

Prevalence, predictors and outcome of carotid stenosis. A sub study in the Preventive Antibiotics in Stroke Study (PASS)

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Abstract

Background:

The prevalence of carotid artery stenosis (CAS) in acute ischaemic stroke (AIS) patients is historically reported at 15-20%, but an up-to-date estimate is lacking. We hypothesise it is lower than historically reported, due to better risk management to date. The study aims to study prevalence, predictors and survival of CAS in AIS patients.

Methods:

We included patients with AIS from the Preventive Antibiotics in Stroke Study (PASS), a large Dutch randomized, multicentre, open-label phase III trial that included 2538 patients with acute stroke and randomised between standard care or preventive ceftriaxone. Patients with stroke in the anterior circulation that underwent diagnostic testing of the internal carotid artery (ICA) were eligible for this sub study and used in these secondary analyses. Logistic regression analyses were performed to identify predictors for CAS $\geq 50\%$. Additionally, an ordinal regression was performed to assess the association between presence of CAS at baseline and functional outcome at three months on the modified Rankin scale (mRS).

Results:

1480 patients with AIS were included; 277 had CAS (18.7%; 95%CI:17.7-19.7). Age, hypertension, smoking and male gender were found as best-fit predictors for presence of CAS. Significant shift in mRS score after 90 days for CAS $\geq 50\%$ towards a higher mRS score with an OR of 1.66 (95% CI 1.30-2.10) was found.

Conclusions:

Current prevalence of CAS is 18.7%, which is higher than we expected. Gender, smoking and hypertension are important factors associated with CAS. Patients with CAS had a significantly higher mRS score after 90 days.

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Background

The prevalence of internal carotid artery stenosis (CAS) of $\geq 50\%$ in acute ischaemic stroke (AIS) patients has previously been estimated between 15% and 20%.(1–3) All of the reported patient populations were collected around the year 2000. Since then, the prevalence of several risk factors for cardiovascular disease (CVD) has decreased and treatment of risk factors effects has largely been improved.(4) Some of these factors are known predictors for carotid disease specifically, e.g. hypertension and smoking.(5, 6) In

addition, statins are widely used to date. With the declining number of risk factors for carotid disease, we hypothesize that the prevalence of CAS has decreased. The prevalence of CAS is important as it indicates the burden of disease and the scale of patients that might benefit from changes made to the current protocol for treatment of CAS. Furthermore, it is an indication of the impact of changes that have been made in treatment of CVD and the healthier life style that is thought to have taken place in recent years. Finally, a valid estimate is needed for power calculations of novel studies. The aims of this study are to estimate the current prevalence of CAS in AIS patients, to identify predictors for CAS and describe survival in these patients.

Methods

Data source

Data from the Preventive Antibiotics in Stroke Study (PASS) cohort were used for these secondary analyses. PASS is a large, multicentre, randomised, open-label trial with masked endpoint assessment investigating the effect of preventive antibiotic therapy on functional outcome at three months in patients with AIS or haemorrhagic stroke with a National Institutes of Health Stroke Scale (NIHSS) score ≥ 1 . Patients with infarction or occlusion in more than one vessel territory or patients with transient ischemic attack (TIA) are potentially included, since data on multi-vessel problems were lacking. The study was conducted between 2010 and 2014 and results were published in 2015.(7, 8)

Inclusion criteria

For this sub study, patients with AIS with symptoms of the anterior cerebral circulation from the PASS cohort were included. Patients whose diagnostic test results regarding the carotid artery stenosis or the possible predictive factors of CAS were unavailable were excluded. Computer tomography angiography (CTA), magnetic resonance angiography or Doppler ultrasound were used to determine the presence of CAS. The presence of CAS was defined as stenosis in the internal carotid artery $\geq 50\%$. The additional data on presence of CAS was retrospectively derived from the medical records, whereas all other baseline data in PASS were collected prospectively. Reports about the degree of stenosis of the carotid artery as assessed by a radiologist were used. Information regarding the possible predictive factors was derived from the PASS database and used in this sub study.

