Incidence, Time Trends, and Predictors of Intracranial Hemorrhage During Long-Term Follow-up After Acute Myocardial Infarction

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Background—To address the lack of knowledge regarding the long-term risk of intracranial hemorrhage (ICH) after acute myocardial infarction (AMI), the aims of this study were to: (1) investigate the incidence, time trends, and predictors of ICH in a large population within 1 year of discharge after AMI; (2) investigate the comparative 1-year risk of ICH in AMI patients and a reference group; and (3) study the impact of previous ischemic stroke on ICH risk in patients treated with various antithrombotic therapies.

Methods and Results—Data about patients whose first AMI occurred between 1998 and 2010 were collected from the Swedish Register of Information and Knowledge about Swedish Heart-Intensive-Care Admissions (RIKS-HIA). Patients with an ICH after discharge were identified in the National Patient Register. Risk was compared against a matched reference population. Of 187 386 patients, 590 had an ICH within 1 year. The 1-year cumulative incidence (0.35%) was approximately twice that of the reference group, and it did not change significantly over time. Advanced age, previous ischemic or hemorrhagic stroke, and reduced glomerular filtration rate were associated with increased ICH risk, whereas female sex was associated with a decreased risk. Previous ischemic stroke did not increase risk of ICH associated with single or dual antiplatelet therapy, but increased risk with anticoagulant therapy.

Conclusion—The 1-year incidence of ICH after AMI remained stable, at ≈0.35%, over the study period. Advanced age, decreased renal function, and previous ischemic or hemorrhagic stroke are predictive of increased ICH risk. (***J Am Heart Assoc***. 2015;4: e002290 doi: 10.1161/JAHA.115.002290)

Key Words: acute myocardial infarction • intracranial hemorrhage • ischemic stroke

I ntracranial hemorrhage (ICH) is an infrequent, but serious, complication subsequent to acute myocardial infarction (AMI), which is associated both with great disability and a high risk of death.[1–3] It has a high risk of recurrence and it is therefore important to be able to accurately assess hemorrhage-associated risk factors to reduce the risk of new and recurrent events.[1,4–9]

During the last decade, the inpatient treatment of myocardial infarction (MI) has changed drastically. In many countries, there has been a shift in approach from thrombolysis to primary percutaneous coronary intervention (PCI), an increase in the use of parenteral anticoagulants, and more-aggressive treatment of elderly patients. These changes have affected the short-term occurrence of ICH.[1,3,5,7,8,10–12] However, data remain limited regarding any change in the postdischarge risk of ICH over time and long term. Furthermore, previous data originate primarily from clinical trials with patient populations who have a fairly modest risk profile.[13–15]

There are discrepancies among the predictors of ICH determined by earlier studies, presumably attributable to differences in the reperfusion methods used (fibrinolysis vs primary PCI), in patient selection (clinical trials vs registry or community-based studies), and in the duration of follow-up. However, advanced age, previous ischemic or hemorrhagic stroke, hypertension, female sex, lower weight, diabetes, atrial fibrillation, and renal failure are factors that have been associated with increased risk.[1,8,16,17] The subgroup of patients who have had a previous ischemic stroke is fairly large among unselected AMI populations. Whether or not a previous ischemic stroke is associated with an increased risk of ICH when dual antiplatelet therapy is used is, however, not known. Furthermore, conflicting data exist regarding the

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potential association between lipid levels and statin treatment and risk of ICH.[18–21]

The present study had 3 aims. First, we investigated the incidence, time trends, and predictors of ICH within 1 year of discharge after AMI in a large, fairly unselected population. Second, we investigated the 1-year risk of ICH after AMI compared to a reference group. Third, we studied the impact of a previous ischemic stroke on ICH risk in patients who received different antithrombotic therapies.

