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Recurrent Stroke After Cervical Artery Dissection

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Abstract

Objective: Cervical artery dissection (CAD) accounts for 10-20% of all strokes in young adults but no randomized controlled trial has investigated best secondary prevention after ischemic stroke or transient ischemic attack (TIA). Because only small patients numbers with CAD have been prospectively documented and followed-up, we aimed to investigate the prognosis under various prevention regimens.

Methods: 30 German departments of Neurology with acute stroke units prospectively documented 250 patients with acute ischemic stroke or TIA due to CAD. A central follow-up (median 31 months) assessed recurrent stroke, recurrent CAD and death in 198 patients.

Results: CAD was found more often in the carotid arteries (52.0%) than in the vertebral arteries (46.8%). Thirteen patients (5.2%, CI 3.1-8.6%) suffered a recurrent stroke during the acute hospital stay. The rate of recurrent CAD during the first year was 1.7% (95% CI 0.3-3.6%). The cumulative recurrent stroke rate during the first year was 10.7% (95% CI 6.5 – 14.9%) and 14.0% (95% CI 8.9-19.1%) over three years. After discharge, the rate of recurrent stroke up to 6 months in patients treated with anticoagulants was 2.0% (95% CI 0.6-7.1%) and in those treated with antiplatelets 16.7% (95% CI 5.8-39.2 %) which was statistically significant (HR 0.11; CI 0.02-0.69, p=0.02).

Conclusions: Our observational study confirms a high risk of early recurrent stroke following acute IS or TIA due to CAD. Whether anticoagulation provides any benefit over antiplatelets needs to be investigated in a randomized controlled trial.

Cervical artery dissection (CAD) accounts for 10-20% of all strokes in young adults (≤45 years),[1-6] but is a rare cause of ischemic stroke overall.[7] The incidence of detected CAD is estimated between 1.7 to 3 per 100.000 for carotid and between 1 to 1.5 for vertebral artery dissection.[8, 9] The risk of recurrent dissection is reported to be about 2% in the first month and 1% annually therafter.[4, 10, 11] In previous studies including CAD patients with and without focal cerebral ischemia, the risk of (recurrent) stroke was around to 4-5% in the first 2 weeks after CAD and thereafter fell to <1% annually.[4, 8-10, 12-14] Anticoagulation for prevention of (recurrent) stroke after CAD is widely advocated, but evidence from randomized trials is missing. Arguments against and in favor of anticoagulation after CAD have been summarized in a recent review.[15] We therefore conducted a prospective observational study in 30 German stroke centers to investigate the prognosis of patients with TIA or ischemic stroke due to CAD under various prevention regimens.

Methods

This study was part of a cohort study conducted by the German stroke study collaboration funded by the German Research Council. During 09/2002 and 12/2006 patients with TIA or ischemic stroke were recruited consecutively by 21 participating neurology departments with acute stroke unit (not all centers participated during the whole study-period, mean duration 31 months) on standardized case report forms which included demographic information, risk factors, comorbidities (prior stroke, coronary artery disease, peripheral arterial disease, atrial fibrillation, acute infection <1 week prior to index event), neurological deficits on the National Institutes of Stroke scale (NIH-SS) at admission, modified Rankin Scale at discharge, results of diagnostic work-up, length of hospital stay and secondary prevention at discharge. In addition, nine centers consecutively documented only those patients with CAD (N=70). Neuroimaging was performed as part of the initial evaluation in all patients. CAD was defined by one or more of the following criteria: (1) vessel wall hematoma on fat

suppressed MRI sequences (2) typical findings on MR angiography, CT angiography, Duplex sonography, or conventional angiography (string sign, pseudoaneurysm, flame-shaped occlusion), (3) carotid occlusion with subsequent recanalisation and long-segment stenosis. The final diagnosis of CAD and its location was determined by the documenting center. While we excluded 3 patients with aortic dissection and 36 patients with intracranial dissection only, intracranial continuation of CAD into the distal carotid or vertebral artery was not an exclusion criterion.

After central double key stroke input of all baseline data, data quality was monitored via automated consistency checks and queries were sent to the documenting center. Patients were asked to provide informed consent for participation in the long-term follow-up study. If consented, a central follow-up interview via telephone (or paper questionnaire upon request) was performed biannually with screening for recurrent cerebrovascular events and assessment of functional disability scales (Barthel Index, modified Rankin Scale) or cause of death. In case of a suspected recurrent cerebrovascular event, confirmation could be obtained in >95% of cases from the treating general physician or hospital. Local citizen registries were checked if any patient could not be reached for follow-up and uncertain causes of death were confirmed on death certificates. Biannual follow-up was stopped due to lack of funding in June 2007 resulting in a mean follow up duration of 30.9 (range 5 – 58) months. The study was approved by the ethics committee of the University of Essen.

