Predictors of stroke within 30 days in patients with non-ST-segment elevation acute coronary syndromes

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Aims Stroke is an uncommon but serious complication after non-ST-segment elevation acute coronary syndrome (NSTE-ACS). We aimed to identify predictors of stroke within 30 days in patients who suffered NSTE-ACS.

Methods and results We pooled data from six trials (n = 31,402) that randomized NSTE-ACS patients either to platelet glycoprotein (GP) IIb/IIIa receptor blockers or to placebo/control therapy. Potential predictors of stroke included treatment, demographic, and clinical characteristics. We identified predictors using univariable and multivariable logistic models, and their performance was evaluated with calibration (Hosmer–Lemeshow test) and discrimination (c-statistic). We found 228 (0.7%) all-cause strokes: 155 (0.5%) non-haemorrhagic, 20 (0.06%) haemorrhagic, and 53 without computed tomography (CT) confirmation. Patients with any type of stroke had a 30-day mortality of 25%. Randomization to GP IIb/IIIa receptor blockers was not significantly associated with all-cause stroke [OR (95% CI) 1.08 (0.83–1.41)]. Older age [OR per 10-year increase 1.5 (1.3–1.7)], prior stroke [2.1 (1.4–3.1)], and elevated heart rate [per 10-beat increase 1.1 (1.0–1.2)] were the strongest predictors of all-cause stroke. Similar predictors were found for non-haemorrhagic and haemorrhagic strokes. Smoking, previous myocardial infarction, diabetes, and hypertension were not independent predictors of all-cause stroke. The multivariable model to predict all-cause stroke was well calibrated, but its discrimination was only moderate [c-statistic 0.69 (0.65–0.72)].

Conclusion Stroke is a rare complication occurring early after NSTE-ACS, but is associated with high mortality. We found no evidence that GP IIb/IIIa receptor blockers increase stroke risks. A few clinical characteristics predicted higher stroke risks. Thus, incident strokes in NSTE-ACS patients remain largely unexplained.

Introduction

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is a heterogeneous disease. Risk stratification is essential for predicting prognosis, planning treatment strategy, and providing information to patients and relatives.1,2 Previous papers in patients with NSTE-ACS have evaluated the predictors associated with a range of clinical outcomes at 30 days or 6 months, such as death, cardiovascular death, and cardiovascular death or myocardial infarction (MI).2-5

Stroke is an uncommon but severe event in patients presenting with NSTE-ACS. Analyses with a few events in the PURSUIT trial found several clinical predictors of non-haemorrhagic stroke at 30 days.6 These patients are also at increased risk for haemorrhagic strokes from polypharmacy anticoagulation. However, the confirmation of the importance of these predictors of stroke with a larger number of patients and events is desirable.

We aimed to identify the baseline clinical and demographic patient characteristics that predict the development of all-cause, non-haemorrhagic, and haemorrhagic strokes within 30 days. We analysed patients with NSTE-ACS from six large international trials. Moreover, we evaluated whether the use of GP IIb/IIIa receptor blockers was associated with an increased risk of stroke.

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Methods

Clinical trials

We used individual patient data from six trials (PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, and GUSTO IV-ACS).7–12 These trials were reported since 1990 with the following characteristics: randomization of patients with NSTE-ACS, comparison of platelet glycoprotein (GP) IIb/IIIa receptor blockers with placebo or control therapy, no-recommendation for early (<48 h) coronary revascularization during study-drug infusion, and enrolment of at least 1000 patients. Heparin was usually begun with 5000 IU and then followed with 1000 IU/h. Heparin was part of the study regimen in the PRISM, PRISM-PLUS, and PARAGON-A trials and was given to all patients in the PURSUIT, PARAGON-B, and GUSTO IV-ACS trials. In addition, all trials excluded patients with thrombocytopenia (platelets <100 000 cells/μL). Five of the trials excluded patients with renal failure (serum creatinine >2 mg/dL or creatinine clearance <30 mL/min), except the GUSTO IV-ACS trial. All trials excluded patients with a prior stroke: PRISM, PRISM-PLUS, PARAGON-A, and PARAGON-B in the last year; PURSUIT in the last 2 years. Further details of the trial designs are available elsewhere.13 A total of 31 402 patients participated in these trials. Data on 31 387 patients were available for this analysis.