Methods

Study Design

Patient data were obtained from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA), which has now become a part of the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). Detailed descriptions of these registries have previously been published.[22,23]

RIKS-HIA is a national registry including all patients with an acute coronary syndrome (ACS) who were admitted to a Swedish hospital coronary care unit (CCU). The registry started in 1995 with 19 hospitals participating. In 1998, coverage increased to 58 hospitals, and by 2007, 74 of 77 hospitals were participating, covering almost 100% of Swedish CCU admissions (detailed information and the complete protocol are available online at http://www.ucr.uu.se). All participating hospitals use standardized and identical criteria for defining AMI.[24,25] Patient data are collected on case record forms that include over 100 variables, including information about patient characteristics, diagnosis, medication, and procedures that were recorded upon admission, during hospital stay, and at discharge. The validity of the data entered is evaluated annually and 94% to 7% conformity between RIKS-HIA records and patient records has been demonstrated.

To identify cases in which ICH occurred after AMI, the RIKS-HIA database was amalgamated with the Swedish National Patient Register (NPR). The NPR has complete national coverage since 1987 and it contains diagnoses at discharge for all hospital stays in Sweden. A full description of the registry has been published previously.[26]

Diagnoses are recorded in the NPR using codes defined by the Swedish International Classification of Disease (ICD) system, which was adapted from the World Health Organization ICD classification system. ICH cases were identified in the registry by searches for the following codes from the 10th Revision of the ICD: subarachnoid hemorrhage (I60); intracerebral hemorrhage (I61); and other ICH (I62). The NPR lacks information about the principal diagnosis for 0.5% to 0.9% of somatic care-related hospitalizations. A diagnosis of stroke or transient ischemic attack (TIA) in the NPR was determined to be correct in 98.6% of the cases, and the proportion of stroke events identified ranges from 84.2% to 98%, as shown by validation studies.[26,27] No published studies have specifically validated the diagnosis of ICH in the NPR; however, the validity is expected to be at least as good as that of the diagnosis of ischemic stroke, because the diagnosis of ICH can only be made after a positive computed tomography scan, magnetic resonance tomography scan, or at autopsy.

A total of 202 366 patients were added to the RIKS-HIA registry between 1998 and 2010. To study ICH predictors and time trends after discharge, we excluded all patients who had died or who had an ICH during their hospital stay, resulting in a set of 187 671 patients with an ICH diagnosis and follow-up through December 31, 2010. After exclusion of patients with extreme values (creatinine <30 or over >1500 μmol/L, age <18 years), a database of 187 386 patients remained. To compare the incidence of ICH in the study group with that in a group representative of the general Swedish population, we used a reference population that had previously been obtained from Statistics Sweden. The reference subjects were sampled with a similar yearly distribution from 1998 to 2009 as the AMI cases and were linked to the NPR using the same algorithm as that used for the study population. Subjects with a previous MI were excluded from the reference group. AMI patients were matched with references by both age (exact in years) and sex, resulting in 147 475 matched pairs. Follow-up for a diagnosis of ICH was performed until December 31, 2010.

All patients were informed of their participation before data were entered in RIKS-HIA and they could request to be excluded. The National Board of Health and Welfare and the Swedish Data Inspection Board approved the registry. The regional ethics committee approved the merging of registries.

Statistical Analysis

Clinical characteristics and medications at discharge were extracted from the amalgamated database. Data for patients with and without ICH were summarized as means or percentages and were tested for differences using a t test or chi-square test, as appropriate. In order to study trends over time for each of the different variables, the study period was divided into 6 time periods preceding the analyses, as follows: 1998–2000; 2001–2002; 2003–2004; 2005–2006; 2007–2008; and 2009–2010.

The technique by Kaplan–Meier for estimating survival functions was used to estimate the cumulative incidence, hereafter called cumulative incidence. For group comparisons, the log-rank test was used. Cumulative incidence of ICH

within 1-year postdischarge was calculated for each sub-period, and these incidences were then used to study changes over time. The same technique was used to assess the cumulative incidence of ICH in the reference population and compare incidence between the cases and references.