Statistics

Baseline characteristics of all CAD-patients were stratified by carotid versus vertebral artery dissection as well antithrombotic medication at discharge and reported as percentages or mean (median). In case of missing values, percentages of valid cases are provided. Statistical comparisons were carried out via Fisher's exact test, Pearson's chi-square or Mann-Whitney U test for categorical and continuous variables, as appropriate. Recurrent stroke and stroke

free-survival rates were calculated using the life table method (monthly intervals). Univariate associations of baseline variables (including treatment) to stroke recurrence were tested by separately including each baseline variable in a Cox-regression model with one covariate. Correction for age was carried out by including age as a second covariate. All statistical analyses were performed in SPSS 14.0

Results

The 30 centers listed in the appendix documented 250 patients with ischemic stroke or TIA due to CAD. Mean age of all patients was 48.1 years (SD 12.1) and 101 (40.4 %) were women. In those centers with consecutive documentation of all stroke patients, CAD was found in 1.1% of 16714 patients overall, 8.2% of 1011 patients aged <45 years, 1.7% of 4431 patients aged 45-<65 years, and 0.2% of 11272 patients aged 65 years or older. Internal carotid artery (ICA) dissection was found in 123 patients (49.2%), vertebral artery (VA) dissection in 117 (46.8%), common carotid artery dissection in 7 patients (2.8%) (5 with concomitant ICA dissection) and multiple vessel (ICA and VA) dissections in 3 patients (1.2%). Extracranial ultrasound studies were performed in 240 patients (96.0%), MR angiography in 222 (88.8%), CT angiography in 39 (15.6%) and conventional angiography in 43 (17.2%). The most frequent neurovascular findings were a long-segment stenosis in 131 patients (52.4%) and vessel wall hematoma in 117 (46.8%). Forty-two patients had occlusive ICA dissection (31.6%), which resulted in a significantly higher initial stroke severity on the NIH-SS compared to stenotic ICA dissection (median 7 vs. 3; p=0.004). Twenty patients (8%) received i.v. thrombolysis and 3 patients (1.2%) received intraarterial thrombolysis. High-dose intravenous heparin for early secondary prevention was given to 199 patients (79.6%). Five patients (2.0%) died in the documenting hospital and 13 patients (5.2%) suffered a recurrent stroke during hospital stay. Of 245 surviving patients, 151 (61.6%) were discharged on oral anticoagulation, 36 patients (14.7%) on high dose heparin, 9 (3.6%) on body weight

adjusted low molecular weight heparin, 32 (13.1%) on antiplatelet agents only, and 17 patients (6.9%) received only low dose heparin or no antithrombotic medication. Baseline characteristics in all patients stratified to involved artery and antithrombotic medication at discharge are presented in table 1.

Of 245 survivors, 200 patients gave informed consent for long-term follow-up which could be obtained in 198 patients (80.8%) while 2 patients later withdrew consent or were lost to follow up. Patients without follow-up had significantly more recurrent stroke events during hospital stay (p=0.02) and a higher initial NIH-SS (p=0.04) but no significant differences were found with regard to age, modified Rankin score at discharge, antithrombotic medication at discharge, comorbidities or cardiovascular risk factors. Most patients had a good outcome after 6 months: 154 (80.6% of those with data available) had a modified Rankin score of 0-2, and 47 patients (25.0% of those with data available) reported complete recovery. During 3 years of follow-up after discharge from hospital, 14 patients suffered a recurrent stroke (11 ischemic strokes, 1 intracerebral hemorrhage and 2 strokes of unknown cause) and 5 patients died (1 of medical complications as a consequence of the initial stroke, 2 of recurrent stroke, 1 of cancer and 1 of an unknown cause). All deaths occurred more than 1 year after the index event. The cumulative recurrent stroke rate during the first year was 10.7% (95% CI 6.5 – 14.9%) and 14.0% (95% CI 8.9-19.1%) over three years. No significant differences between carotid and vertebral CAD could be shown for cumulative recurrent stroke rate up to one year (12.5 % versus 8.0 %).