Potential predictors

An electronic database consisting of data from individual patients in all eligible trials was available.13 These data were checked for completeness, internal consistency of patients’ records, and consistency with the published reports. For this analysis, we used available baseline demographic and clinical characteristics, regarded as potential predictors of stroke.6 Those with almost complete information (<1% of missing values) included age, gender, smoking, weight, and prior history of all the following: hypertension, diabetes, stroke, MI, heart failure, angina pectoris, coronary artery bypass surgery, percutaneous coronary intervention, and use of aspirin. Two variables had 2% of missing values: history of hypercholesterolaemia and ST-depression at baseline.

Other variables had ~20% of missing data: race, heart rate, systolic and diastolic blood pressures, and baseline creatinine kinase MB (CK-MB). Blood pressure and heart rate were not recorded in the GUSTO IV-ACS trial (n = 7800); baseline CK-MB was missing in 7469 patients across different trials. Variables with far more than 20% of missing values were excluded from the analysis, such as prior use of beta-blockers, angiotensin-converting enzyme-inhibitors, nitrates, and calcium antagonists. Troponin levels were systematically collected in only two of the most recent trials (PARAGON-B and GUSTO IV-ACS), in which it was available in 7161 of 13 025 patients. Predictors with ~20% or less of missing values were imputed using the estimated mean procedure in SPSS (SPSS Inc., Chicago, IL, USA), and PARAGON-B14 used the imputation (AF) and in-hospital 30 days; and GUSTO IV-ACS in the last 2 years. Further details of the trial designs are available elsewhere.13 A total of 31 402 patients participated in these trials. Data on 31 387 patients were available for this analysis.

Outcomes

For this analysis, the primary outcomes defined a priori were all-cause stroke, non-haemorrhagic stroke, and haemorrhagic stroke within 30 days of the index ACS. Non-haemorrhagic and haemorrhagic strokes needed CT confirmation. All-cause stroke was missing in 12 patients. Non-haemorrhagic and haemorrhagic stroke was missing in 7434 and 7474 patients, respectively. No formal attempt to impute these outcomes was done.

Statistical analysis

This is a prediction analysis that pools data from six large-scale randomized clinical trials, and it is not a formal meta-analysis. Univariable logistic regression models were used to evaluate the association between each potential predictor and the outcome. We checked the linearity assumption of continuous variables using restrictive cubic splines. The predictive weight of each variable was expressed as a $\chi^2$ statistic, which was calculated on the −2 log likelihood scale. The higher the number, the more important the predictor; a $\chi^2$ exceeding 3.84 corresponds to $P < 0.05$ for a predictor with one degree of freedom. All predictors were entered in a multivariable logistic regression model without further selection to properly evaluate their predictive effects while adjusting for the effects of each other predictor.15

The performance of the multivariable models was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish a stroke from no stroke. It was quantified by a measure of concordance, the c-statistic. For binary outcomes, the c-statistic is identical to the area under the receiver operating characteristic curve. The c-statistic lies between 0.5 and 1 and is better if closer to 1.16 Because the apparent c-statistic is optimistic with low numbers of events, we used a standard bootstrapping procedure to correct the estimates.15,16 Calibration refers to whether the predicted risks agree with the observed risk frequencies. Calibration was measured with the Hosmer-Lemeshow goodness-of-fit test.17 Analyses were performed in SPSS 10.0 and S-PLUS 2000 (Insightful Inc., Seattle, WA, USA).

Results

Patient characteristics

We found 228 (0.7%) all-cause strokes in the study population: 155 (0.5%) were non-haemorrhagic, 20 (0.06%) haemorrhagic, and 53 (0.2%) without CT confirmation. Older patients with a prior stroke, prior MI, diabetes, hypertension, and patients with elevated heart rate had higher risks of all-cause and non-haemorrhagic strokes (Table 1). Smoking was not clearly related with the stroke incidence. Patients with previous percutaneous transluminal coronary angioplasty were at lower risk to develop any stroke. Less clear associations were seen in haemorrhagic strokes, probably due to small numbers. The risks of haemorrhagic stroke due to GP IIb/IIIa receptor blockers were tiroliban 0% (0/5147), lamifiban 0.1% (5/7507), eptifibatide 0.1% (7/10948), and abciximab 0.1% (8/7800). There was no statistical difference among these risks.

A high proportion of patients who suffered a stroke died: 56 (25%) of those with all-cause stroke, 27 (17%) of those with non-haemorrhagic stroke, and 13 (65%) of those with haemorrhagic stroke. The difference in mortality between non-haemorrhagic and haemorrhagic strokes was highly statistically different ($P < 0.001$). Thirty-day mortality in patients without stroke was 3.4% (1060/31 162), and the difference in mortality between patients with and without stroke was highly significant ($\chi^2 259, P < 0.00001$). No clear relation was observed between predictors and death in patients who suffered any type of stroke (Table 1).

