy; HDL = high-density lipoprotein; IQR = inter-quartile range; IVT = intravenous thrombolysis; LDL = low-density lipoprotein; SD = standard deviation; TACNOS = transatlantic carotid near-occlusion study; TIA = transient ischemic attack; UCC = Umeå carotid cohort.

[a]2-sided χ^2-test for categorical and *t*-test for continuous data except for Mann-Whitney used for delay to CEA/CAS.

[b]1–5 missing values.

[c]>6 months before presenting event.

[d]>140/90 mmHg and/or use of blood pressure reducing medication.

[e]Thirty missing values, i.e. not included in multivariable analyses.

[f]Previous medications when seeking health care, data available for TACNOS and UCC cohorts. In total, 8–15 missing values for all three medication classes.

[g]Usually aspirin. Anticoagulant usually only used when otherwise indicated (such as atrial fibrillation).

[h]Medications after adjustment for presenting and recurrent events. Only includes adjustments before revascularization except for cases undergoing acute CAS as part of thrombectomy, where it also includes adjustments based on the thrombectomy and CAS. Data available for ANSYSCAP and UCC cohorts. In total, 1–2 missing values for all three medication classes.

[i]First exam with CTA or ultrasound in any hospital except for that date of ultrasound in referring hospitals was not recorded for TACNOS and UCC, why this delay is occasionally overestimated in these studies. Nevertheless, first recorded carotid exam was on the day of presenting event in 6 (10%) in ANSYSCAP, 47 (35%) in TACNOS and 73 (62%) in UCC ($p < 0.001$); Similarly, first recorded carotid exam was on the day of presenting event in 83 (33%) of non-IVT-treated and 43 (67%) of IVT-treated ($p < 0.001$).

[j]3 missing values, all had ≥ 50% conventional stenoses but had too calcified stenosis to distinguish between 50% and 69% and ≥ 70%.

[k]Data missing in the 63 cases from the ANSYSCAP cohort.

[l]Among those that underwent CEA/CAS.

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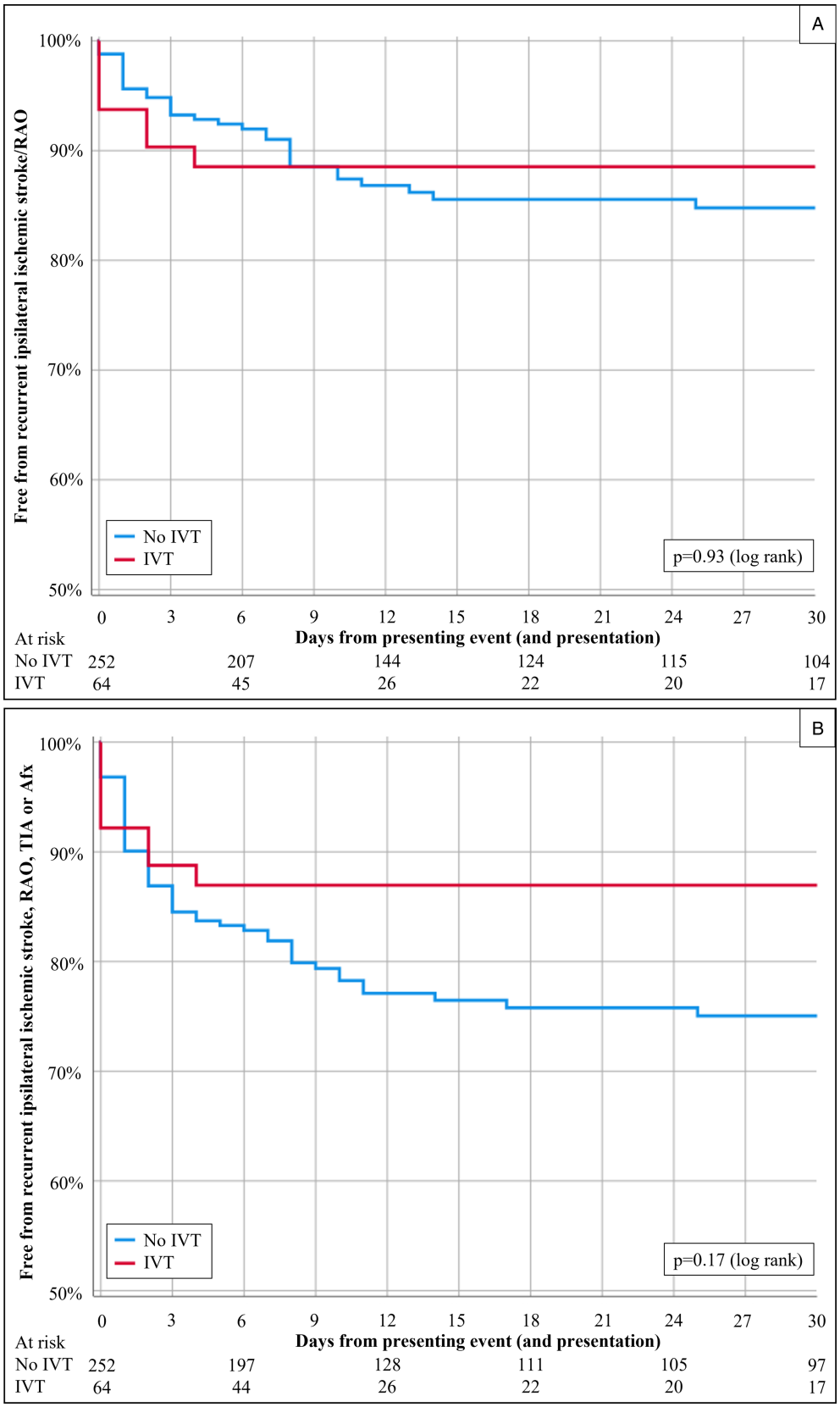