The survival curve free of stroke is displayed in figure 2. With the exception of increasing age, we could not identify any significant predictors for recurrent stroke. Compared to stenotic ICA dissection, patients with occlusive ICA dissection had non-significantly elevated rates of stroke during hospital stay (11.9% vs. 4.9%) and of cumulative recurrent stroke from admission up to one year (18.5% vs. 9.0%). Recurrent CAD was reported by overall 4 patients corresponding to a cumulative rate of 1.7% (95% CI 0.3 – 3.6%) for the first year.

Only one recurrent CAD was associated with recurrent stroke symptoms. The proportion of patients on different antithrombotic prevention regimens during follow-up is displayed in figure 1. Anticoagulation at discharge was maintained for at least 6 months or until recurrent stroke in 98 patients and was associated with a significantly lower rate of recurrent stroke during this period compared with antiplatelet therapy in 18 patients (2.0% vs. 16.7%, HR 0.11; CI 0.02-0.69, p=0.02) which remained unchanged after correction for age. One cerebral hemorrhage occurred under antiplatelet medication after 1 month.

Discussion

To summarize our results, we found a considerable risk for recurrent stroke of 5.2% during the acute hospital stay and 10.7% during the first year. Patients discharged and maintained on anticoagulation for at least 6 months or until recurrent stroke showed a significantly lower rate of recurrent stroke during this period compared with antiplatelets even after correction for age.

In the absence of any completed randomized trial, our observational study to date is the largest prospective case series of patients with stroke or TIA due to CAD. Because no patients with asymptomatic CAD or with isolated non-stroke symptoms were included, our results should only be regarded as representative for patients with acute cerebral ischemia admitted to acute stroke centers. Among those centers with consecutive documentation of all acute stroke patients, an annual average of 4 patients met our definition of CAD. Although we cannot exclude a referral bias in the participating centers, this seems unlikely to have influenced the risk of recurrence. While we did suggest diagnostic criteria for CAD, the final diagnosis of CAD was determined by the documenting center without central adjudication of imaging. For the comparison of secondary prevention regimens, we based our stratification on medication at discharge rather the acute phase because it would have been impossible to define the intention to treat during the acute phase in those CAD patients who received both

antiplatelets and heparin or were switched to another regimen due to an early recurrent stroke. Additional limitations of our study include a telephone follow-up with screening for recurrent cerebrovascular events but no assessment of INR values nor compliance with antithrombotic medication at the time of recurrent stroke. Although the majority of stroke events occurred in the first 6 months after index event during which most patients remained on their discharge medication (figure 1), any non-compliance or discontinuation of medication may have artificially increased the recurrent stroke rate in these patients. In addition, a follow-up rate of 80.8% in surviving patients may have resulted in an overall underestimation of recurrent stroke. Neverteless, follow-up in patients who gave consent was near complete and confirmation of recurrent stroke events could be obtained from the treating physician in >95%.

In previous studies, the proportion of cervical artery dissections ranged from the 2% seen earlier,[16] to 24% in a more recent prospective study.[2] The relatively low prevalence of CAD in patients aged <45 in our hospital-based cohort could be due to case-mix or methodological variations as well as ethnic differences. While population-based studies in CAD patients with and without focal cerebral ischemia have found an almost double frequency of carotid versus vertebral CAD,[9, 11] we could not confirm this finding in consecutive patients presenting with TIA or ischemic stroke. We could confirm a greater stroke severity in patients with occlusive compared with stenotic carotid CAD, as previously suggested.[17] In accordance with previous longitudinal studies in CAD patients,[4, 12] our data indicate a considerable risk for recurrent stroke of 5.2% during the acute hospital stay and 10.7% during the first year. In contrast, retrospective studies as well as a systematic review of mostly small observational studies found a much lower risk of (recurrent) stroke in CAD patients.[13, 18-20] However, most of these studies also included CAD patients with only non-stroke symptoms which are known to have a lower stroke risk compared to CAD patients presenting with TIA or previous stroke.[20]