Predictors of stroke

The rate of stroke was 0.8% (137/18 291) among users of GP IIb/IIIa receptor blockers and 0.7% (91/13 099) among non-users of GP IIb/IIIa blockers. There was no difference between users and non-users ($\chi^2 0.3, P = 0.6$). The use of
The strongest univariable predictors of all-cause stroke were older age ($\chi^2 = 12$), prior stroke ($\chi^2 = 8$), and lighter weight ($\chi^2 = 5$). Similarly, the three most important predictors were those of the non-haemorrhagic strokes (Table 2).

**Performance of predictive models**

The calibration of the predictive model of all-cause stroke was good (Hosmer–Lemeshow test 10.4, $P = 0.24$), but the discriminative power of this model was moderate [c-statistic (95% CI): 0.69 (0.65–0.72)]. Although the calibration of the predictive models of non-haemorrhagic and haemorrhagic strokes was good, the discriminative power was either moderate [c-statistic 0.67 (0.63–0.71)] or poor [c-statistic 0.58 (0.54–0.63)], respectively.

**Discussion**

Stroke occurred in 0.7% of patients within 30 days of presenting with NSTE-ACS. Two-thirds of the strokes were non-haemorrhagic. Older age, prior stroke, and elevated heart rate were the strongest predictors of all-cause, non-haemorrhagic, and haemorrhagic strokes. However, the discriminative power of these predictors was moderate and especially poor for haemorrhagic strokes. Thus, it is difficult to accurately predict the incidence of stroke in this population.

The incidence of 30-day all-cause stroke in our patients is comparable with that in similar populations: 0.8% in the patients with positive troponin levels ($\geq 2$).

The strongest univariable predictors of non-haemorrhagic stroke were older age ($\chi^2 = 38$), prior stroke ($\chi^2 = 18$), elevated heart rate ($\chi^2 = 9$), prior MI ($\chi^2 = 7$), and diabetes ($\chi^2 = 7$). Lighter weight ($\chi^2 = 4$) and hypertension ($\chi^2 = 3$) had minor importance. The three most important predictors of non-haemorrhagic stroke had comparable associations as those described for all-cause stroke. For haemorrhagic strokes, the strongest univariable predictors were older age ($\chi^2 = 12$), prior stroke ($\chi^2 = 8$), and lighter weight ($\chi^2 = 5$). Similarly, the three most important predictors were those of the non-haemorrhagic strokes (Table 2).

**Table 1** Distribution of patient baseline characteristics across stroke types (all-cause, non-haemorrhagic, and haemorrhagic).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>All-cause strokes $n = 228$</th>
<th>Non-haemorrhagic strokes $n = 155$</th>
<th>Haemorrhagic strokes $n = 20$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N$</td>
<td>$n$ (%)</td>
<td>Deaths (%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;70$ years</td>
<td>20874</td>
<td>98 (0.5)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>$\geq 70$ years</td>
<td>10513</td>
<td>130 (1.2)</td>
<td>36 (28)</td>
</tr>
<tr>
<td><strong>Prior stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>29890</td>
<td>201 (0.7)</td>
<td>50 (25)</td>
</tr>
<tr>
<td>Yes</td>
<td>1446</td>
<td>27 (1.9)</td>
<td>6 (22)</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;75$</td>
<td>16807</td>
<td>104 (0.6)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>$&gt;75$</td>
<td>14580</td>
<td>124 (0.9)</td>
<td>23 (19)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>11499</td>
<td>68 (0.6)</td>
<td>15 (22)</td>
</tr>
<tr>
<td>Former</td>
<td>10429</td>
<td>91 (0.9)</td>
<td>21 (23)</td>
</tr>
<tr>
<td>Current</td>
<td>9307</td>
<td>68 (0.7)</td>
<td>20 (29)</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20648</td>
<td>125 (0.6)</td>
<td>31 (25)</td>
</tr>
<tr>
<td>Yes</td>
<td>10646</td>
<td>103 (1.0)</td>
<td>25 (24)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24488</td>
<td>159 (0.6)</td>
<td>43 (27)</td>
</tr>
<tr>
<td>Yes</td>
<td>6860</td>
<td>68 (1.0)</td>
<td>12 (18)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14417</td>
<td>81 (0.6)</td>
<td>21 (26)</td>
</tr>
<tr>
<td>Yes</td>
<td>16935</td>
<td>147 (0.9)</td>
<td>35 (24)</td>
</tr>
<tr>
<td><strong>GP IIb/IIIa RB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13097</td>
<td>91 (0.7)</td>
<td>21 (23)</td>
</tr>
<tr>
<td>Yes</td>
<td>18290</td>
<td>137 (0.8)</td>
<td>35 (26)</td>
</tr>
</tbody>
</table>

N, number of patients in a defined subgroup; n, number of patients with a stroke within a subgroup, and its percentage of ($n/N$) x 100.