Figure 1: Kaplan-Meier analyses of outcomes with censoring at CEA/CAS, death, and at 30 days. ***a***) Risk of recurrent ipsilateral ischemic stroke or retinal artery occlusion. ***b***) Risk of recurrent ipsilateral ischemic stroke, retinal artery occlusion, TIA, or amaurosis fugax. CAS = carotid artery stenting; CEA: carotid endarterectomy; IVT = intravenous thrombolysis; TIA = transient ischemic attack.

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Table 3: Kaplan-Meier derived risk of preoperative events. Censoring at CEA/CAS, death, and at 30 days

	All n = 316		Not treated with IVT n = 252		Treated with IVT n = 64	
	Events	% risk (95% CI)	Events	% risk (95% CI)	Events	% risk (95% CI)
Recurrent ipsilateral ischemic stroke or retinal artery occlusion						
Day 0	7	2 (1–4)	3	1 (0–3)	4	6 (0–12)
Day 2[a]	19	6 (4–9)	13	5 (2–8)	6	10 (2–17)
Day 3[a]	23	7 (4–10)	17	7 (4–10)	6	10 (2–17)
Day 7	29	10 (6–13)	22	9 (5–13)	7	12 (3–20)
Day 14	39	14 (10–18)	32	14 (10–19)	7	12 (3–20)
Day 30	40	15 (10–19)	33	15 (10–20)	7	12 (3–20)
Recurrent ipsilateral ischemic stroke, retinal artery occlusion, TIA or amaurosis fugax						
Day 0	13	4 (2–6)	8	3 (1–5)	5	8 (1–14)
Day 2[a]	40	13 (9–17)	33	13 (9–17)	7	11 (3–19)
Day 3[a]	46	15 (11–19)	39	16 (11–20)	7	11 (3–19)
Day 7	53	17 (13–22)	45	18 (13–23)	8	13 (5–21)
Day 14	63	22 (17–27)	55	24 (18–29)	8	13 (5–21)
Day 30	65	23 (18–28)	57	25 (19–31)	8	13 (5–21)

CI = confidence interval; IVT = intravenous thrombolysis; TIA = transient ischemic attack.
[a]Data presented at day 2 as this has been standard reporting,[2,11] and at day 3 as this was relevant in a recent meta-regression.[9]

Table 4: Bivariate and multivariable Cox-regression analysis of the risk of recurrent ipsilateral ischemic stroke or retinal artery occlusion

		Bivariate HR (95% CI)	p	Multivariable HR (95% CI)	p
IVT treatment		1.0 (0.4–2.2)	0.93	0.9 (0.4–2.2)	0.84
Atrial fibrillation		2.5 (1.2–5.2)	0.02	2.6 (1.2–5.4)	0.02
Hypertension		1.9 (0.5–7.9)	0.37	1.6 (0.4–7.1)	0.50
Degree of ipsilateral stenosis	50%–69%	Ref	–	Ref	-
	≥70%	1.8 (0.8–4.0)	0.14	2.0 (0.9–4.3)	0.10
	Near-occlusion without full collapse	1.4 (0.4–4.6)	0.54	1.5 (0.5–5.0)	0.47
	Near-occlusion with full collapse	3.4 (1.4–8.3)	0.008	3.2 (1.3–8.4)	0.02
Contralateral 50-100% stenosis		0.5 (0.2–1.1)	0.08	0.4 (0.2–1.1)	0.07