Cox proportional hazards model regression analysis was used to assess uni- and multivariate predictors of risk. For our multivariate model, we used previously established predictors of hemorrhagic stroke risk. Additional candidate variables were selected based on whether they predicted a significantly increased or decreased risk in our univariate Cox analysis. Collection of some variables (ie, body mass index [BMI], blood pressure, serum lipids, and kidney function) was not compulsory during the first years of the RIKS-HIA. Therefore, to obtain a fairly recent and complete data set, we did not include data before 2003 in the regression analyses. Of 111 749 patients, 107 431 were included in the final multivariate model that included variables with >90% valid cases. We used the same Cox model to investigate whether a previous ischemic stroke affected risk for ICH in subgroups with different antithrombotic treatment regimes. The proportionality assumption for appropriate use of Cox proportional hazards regression was examined using a time varying interaction.

Statistical analyses were performed using SPSS (version 22.0; IBM Corp, Armonk, NY) and SAS software (version 9.4; SAS Institute Inc, Cary, NC). A *P* value less than 0.05 was considered significant.

Results

Patient Characteristics, Incidence, and Time Trends

An overview of the different patient groups and study periods is depicted in Figure 1.

The baseline characteristics of the 187 386 patients who were discharged after AMI are shown in Table 1, grouped by subsequent occurrence of ICH. A total of 590 patients suffered an ICH within 1 year postdischarge (0.32%; 95% confidence interval [CI], 0.30–0.34). According to Kaplan–Meier analysis, this corresponds to a cumulative incidence of 0.35% (95% CI, 0.32–0.38). Mean age in the matched groups of AMI patients and reference subjects was 71.9 years. The patients with an ICH were significantly older (mean of 75 vs 70 years; *P*<0.001), with increased history of previous hemorrhagic stroke (7.5% vs 1.2%; *P*<0.001) and ischemic stroke (17.7% vs 7.9%; *P*<0.001). The patients in the ICH
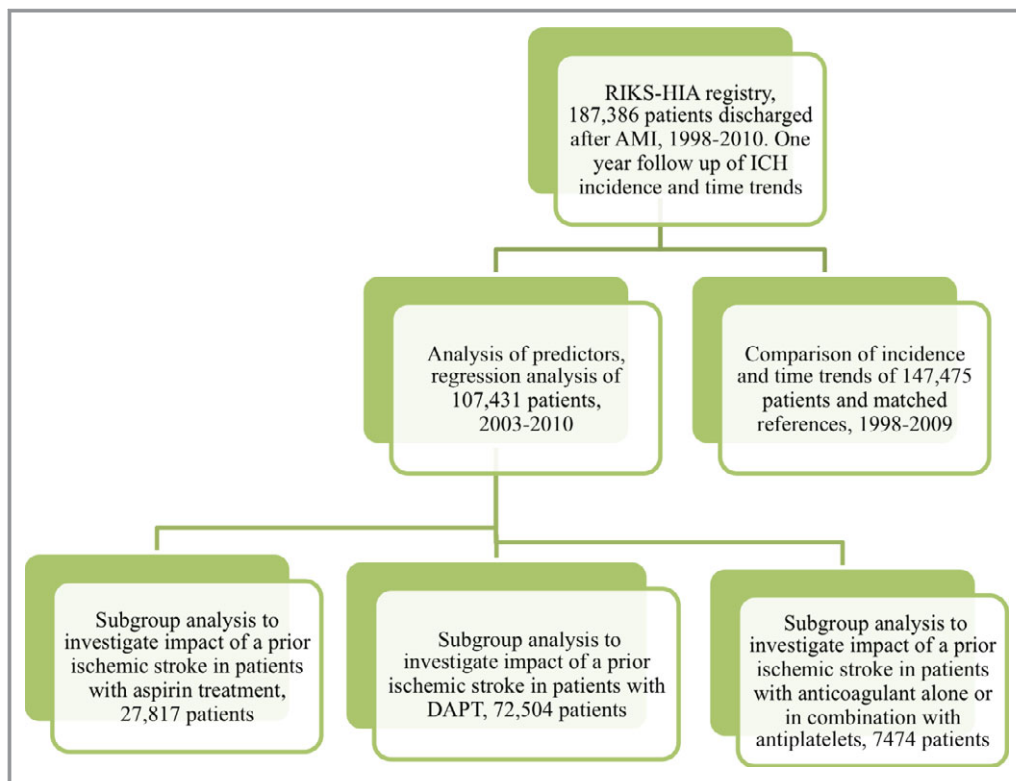