Outcomes

The primary outcome is the prevalence of CAS $\geq 50\%$. Secondary outcomes are predictors of CAS $\geq 50\%$ and the association between CAS $\geq 50\%$ and functional outcome at 90 days after stroke, defined as the modified Rankin Scale (mRs) score < 3 . This outcome was assessed by a structured telephone interview by trained trial nurses.(7)

Statistical analysis

Chi-square tests were used to test for differences in dichotomous variables. Mann-Whitney U test and Kruskal-Wallis tests were used to test for differences in age and NIHSS score/mRS respectively as these factors were not normally distributed. Consecutively, we performed univariate followed by multivariable logistic regression analysis to identify predictors for CAS \geq 50%. If the number of missing variables exceeded 5%, this specific variable was excluded from the analysis. The following possible predictors were tested, based on clinical grounds: atrial fibrillation (AF) or flutter, hypercholesterolemia, hypertension, myocardial infarction, peripheral vascular disease, obstructive pulmonary function or chronic obstructive pulmonary disease, and smoking (both current and former). The predictors with a p-value $<$ 0.1 after univariate logistic regression or based on clinical relevance were included for the multivariate logistic regression analysis. We used backward selection to find the best-fit model and the model was tested for multi-collinearity with testing of the variance inflation factor. An ordinal regression was performed to analyze whether there is a significant shift in mRS after 90 days between patient with and without CAS. Age (rounded), NIHSS at baseline, pre-stroke mRS, gender and acute treatment (intravenously thrombolysis) were used as confounders. Age and NIHSS at baseline were used as continuous factor, the others as categorical factors. Finally, a dichotomized analysis on mRS after 90 days was performed, once with mRS 0–2 versus 3–6 and once with mRS 0–5 versus 6, corrected for the same confounders as the ordinal regression analysis. IBM SPSS Statistics version 25 was used for statistical analyses.

Results

1951 patients with ischemic stroke in the anterior circulation were identified from the PASS cohort. Out of these patients, 471 patients (24.1%), no diagnostic test was performed or reported to assess the presence of CAS. (Fig. 1). These patients more often had AF than patients in which the diagnostic test was reported (26.7% versus 12.4%, $p <$ 0.001). In the remaining 1480 patients, 277 had CAS (18.7%, 95%CI 17.7–19.7%).

Patient characteristics

The patient characteristics are shown in Table 1. The mean age of patients with CAS was 72.5

Table 1
Baseline characteristics.

	ICA stenosis < 50% (n = 1203)	ICA stenosis ≥ 50% (n = 277)
Age (mean)	70.70	72.47
Hypertension	52.99%	61.01%
Hypercholesterolemia	26.7%	32.4%
Smoking	60.1%	70.3%
Gender (male)	56.8%	69.0%
NIHSS (median, IQR)	4 (3–7)	6 (4–12)
Thrombolysis	36.7%	43.3%
Pre-stroke modified Rankin Scale (median, IQR)	0 (0–1)	0 (0–1)
Modified Rankin Scale after 90 days (median, IQR)	2 (1–3)	2 (1–4)

(SD 10.8) and the median NIHSS was 6 (IQR 4–12). Most patients with a CAS suffered from hypertension (61%), had smoked prior to stroke (70%) and were male (69%). Patients with CAS received intravenous thrombolysis more frequent than patients without. Compared to the group without CAS, the median NIHSS is higher in the CAS group.

Logistic regression analyses

Univariate logistic regression analyses showed several associations with the known predictors of presence of CAS (Table 2).

Table 2
Univariate logistic regression analyses with predictors of internal carotid artery (ICA) stenosis as independent variables and ICA stenosis ≥ 50% as the dependant variable.

	p-value	Odds ratio (95% CI)
Age (year)	0.031	1.012 (1.001–1.023)
Hypertension	0.016	1.388 (1.063–1.812)
Hypercholesterolemia	0.060	1.312 (0.988–1.742)
Smoking	0.002	1.578 (1.182–2.107)
Gender (male)	< 0.001	1.691 (1.279–2.235)

Subsequently, a multivariable logistic regression was performed (Table 3).