Patients discharged and maintained on anticoagulation for at least 6 months or until recurrent

stroke showed a significantly lower rate of recurrent stroke during this period compared with antiplatelets even after correction for age. However, the absolute number of recurrent stroke events was very small and our study was not randomized to secondary preventive treatment. Therefore, a bias in treatment allocation cannot be excluded. In addition, we did not assess the territory of recurrent stroke and 39% of patients discharged on anticoagulants had been switched to antiplatelets at follow-up after 6 months (none of which had a stroke during this period). While another multicenter observational prospective study likewise suggested a (non-significant) benefit of anticoagulation over antiplatelets,[12] a meta-analysis of 34 non-randomized studies including 762 CAD patients with and without cerebral ischemia could not show any clear trend in the odds of stroke, nor combined stroke or death when comparing antiplatelet drugs with anticoagulants.[19] Power calculations have suggested a sample size of at least 913 patients per treatment arm to detect a significant effect on stroke recurrence with 80% power.[12, 21] The feasibility of such a trial is currently investigated in the Cervical Artery Dissection in Stroke Study (CADISS) which randomizes patients within 1 week of symptom onset to either anticoagulation or antiplatelet therapy (www.dissection.co.uk).

The rate of recurrent CAD is more difficult to assess because recurrence may be asymptomatic and our study protocol did not enforce a systematic neurovascular follow-up (although most patients were regularly re-examined by ultrasound in their admitting center). Therefore, the rate of 1.7% during the first year is in the lower range of previously reported studies,[10-14] and due to this low rate, no significant predictors could be identified for recurrent CAD (data not shown).

In conclusion, a substantial number of patients with TIA or stroke due to CAD suffered a recurrent stroke within the first year. Despite our finding of a lower rate of stroke recurrence over 6 months in patients discharged on anticoagulants compared with antiplatelets, the potential benefit of anticoagulation over antiplatelets in CAD patients remains unproven.

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Table 1: Baseline characteristics in all patients stratified to the involved artery and to anticoagulation versus antiplatelets on discharge

*significant difference compared with vertebral artery (p<0.05); #significant difference compared with anticoagulation at discharge (p<0.05)