Figure 1. Overview description of the different patient groups included in this analysis. AMI indicates acute myocardial infarction; DAPT, dual antiplatelet therapy; ICH, intracranial hemorrhage; RIKS-HIA, Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admissions.

Table 1. Baseline Characteristics of 187 386 Patients With AMI Who Were Discharged Between 1998 and 2010, Separated According to the Occurrence of ICH Within 1 Year of Discharge

	No ICH (n=186 796)	ICH (n=590)	*P* Value
Demography			
Age, mean, y	70	75	<0.001
Female sex, %	35.5 (n=67 033)	34.1 (n=201)	0.358
Weight, mean kg	78	75	<0.001
Risk factors			
Previous diabetes mellitus, %	19.4 (n=36 175)	24.9 (n=147)	0.001
Previous hypertension, %	44.5 (n=83 117)	56.4 (n=333)	<0.001
Previous atrial fibrillation, %	12.8 (n=23 341)	22.1 (n=127)	<0.001
Smoking history, %	53.7 (n=91 650)	55.7 (n=287)	0.354
Previous cardiovascular disease			
Previous myocardial infarction, %	14.6 (n=27 252)	19.8 (n=117)	<0.001
Previous heart failure, %	10.7 (n=20 019)	16.3 (n=96)	<0.001
Previous ischemic stroke, %	7.4 (n=13 786)	16.4 (n=97)	<0.001
Previous hemorrhagic stroke, %	1.2 (n=2180)	7.5 (n=44)	<0.001
Medication on discharge			
Aspirin, %	88.9 (n=164 271)	81.2 (n=474)	<0.001
P2Y12 inhibitors, %	48.7 (n=89 746)	41 (n=239)	<0.001
Oral anticoagulants, %	7.5 (n=13 727)	11.7 (n=68)	<0.001
Beta-blockers, %	86.3 (n=159 277)	84.7 (n=494)	0.279
ACE-inhibitors/ARB, %	56.3 (n=105 087)	61.4 (n=362)	0.013
Statins, %	67 (n=123 177)	57.1 (n=331)	<0.001
Characters on presentation			
STEMI, %	34 (n=62 189)	29.2 (n=169)	<0.001
NSTEMI, %	66 (n=120 827)	70.8 (n=410)	<0.001
Systolic BP, mean mm Hg	147	147	0.791
P-glucose, mmol/L	8	8	0.724

ACE indicates angiotensin converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ICH, intracranial hemorrhage; n indicates number of cases; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

group also had a higher prevalence of diabetes (24.9% vs 19.4%; *P*<0.001), atrial fibrillation (22.1% vs 12.9%; *P*<0.001), and previous cardiac failure (16.3% vs 10.7%; *P*<0.001). In addition, ICH patients also had significantly lower weight (75 vs 78 kg; *P*<0.001). Sex ratio, smoking history, and systolic blood pressure did not differ significantly between groups.

The baseline characteristics of the population, divided into the 6 consecutive time periods, are shown in Table S1.

Table 2 shows medications being taken at discharge, separated by the 6 consecutive time periods from 1998 to 2010. Over time, there was a rapid increase in the use of P2Y12 inhibitors, in most cases clopidogrel in addition to aspirin. The use of statins, angiotensin converting enzyme

(ACE) inhibitor/angiotensin receptor blocker (ARB), and beta-blockers also increased over the time periods studied.