Table 3
Multivariate logistic regression analyses with associated predictors of CAS as independent variables and CAS \geq 50% as the dependant variable. Backward selection was used with the univariate associated variables.

	p-value	Odds ratio (95% CI)
Age (year)	0.002	1.02 (1.007–1.033)
Hypertension	0.021	1.386 (1.05–1.83)
Smoking	< 0.001	1.782 (1.305–2.433)
Gender (male)	< 0.001	1.837 (1.38–2.447)

This analysis showed a best-fit model with age, hypertension, gender and smoking as variables for presence of CAS. The test for multi-collinearity indicated no multi-collinearity.

Survival and functional outcome 90 days after stroke

A median mRS after 90 days of 2 was found in both groups, with a different IQR (see Table 1). A multivariate ordinal regression analysis showed a significant shift towards a higher mRS in patients with CAS (Fig. 2) ($p < 0.001$). It showed an adjusted common odds ratio (OR) for CAS of 1.66 (95% CI 1.30–2.10), for male gender an OR of 0.76 (95% CI 0.63–0.91), for NIHSS of 1.18 (95% CI 1.16–1.21) and for thrombolysis an OR of 0.76 (95% CI 0.62–0.92). For pre-stroke mRS, only a significant shift was found for either mRS 0 and mRS 1, with OR for pre-stroke mRS of 0 of 0.29 (95% CI 0.16–0.52) and for pre-stroke mRS of 1 of 0.44 (95% CI 0.23–0.83). Age showed no significant relation with mRS ($p = 0.078$).

A significant difference was seen for mRS 0–2 versus > 2 between patients with a carotid stenosis compared to patients without, with a larger proportion of patients with a good functional outcome in the group without stenosis (72.0% versus 52.0%, $p < 0.001$). Mortality was significantly increased in patient with carotid stenosis with 12.6% in the stenosis group versus 3.5% in the group without stenosis ($p < 0.001$).

Discussion

This sub study in PASS, a large Dutch stroke with acute stroke patients, showed an up-to-date prevalence of CAS in patients with AIS of 18.7% with age, hypertension, male gender and smoking identified as predicting factors for the presence of ICA stenosis. This prevalence is in line with published research, as well as the found predictors for ICA stenosis.(2–6) Ordinal regression analysis showed an adjusted common OR of 1.66 for ICA stenosis for a worse outcome after stroke in patients who also have CAS. Dichotomized, the mRS showed a worse functional outcome in these patients as well, both in mortality and in less patients in the group with good functional outcome (mRS 0–2). An ICA stenosis \geq 50% as a predictor for worse functional outcome after stroke is a new finding and has not been reported before.

Even though the prevalence that was found is in line with the previous reports on prevalence of CAS in AIS, it is higher than we expected. While in the last decade major improvements have been made in reducing CVD risk factors, some of which we specifically found as predictors for presence of CAS, it had no effect on the shown prevalence of CAS in this sub study. In 2007 Ford et al. reported that the decrease in deaths from coronary disease and they attributed 44% of the decrease to improvement of CVD risk factors. Mostly caused by the lowering of systolic blood pressure, reduction in percentage of smokers and lowering of blood cholesterol.(9) Furthermore, it has been reported that the overall diet in the population have become healthier and people have accustomed a less sedentary life-style.(10–12) Considerable differences in change of risk factors have been described between countries and continents with potentially a less healthy food pattern in developing countries. Overall, CVD remain the most important cause of death worldwide. Even though western countries did see decreasing numbers of CVD death, with a sharper decrease in coronary death compared to stroke mortality, while developing countries saw an increase in both complications.(13) The fact that in these recent data we did not find a lower prevalence of CAS, as marker of large-vessel disease, remains surprising.