Deaths within 30 days. The percentage refers to the number of deaths in patients who suffered a stroke.

\(P < 0.001\) for the comparison between categories.

\(\text{Platelet GP IIb/IIIa receptor blocker.}\)

GP IIb/IIIa receptor blockers was not associated with a higher incidence of all-cause [OR (95% CI): 1.08 (0.83–1.41)], non-haemorrhagic [1.06 (0.77–1.47)], and haemorrhagic [1.70 (0.65–4.45)] strokes. A subgroup analysis of the 3730 patients with positive troponin levels (upper limit of normality) was performed. All-cause stroke was observed in 26 patients, and the use of GP IIb/IIIa antagonists was not associated with stroke in the univariate analysis (OR 0.94, 95% CI 0.4–2.1).

The strongest univariable predictors of all-cause stroke were older age ($\chi^2 = 69$), prior stroke ($\chi^2 = 19$), prior MI ($\chi^2 = 12$), hypertension ($\chi^2 = 10$), elevated heart rate ($\chi^2 = 9$), lighter weight ($\chi^2 = 9$), diabetes ($\chi^2 = 8$), and smoking ($\chi^2 = 6$). The associations are shown in Table 2.
in-hospital strokes. The proportion of haemorrhagic stroke, including both NSTE- and STE-ACS patients, had 1.5% (95% CI 0.8%–2.3%) in nine trials from a meta-analysis. The VALIANT registry, including both NSTE- and STE-ACS patients, had 1.5% in-hospital strokes. The proportion of haemorrhagic strokes was ~50% of the total number of strokes in the GUSTO-I trial and 0.8% in nine trials from a meta-analysis. The VALIANT registry, including both NSTE- and STE-ACS patients, had 1.5% in-hospital strokes. The proportion of haemorrhagic strokes was still limited.

Haemorrhagic strokes were not studied. The strongest predictors were higher heart rate, older age, prior MI, prior stroke or transient ischaemic attack (TIA), and hypertension. Our analysis of 31 387 patients increased the number of events and the power to find predictors of any type and all-cause stroke. However, the number of haemorrhagic strokes was still limited.

Age was an important predictor of non-haemorrhagic stroke in the PURSUIT and GUSTO-I trials. In our analysis, age was the strongest predictor of all-cause, non-haemorrhagic, and haemorrhagic strokes, and its relative importance was slightly higher than the results of the PURSUIT trial. Elderly patients probably have a higher risk of stroke because of multiple co-morbidities associated with older age, such as AF, hypertension, physical inactivity, and asymptomatic carotid stenosis.

Prior stroke has been described as a predictor of stroke in the OPUS-TIMI 16 trial. In this trial, the proportion of 10-month all-cause stroke was 2.9% in 1173 patients with prior extra-cardiac vascular disease (peripheral stroke + TIA) in comparison with 1.1% in 9108 patients without prior extra-cardiac vascular disease. In the PURSUIT and GUSTO-I trials, prior stroke was analysed in conjunction with prior TIA, and this combined predictor was important. Prior stroke may be a marker of underlying cardiac, carotid, or cerebral vascular disease in ACS patients.

Elevated heart rate was very important in the PURSUIT and GUSTO-I trials. An explanation for the association between elevated heart rate and stroke is not clear. The heart rate may correlate with larger infarctions that predispose patients to a higher likelihood of atrial arrhythmia and left ventricular thrombi. Heart rate is strongly associated with prior extra-cardiac vascular disease (peripheral stroke + TIA) in comparison with 1.1% in 9108 patients without prior extra-cardiac vascular disease. In the PURSUIT and GUSTO-I trials, prior stroke was analysed in conjunction with prior TIA, and this combined predictor was important. Prior stroke may be a marker of underlying cardiac, carotid, or cerebral vascular disease in ACS patients.