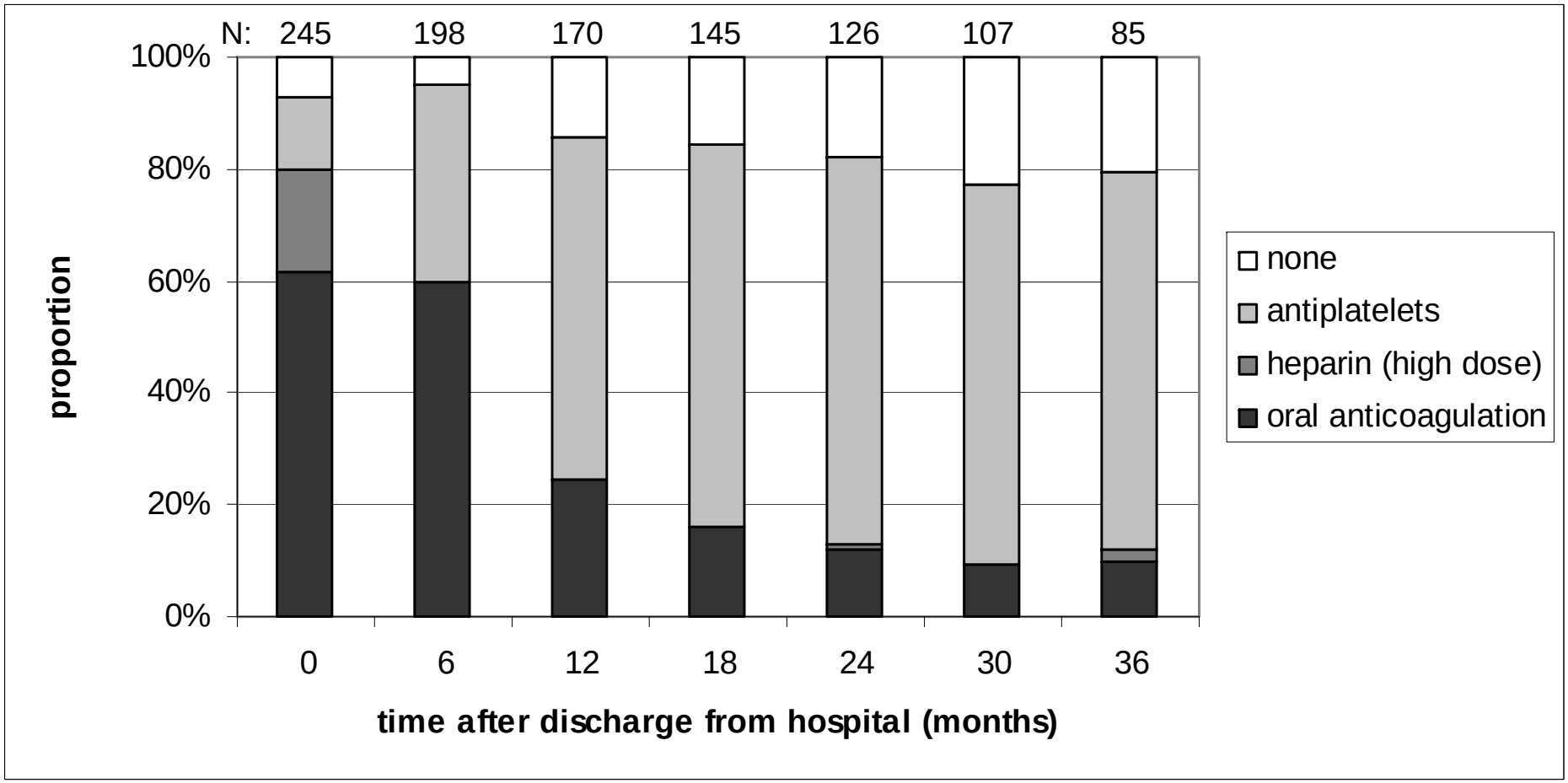
	All patients (N=250)	Carotid artery (N=130)	Vertebral artery (N=117)	Anticoagulation (N=196)	Antiplatelets (N=32)
Mean age	48.1	48.0	48.3	47.7	50.4
Women	101 (40.4)	56 (43.1)	43 (36.8)	78 (39.8)	12 (27.5)
Arterial hypertension	100 (40.0)	50 (38.5)	49 (41.9)	74 (37.8)	18 (56.3)
Diabetes mellitus	29 (11.6)	14 (10.8)	15 (12.9)	19 (9.7)	6 (18.8)
Hypercholesterolemia	58 (23.9)	28 (22.0)	30 (26.5)	49 (25.8)	6 (19.4)
Smoking	84 (34.6)	45 (36.0)	37 (32.2)	66 (34.7)	9 (29.0)
Previous infection	6 (2.4)	4 (3.1)	1 (0.9)	4 (2.1)	2 (6.3)
Additional intracranial dissection	17 (6.8)	16 (12.3)*	1 (0.9)	15 (7.6)	2 (6.3)
occlusive dissection	68 (27.2)	42 (32.3)	26 (22.2)	52 (26.4)	10 (31.3)
Putative risk factors					
Direct Trauma	7 (2.8)	3 (2.3)	4 (3.4)	3 (1.5)	1 (3.1)
Complex trauma	13 (5.2)	8 (6.2)	5 (4.3)	9 (4.6)	2 (6.3)
Minor trauma	21 (8.4)	10 (7.8)	10 (8.5)	17 (8.7)	3 (9.4)
Chiropractic treatment	9 (3.6)	2 (1.6)	7 (6.0)	7 (3.6)	2 (6.3)
Connective tissue disease	7 (2.8)	5 (3.9)	1 (0.9)	6 (3. 1)	1 (3.1)
Other / Unknown	193 (77.2)	101 (78.3)	90 (77.0)	154 (78.6)	23 (71.9)