An important consideration is that the formation of carotid atherosclerosis and stroke as final effect take a substantial amount of time to develop. The patients that finally suffer from a stroke as a result of CAS are probably the patients with most comorbidities in the CAS group. It can be expected that this group will need far more reduction of risk factors in the general population to reverse CAS in these patients, if it is possible to reverse CAS at all. The majority of patients with CAS that we included in this study, could have been established before the reduction of risk factors was started, as the formation of atherosclerosis takes multiple decades.

Another explanation could be that the decrease in risk factors is not of a sufficient significance or that other (unknown) risk factors become more important if you look at the overall effects after the reduction of the known risk factors. Taking these factors into account, one could hypothesize that it could take a longer time to find the decreasing prevalence of CAS caused by the measures decreasing CVD risk factors and CAS predictors.

The major strength of this study is the large number of AIS patients with complete follow-up that was used in this sub study. The most important limitation is that patients with TIA were excluded and that in a large number of patients (24.1% of the initial 1951 patients), it is unclear why the information regarding the status of CAS is lacking. This could cause an overestimation of the prevalence of CAS. A possible reason for missing this information is AF as cause of stroke. In these patients, the degree of stenosis of the carotid artery is often not investigated. Furthermore, octogenarians or patients with poor mRs or comorbidities, such as dementia, are often not eligible for revascularization and consequently are not investigated by imaging.

The worse functional outcome of patients with CAS is an interesting finding, even though PASS was not powered to show this difference, which deserves further attention. The general functioning of CAS patients and their overall high CVD risk could be an explanation for the worse outcome in these patients

and thus making CAS a symptom of the worse outcome and not necessarily the cause of the worse outcome itself. Furthermore, CAS could be caused by the low-socio economic status that is correlated with most CVD risk factors that were found and are linked to worse outcome overall.(14)

Another explanation for the worse functional outcome could be the chronic inflammatory activity in the local carotid plaque. The specific role of the inflammatory reaction in the vessel wall remains unclear, but it could be a causative factor in more CVD complications. Since in several auto-immune diseases, patients suffer CVD more frequently and lower life-expectancy is seen in these patients.(15, 16) How this elevated CVD cases can be explained is still unknown, but it cannot be described by the traditional CVD risk factors alone. Whether treating the inflammatory reaction is beneficial for CAS patients should be elucidated and CONVINCE will be the first study in neurology focussing on that research question. In this randomized study low-dose colchicine is used as additive to standard secondary prophylaxis in non-cardio embolic stroke patients.(17)

Conclusions

We conclude that the prevalence of ICA stenosis remains as high as reported before and the same predictors were found. A shift towards worse outcome after 90 days has been found for CAS patients, but this needs further attention, for example by the following means. First, our findings demand further research on survival of patients with CAS, both symptomatic, as is done in this sub study, as in asymptomatic CAS. Second, these findings indicate the urgent need for stratified analysis of different causes of stroke, regarding outcome, survival and predictors of these patients. This could lead to better understanding of patient groups with worse outcome and a better prediction of stroke outcome. Finally, further decreasing smoking and increasing the treatment of hypertension in the population can potentially decrease the number of CAS in AIS.

Abbreviations

AIS

acute ischemic stroke

AF

atrial fibrillation

CAS

carotid artery stenosis

CI

confidence interval

CTA

computed tomography angiography

CVD

cardiovascular disease

ICA

internal carotid artery
IQR
interquartile range
mRS
modified Rankin Scale
NIHSS
National Institutes of Health Stroke Scale
PASS
Preventive Antibiotics in Stroke Study
SD
standard deviation
TIA
transient ischemic attack

Declarations

Ethics approval and consent to participate:

Ethics approval was obtained from the *Medisch Ethische Toetsings Commissie AMC* (METC AMC) (Medical Ethics Review Commission AMC), this institute belongs to the Amsterdam UMC, location AMC. Committee's reference number: METC 10/063. Written informed consent was obtained from all patients.

Consent for publication:

not applicable to this study.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contribution:

The design of this sub study was done by TV/PN. TV/LK/WW created the analysis plan, in close correspondence with DB/PN. The interpretation was done by all authors. The manuscript was drafted by TV. All authors read, critically reviewed and approved the final manuscript.