The 1-year cumulative incidence, as determined by Kaplan–Meier analysis, did not change significantly over time (Figure 2): 0.29% from 1998 to 2000; 0.36% from 2001 to 2002; 0.39% from 2003 to 2004; 0.32% from 2005 to 2006; 0.37% from 2007 to 2008; and 0.37% from 2009 to 2010 (*P*=0.2).

The 1-year cumulative incidence of ICH in the AMI patients and matched reference subjects was 0.39% and 0.18% (*P*<0.001), respectively (Figure 3). The corresponding incidences at 3 years were 0.92% and 0.57% (*P*<0.001) and at 5 years were 1.56% and 0.95%, (*P*<0.001), respectively. The 1-year cumulative incidence in the matched reference subjects did not change over time.

Table 2. Medication at Discharge, Stratified by Time Period and Occurrence of ICH Within 1 Year of Discharge

ICH	1998–2000		2001–2002		2003–2004		2005–2006		2007–2008		2009–2010	
	No ICH N=38 291	ICH n=104	No ICH n=29 453	ICH n=98	No ICH n=29 877	ICH n=110	No ICH n=29 498	ICH n=89	No ICH n=30 694	ICH n=108	No ICH n=28 983	ICH N=81
Oral anticoagulants, %	9.8 n=3645	12.7 n=13	8.4 n=2378	8.2 n=8	7.1 n=2078	9.5 n=10	6 n=1759	10.2 n=9	6.4 n=1948	15.7 n=17	6.7 n=1920	13.8 n=11
Aspirin, %	85.5 n=32 065	76.7 n=79	84.7 n=24 357	77.6 n=76	87.5 n=25 804	80.4 n=86	90.8 n=26 728	84.1 n=74	92.4 n=28 334	78.7 n=85	93.3 n=26 990	92.5 n=74
P2Y12 inhibitors, %	6.3 n=2366	8.7 n=9	25.6 n=7343	15.3 n=15	50.2 n=14 725	43.4 n=46	67.1 n=19 612	67 n=59	74.2 n=22 648	50 n=54	79.9 n=23 054	70 n=56
Statins, %	39.6 n=14 722	26.5 n=27	57 n=16 231	39.2 n=38	67 n=19 656	64.8 n=68	76.1 n=22 392	68.2 n=60	82.7 n=25 340	76.9 n=83	85.9 n=24 841	68.8 n=55
Beta-blockers, %	80.9 n=30 320	73.8 n=76	84.9 n=24 389	86.7 n=85	86.8 n=25 543	81.1 n=86	87.7 n=25 821	87.5 n=77	89.2 n=27 353	92.6 n=100	89.4 n=25 860	87.5 n=70
ACE/ARB blockers, %	39.4 n=15 096	49 n=51	46.3 n=13 649	49 n=48	52.1 n=15 559	58.2 n=64	61.2 n=18 055	64 n=57	69.1 n=21 198	75 n=81	74.3 n=21 535	75.3 n=61

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; ICH, intracranial hemorrhage; n, number of cases.
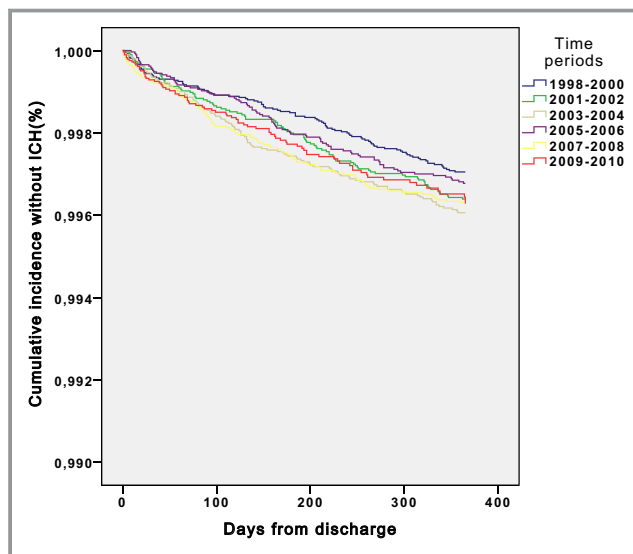