HR = hazard ratio; IVT = intravenous thrombolysis.
Censoring at CEA/CAS, death, and at 30 days. Variables not associated ($p < 0.10$) with outcome or IVT treatment not listed.

reasonable.[8] However, we found a lower risk among those treated with CEA/CAS and previous study had that as selection criteria. Assessing only CEA/CAS-treated cases makes for a homogeneous group, but it also excludes cases not undergoing CEA/CAS due to major recurrent strokes (we had 10 such cases). Also, we found a very high risk in near-occlusion with full collapse (previously presented from same cohorts),[12] and such cases might undergo CEA/CAS less often.[2] Also, we assess recurrences from presenting events, regardless of where the patients presented. The previous study was vague, assessing recurrences "while waiting for CEA",[8] but the same group clearly presented in another study that recurrences were counted from after a decision to perform CEA was made.[17] Thus, it seems reasonable that differences in preoperative stroke risk seen when comparing previous studies[2,3,8] were most likely due to differences in study design and populations, not because IVT reduces the risk of preoperative stroke.

A recent meta-regression has suggested that CEA within 3 days of IVT caused a 13% perioperative risk of stroke and death, and 6.8 days had to pass for the perioperative risk of CEA to reach < 6%.[9] Our data suggest that the risk of recurrent ipsilateral ischemic stroke before CEA/CAS is 10% at day 3 and 12% at day 7 in IVT-treated patients. Whether waiting with CEA until day 7 in IVT-treated patients is preferable to treatment at day 3 remains unclear, as a randomized approach would be preferable method to assess this to an error-prone direct numerical comparison of our three merged cohorts and the meta-regression. Also, it is unclear if the increased perioperative risk is valid for all IVT-treated patients,[9,10] but we show that degree of stenosis (near-occlusion with full collapse) affects the risk of preoperative stroke in IVT-treated patients (and non-IVT-treated patients), with a less clear finding for atrial fibrillation. However, treatment of near-occlusion with full collapse is controversial, especially as there might be an

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increased risk of postoperative hyperperfusion in this group.[10,18] Thus, management of IVT-treated patients with symptomatic carotid stenosis is a field in need of further study.

There are several limitations. The data were gathered for other analyses, outcomes were not blinded to IVT treatment and there was a limited number of cases treated with IVT. As the aim of the underlying cohorts was not IVT treatment, commonly used IVT parameters were not recorded, such as NIH stroke scale and onset to arrival expressed in hours (not in days). Time to carotid screening was also recorded in days, not before or after IVT treatment, and might be overestimated in TACNOS and UCC as date of local hospital ultrasound was not recorded in those studies. The assessments relied on medical records review, data accuracy would likely be even better if this had been augmented by study face-to-face interviews. Stroke severity was mild to moderate by selection criteria. Among the cases with a moderate initial stroke, a minor recurrence might be more difficult to detect than among those with mild inital stroke, which is problematic as cases with moderate stroke were at increased chance of receiving IVT compared to cases with mild stroke. The mechanism of event recurrence (recurrent embolism versus oligemia turning into ischemic core) was not assessed. The date of CTAs was systematically recorded, but not the date of screening exams at referring hospitals when performed with ultrasound. The statistical approach with censoring at CEA/CAS causes uncertainties when many have undergone CEA/CAS. However, for the issue of timing (within 7 days) and early recurrence risk, the findings are likely valid as almost three-quarters of the patients had still not undergone CEA/CAS at day 7.

Summary

Intravenous thrombolysis treatment does not seem to affect the risk of recurrent ipsilateral ischemic stroke in patients with symptomatic ≥ 50% carotid stenosis: The risk is high in both IVT-treated and non-IVT-treated. However, there might be a risk increase on the day of IVT treatment that is offset by a risk decrease during the first week.

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Statement of authorship. AN: Co-designed the study and its analyses. Co-wrote first draft and revised later drafts.

TG: Gathered data in an underlying cohort. Revised manuscript drafts.

AH: Gathered data in an underlying cohort. Revised manuscript drafts.

PW: Gathered data and supervised an underlying cohort. Revised manuscript drafts.

AJF: Gathered data in all underlying cohorts. Revised manuscript drafts.

EJ: Co-designed the study and its analyses. Statistical analyses. Co-wrote first draft and revised later drafts.

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