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Figures

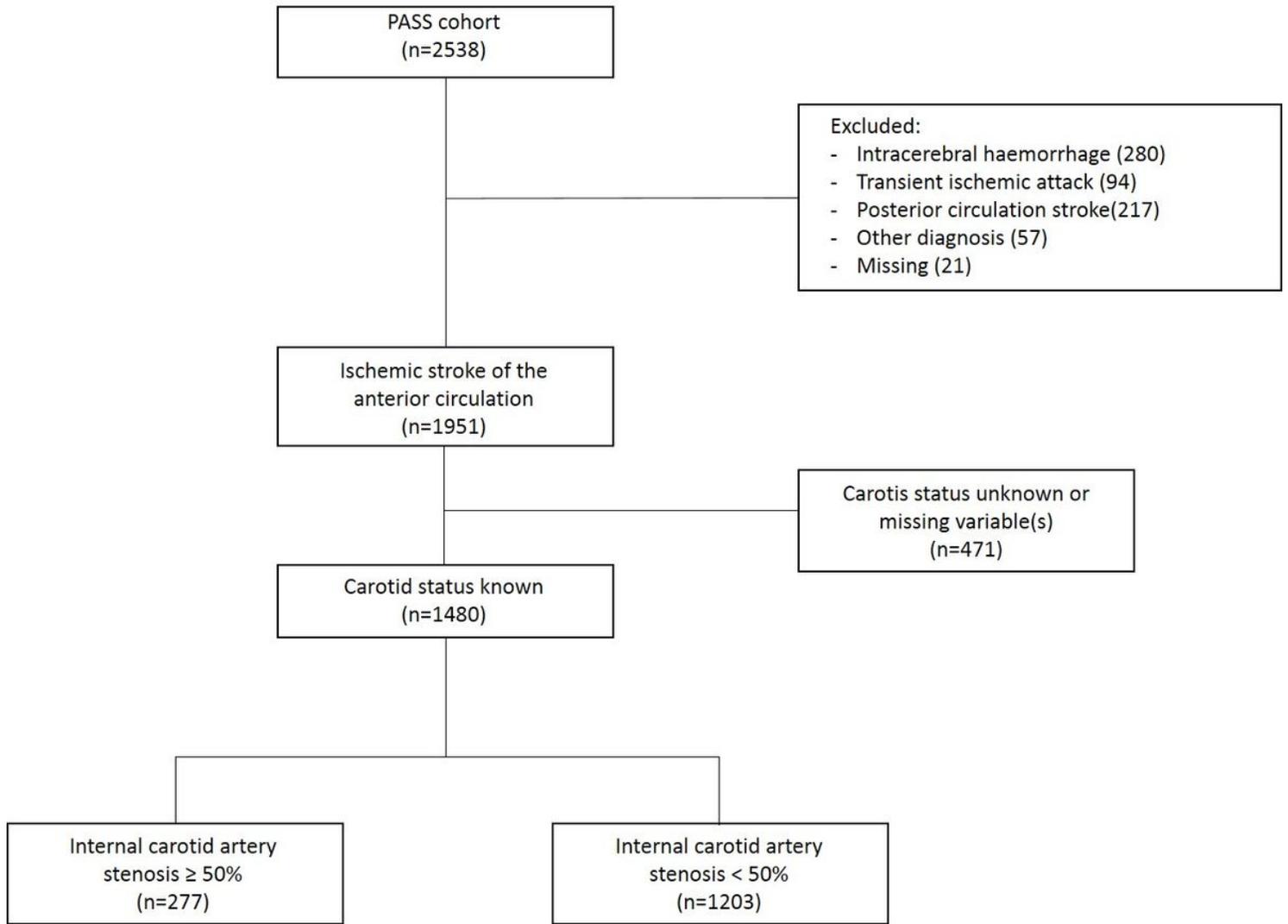


Figure 1

Patient selection flowchart

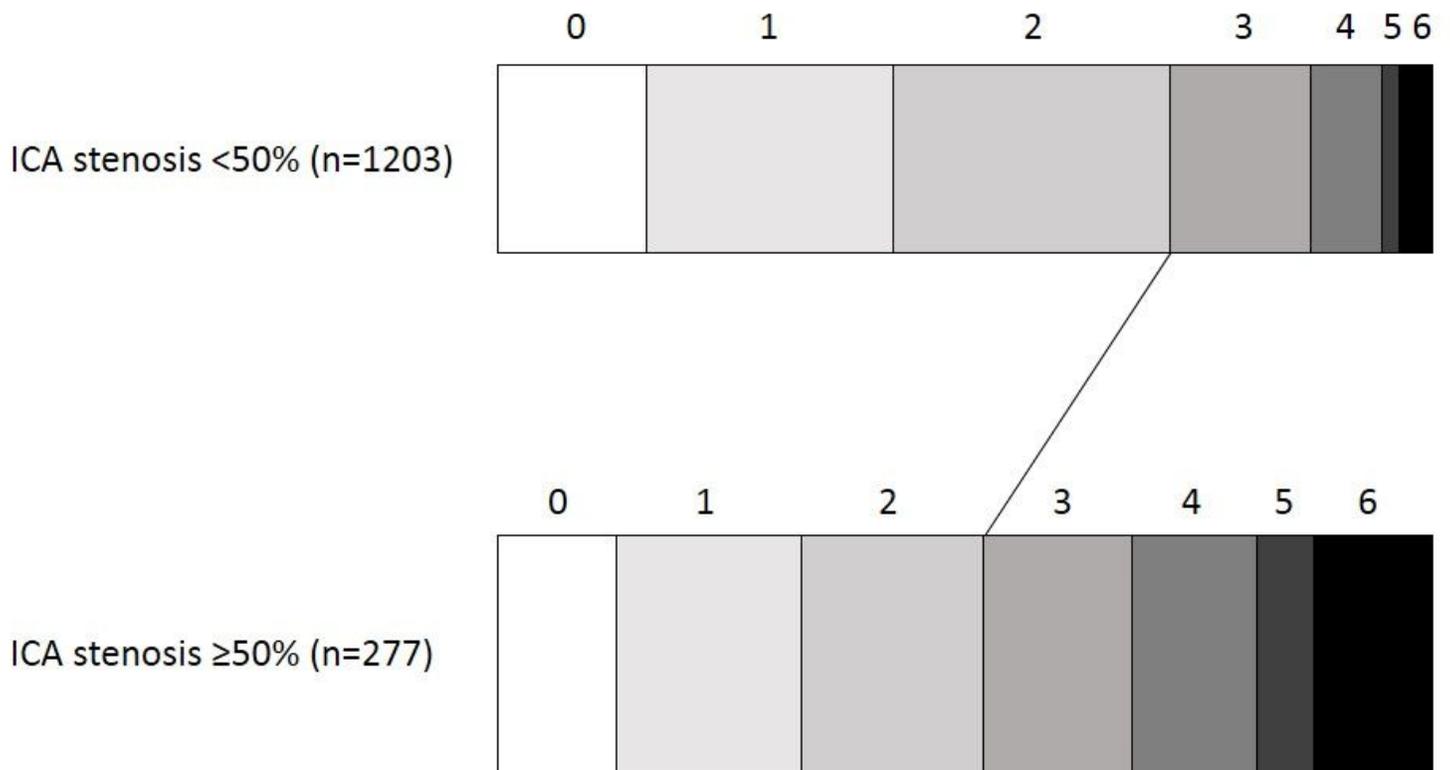


Figure 2

Shift in modified Rankin Scale (mRS) 90 days after stroke. Adjusted common odds ratio for CAS $\geq 50\%$ of 1.66 (95% CI 1.30-2.10). The left side of the diagonal line (mRS 0-2) indicates a good functional outcome with a between groups difference of 20%. 0= no remaining symptoms, 6= dead.