Figure 2. Cumulative incidence, estimated using Kaplan–Meier, without ICH 1 year after hospital discharge after AMI, stratified by time period. AMI indicates acute myocardial infarction; ICH, intracranial hemorrhage.

Predictors of Risk

The univariate analysis of predictors is presented in Table S2. Table 3 shows the multivariate Cox regression model. More-advanced age (hazard ratio [HR], 1.14; 95% CI, 1.13–1.15; $P<0.001$), for a 5 year change, previous ischemic stroke (HR, 1.52; 95% CI, 1.11–2.08; $P=0.010$), or hemorrhagic stroke (HR, 3.58; 95% CI, 2.22–5.80; $P<0.001$), and estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73 m^2 (HR, 1.28; 95% CI, 1.00–1.63; $P=0.049$) were significantly associated with an increased 1-year risk of ICH in the adjusted analysis, whereas female sex (HR, 0.78; 95% CI, 0.62–0.98; $P=0.030$) was associated with a decreased risk. Previous hypertension was also found to be of some importance (HR, 1.31; 95% CI, 1.10–1.56; $P=0.058$). No violations to the assumption of proportional risks could be detected ($P=0.493$).

None of the medications was significantly associated with a change in the risk of ICH. Table 4 shows the unadjusted occurrence of ICH correlated to different antithrombotic treatments (520 events, with 70 events that occurred in patients without treatment), stratified by previous occurrence of ischemic stroke. In the analyses concerning the association between clinical variables and ICH, the different antithrombotic treatments were analyzed separately according to the Methods section. In the Cox model, ischemic stroke was not found to be associated with an increased risk of ICH in patients who were treated either with aspirin only (HR, 1.06; 95% CI, 0.57–1.97; $P=0.846$) or with aspirin combined with clopidogrel (HR, 1.52; 95% CI, 0.97–2.37; $P=0.066$) in analysis
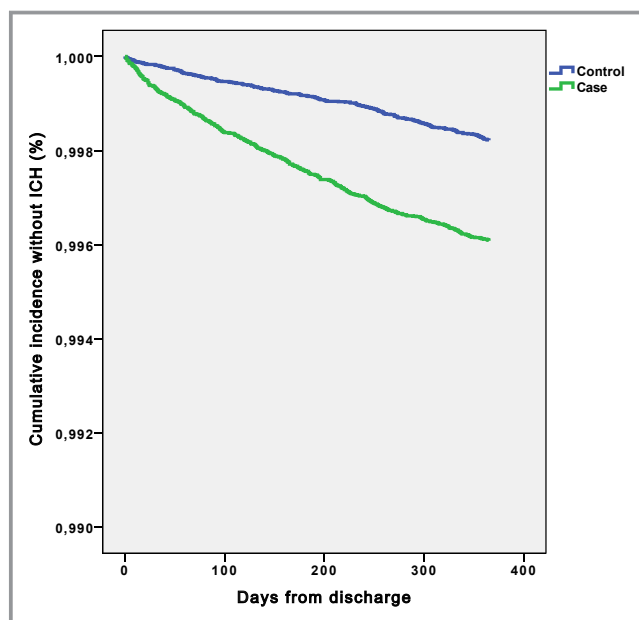
Figure 3. Cumulative incidence, estimated using Kaplan–Meier, without ICH 1 year after hospital discharge after AMI, compared with a matched reference group. AMI indicates acute myocardial infarction; ICH, intracranial hemorrhage.

of 104 and 183 ICH events in these 2 groups, respectively. When an anticoagulant was used (either alone or in combi-