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Stroke has only been studied as an outcome in a secondary analysis of the PURSUIT trial. Sixty-six non-haemorrhagic strokes in 9461 NSTE-ACS patients were studied.

### Table 2: Univariable and multivariable OR (95% CI) of predictors of stroke in NSTE-ACS patients

<table>
<thead>
<tr>
<th>Predictors</th>
<th>All-cause strokes</th>
<th>Non-haemorrhagic strokes</th>
<th>Haemorrhagic strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable</td>
<td>Multivariable</td>
<td>Univariable</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.68 (1.48–1.91)</td>
<td>1.51 (1.31–1.74)</td>
<td>1.59 (1.37–1.86)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>2.81 (1.87–4.21)</td>
<td>2.06 (1.36–3.12)</td>
<td>3.17 (1.99–5.04)</td>
</tr>
<tr>
<td>Heart rate (per 10 beats)</td>
<td>1.11 (1.05–1.19)</td>
<td>1.11 (1.04–1.18)</td>
<td>1.13 (1.05–1.20)</td>
</tr>
</tbody>
</table>

Importantly, the use of GP IIb/IIIa receptor blockers was not clearly associated with an increased incidence of all-cause stroke, non-haemorrhagic stroke, or haemorrhagic stroke. However, it should be recognized that the conclusion regarding the effect of GP IIb/IIIa receptor blockers on haemorrhagic strokes has substantial uncertainty, given the low numbers of events available and, hence, the limited power of the statistical analysis. The low frequency of haemorrhagic stroke in the overall population, coupled with lack of clear evidence of increased risk, provides reassurance that fear of intracranial haemorrhage should not be a reason to avoid these drugs. However, when patients receive these drugs on top of more aggressive antithrombotic therapy, the incidence of haemorrhagic strokes increases, as in patients with STE-ACS who received thrombolytics. In our NSTE-ACS patients, predictors associated with the incidence of haemorrhagic stroke were similar to those associated with non-haemorrhagic stroke. In contrast, STE-ACS patients who take oral anticoagulation before admission, with <70 kg, and older than 65 years were at increased risk of haemorrhagic stroke.

Stroke has only been studied as an outcome in a secondary analysis of the PURSUIT trial. Sixty-six non-haemorrhagic strokes in 9461 NSTE-ACS patients were studied.
described as an independent predictor of in-hospital all-cause stroke in the VALIANT registry.\textsuperscript{24}

Diabetes and prior MI were independent predictors of stroke in the PURSUIT trial,\textsuperscript{6} but not in our analysis. Diabetes has a known association with a widespread atherosclerosis, and prior MI is associated with the formation of mural thrombus and emboli. Finally, lighter weight was weakly associated with haemorrhagic stroke. This was probably related to doses of GP IIb/IIIa receptor blockers and anticoagulants that were not reduced in lighter patients, and especially for the elderly.

Our study has some limitations. We had about 7500 patients with missing values for the non-haemorrhagic and haemorrhagic stroke outcomes. The number of non-haemorrhagic strokes was still larger (n = 155) than the largest previously published (n = 66).\textsuperscript{6} Although we had a few haemorrhagic strokes (n = 20), regression coefficients of the multiple regression model for haemorrhagic stroke are not biased. Although the performance of the prognostic model may be optimistic, it was internally validated using the bootstrap procedure. We imputed several patient characteristics. Of them, only heart rate remained as strong predictor, as demonstrated previously.\textsuperscript{5}

In conclusion, stroke is an infrequent but serious early complication of patients with NSTE-ACS. Mortality is high, especially for haemorrhagic strokes. Platelet GP IIb/IIIa receptor blockers were not significantly associated with any type of stroke. Three main predictors of stroke were older age, prior stroke, and elevated heart rate. Because the discriminative ability of these patient characteristics was at best moderate, it is difficult to predict which ACS patients will suffer a stroke.

Acknowledgements

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Conflict of interest: D.J.M. is a consultant for Merck, Centocor, and Eli Lilly and has received honoraria from the same, as well as from Roche. H.W. is a consultant for and has received honoraria from Merck. P.T. was a principal investigator and chairman of the Steering Committee for the PRISM-PLUS trial. P.W.A. has received research grants and honoraria from Eli Lilly and Schering-Plough. R.M.C. has worked with Centocor, Lilly, COR, Schering-Plough, and Merck. M.L.S. is a consultant for Merck, Centocor, and Lilly and has provided paid expert testimony to Schering-Plough.

References


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