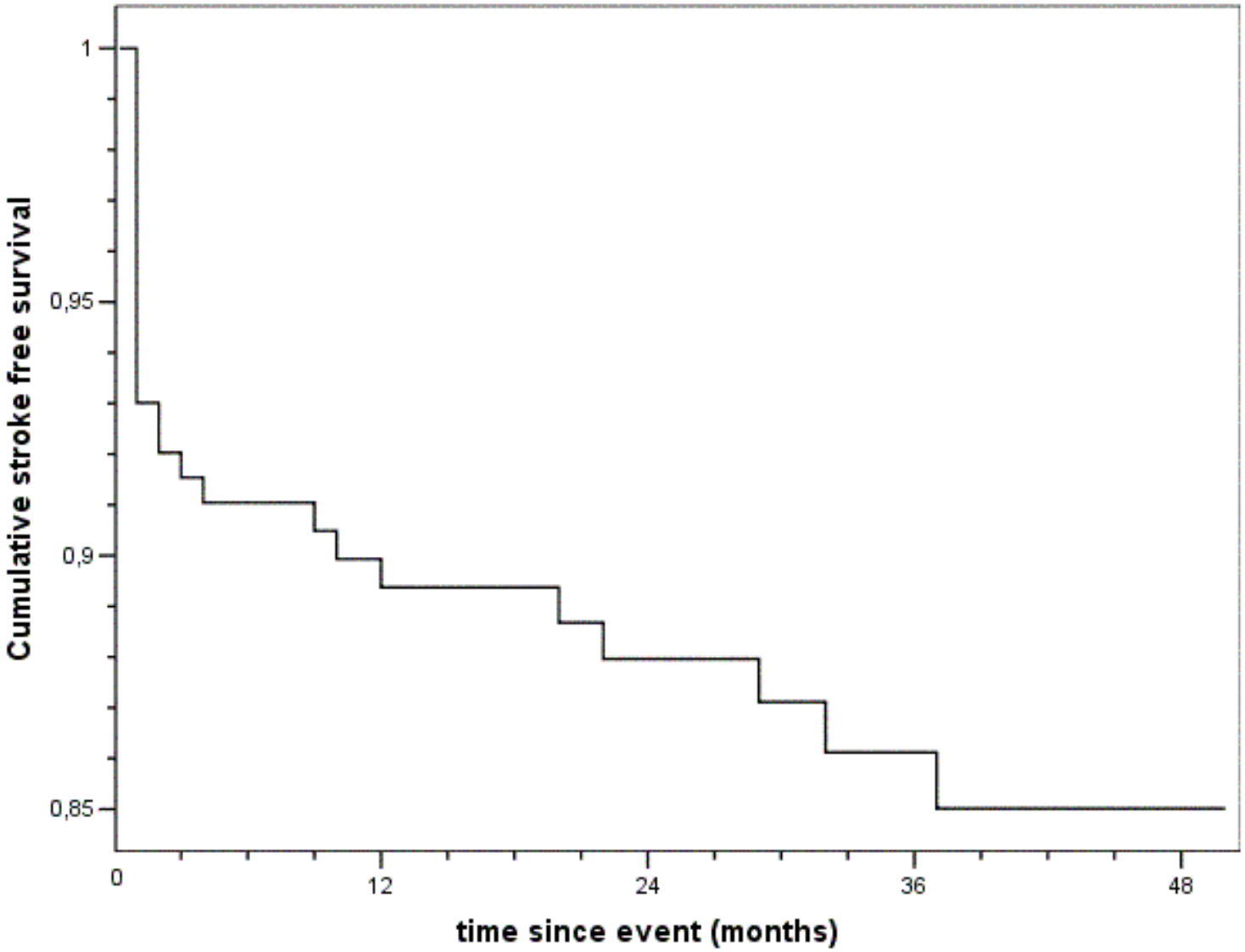
Table 1 (continued)

History of previous stroke	16 (6.4)	11 (8.5)	4 (3.4)	12 (6.1)	3 (9.4)
TIA within preceding week	6 (2.4)	3 (2.3)	3 (2.6)	4 (2.0)	1 (3.1)
History of coronary artery disease	8 (3.2)	2 (1.5)	6 (5.1)	4 (2.0)	3 (9.4)
No infarction on imaging	30 (12.0)	17 (13.1)	12 (10.3)	23 (11.7)	5 (15.6)
High-dose heparin during hospital stay	199 (79.6)	105 (80.8)	92 (80.0)	169 (86.2)	18 (60.0) #
Median NIH-SS at admission	3	5*	2	3	4.5
Recurrent stroke during acute hospital stay	13 (5.2)	9 (6.9)	3 (2.6)	10 (5.1)	2 (6.3)
Death during acute hospital stay	5 (2.0)	3 (2.3)	2 (1.7)	--	--
Antiplatelets at discharge	32 (12.8)	16 (12.3)	15 (12.8)	--	--
Anticoagulation at discharge	197 (78.8)	99 (76.2)	96 (82.0)	--	--
Modified Rankin score 0-2 at discharge	143 (68.2)	65 (59.1)	77 (77.0)	121 (73.8)	17 (60.7)

Figure 1: Antithrombotic medication over time in all CAD patients

Figure 2: Kaplan-Meier curve for survival free of recurrent stroke including initial hospital stay in all CAD patients with censoring at last follow-up


N: 245 198 170 145 126 107 85
100%
80%
60%
40%
20%
0%
proportion
0
6
12
18
24
30
36
time after discharge from hospital (months)
none
antiplatelets
heparin (high dose)
oral anticoagulation


Cumulative stroke free survival
1
0,95
0,9
0,85
0
12
24
36
48
time since event (months)