Table 3. Predictors of ICH After AMI in a Multivariate Cox Regression Model, 1-Year Follow-up

Predictor of Hazard	Hazard Ratio (95% CI)	P Value
Age, 1 year increase	1.03 (1.01–1.04)	<0.001
Female sex	0.78 (0.62–0.98)	0.030
Previous hemorrhagic stroke	3.58 (2.22–5.80)	<0.001
Previous ischemic stroke	1.52 (1.11–2.08)	0.010
Previous hypertension	1.25 (0.99–1.57)	0.058
Previous diabetes mellitus	0.97 (0.74–1.26)	0.801
Previous heart failure	1.02 (0.73–1.43)	0.901
Previous atrial fibrillation	1.24 (0.93–1.65)	0.146
Previous myocardial infarction	1.04 (0.77–1.41)	0.802
STEMI	1.03 (0.81–1.31)	0.820
GFR <60 mL/min	1.28 (1.00–1.63)	0.049
Anticoagulant at discharge	1.27 (0.86–1.89)	0.230
Aspirin at discharge	0.72 (0.51–1.01)	0.059
P2Y12 at discharge	0.87 (0.68–1.12)	0.277
ACE/ARB at discharge	1.20 (0.94–1.52)	0.140
Beta-blocker at discharge	1.10 (0.79–1.53)	0.580
Statin at discharge	0.84 (0.65–1.10)	0.204

ACE indicates angiotensin converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; ICH, intracranial hemorrhage; STEMI, ST elevation myocardial infarction.

Table 4. Proportion of Patients With an ICH Within 1 Year of Discharge, Listed by Type of Antithrombotic Treatment and Stratified by Occurrence of Previous Ischemic Stroke

	ICH and Previous Stroke (n=86)	ICH and No Previous Stroke (n=434)
Aspirin	0.61% (36/5754)	0.29% (202/69 288)
P2Y12 inhibitor	0.45% (2/446)	0.30% (12/3989)
DAPT	0.61% (27/4429)	0.22% (173/77 840)
Anticoagulant alone or with antiplatelet therapy	1.04% (21/2021)	0.40% (47/11 774)

DAPT indicates dual antiplatelet therapy; ICH, intracranial hemorrhage; n, number of cases.

nation with antiplatelet therapy), a previous ischemic stroke was associated with an increased risk of ICH (HR, 2.26; 95% CI, 1.14–4.47; *P*=0.019), in analysis of 47 ICH events (Tables S3 through S5).

Discussion

After an AMI, the incidence of ICH within 1 year of discharge was 0.35% (95% CI, 0.32–0.38). This estimate is based on analysis of a large and fairly unselected population of 187 386 AMI patients and 590 ICH events, which is, by far, the largest data set published to date. The incidence of ICH did not change significantly over the 13-year period from 1998 to 2010. The 1-year cumulative incidence in age- and sex-matched reference subjects sampled from the general Swedish population, at 0.18% (95% CI, 0.16–0.20), was significantly lower than the incidence in AMI patients and did not change over time.

Our analysis confirmed that age, decreased eGFR, previous ischemic stroke, and previous hemorrhagic stroke, in particular, are each associated with an increased risk of ICH. None of the medications included in the analysis were associated with a significant change in ICH risk, despite the large data set and despite there having been large changes in the use of different medical therapies over the time period studied. In patients treated with single or dual antiplatelet therapy, previous ischemic stroke was not associated with an increased risk of ICH; however, increased risk was observed if anticoagulant therapy was used.

The use of P2Y12 inhibitors, which increased from <10% at the beginning of the study period to >70% in the end, was not associated with increased incidence of ICH. Good clinical judgment when prescribing combined antiplatelet therapy may have been of importance for this result. Clinical trials have also demonstrated the safety of clopidogrel with respect to ICH risk. In the CURE (Clopidogrel in Unstable Angina to

Prevent Recurrent Events) trial, combined therapy with clopidogrel and aspirin was found not to increase the risk of life-threatening bleeding or hemorrhagic stroke compared to aspirin alone (2.2% vs 1.8% and 0.1% vs 0.1%, respectively).[28] Similarly, in the COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction) trial, inclusion of clopidogrel with aspirin was shown not to increase the risk of hemorrhagic stroke at 28 days compared to aspirin alone (0.2% vs 0.2%).[29]

Drugs comprising the new generation of P2Y12 inhibitors, ticagrelor and prasugrel, seem to be fairly safe with respect to ICH risk, based on data from the PLATO (a study of PLATelet inhibition and Patient Outcomes) and TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) trials, except for prasugrel treatment in some high-risk groups.[13,30–32] However, because of the small number of ICH events included in these analyses, the data are not conclusive. Analyses of data from large, unselected populations of ACS patients are necessary for confirmation of the safety of these drugs.

To investigate the impact of a previous ischemic stroke on the risk of subsequent ICH in ACS patients who were treated with different antithrombotic therapies, we analyzed the subgroups of patients treated with aspirin alone, with aspirin combined with clopidogrel, and with anticoagulant therapy in any combination with aspirin and/or clopidogrel. In these adjusted analyses, we found that a previous ischemic stroke was not a significant risk factor for ICH in groups receiving single or dual antiplatelet therapy (based on 104 and 183 ICH events in the analyses, respectively). However, in the DAPT group, we observed a trend toward an increased risk (P=0.07). In the group treated with anticoagulants, we found that a history of previous ischemic stroke more than doubled the risk of ICH (Tables S3 through S5). Our observations concerning the unadjusted risk of ICH associated with dual antiplatelet therapy (Table 4), with or without a previous ischemic stroke, correspond well with the PLATO trial data from subgroup analysis of patients with a previous ischemic stroke or TIA. We have not found any published adjusted analysis focused on the impact of a previous ischemic stroke among DAPT-treated patients.

Results from the MATCH (Management of Atherothrombosis with Clopidogrel in High-risk patients) trial, which included patients with a recent ischemic stroke or TIA, indicate that the length of the delay between the ischemic event and the start of DAPT may be an important factor. When DAPT was initiated within 1 month of the ischemic event in the majority of the patients, the risk of intracranial hemorrhage increased significantly.[33] Furthermore, in a similar group of patients, anticoagulant treatment was found to be associated with an increase in the risk of major hemorrhage.[34] Future registry studies of large groups of ACS patients with information about the time of onset of previous cerebrovascular events may

shed further light on the relationship between the timing of antithrombotic treatment and ICH risk.

A study using the REACH (Reduction of Atherothrombosis for Continued Health) registry includes analysis of data from patients with stable coronary artery disease (CAD).[9] The risk of nonfatal cerebral hemorrhage was observed to be particularly high in patients with CAD and a history of previous cerebrovascular disease who were receiving DAPT (HR, 5.2; 95% CI, 1.2–21.9). Unexpectedly, anticoagulant therapy (with or without antiplatelet therapy) did not result in increased risk. However, this result is based on very few cases (8 patients with ICH were included in the DAPT group). This study also found an increased risk of nonfatal cerebral hemorrhage in patients with CAD and a history of ischemic stroke within the previous year (adjusted HR, 3.9; 95% CI, 1.8–8.3; P<0.001), although no increased risk if the stroke occurred more than 1 year previously (HR, 1.0; 95% CI, 0.4–2.6; P=0.95). Again, however, this result is based on fewer than 10 events and is therefore inconclusive.

We did not find any difference in the 1-year ICH risk between the different time periods during the course of the study. This is reassuring, considering the extensive changes in medications that we observed over the study period. There are no similar trend data to use for comparison, but our results seem robust.

Consistent with previous studies, a history of previous hemorrhagic stroke was associated with the highest risk for ICH. A history of ischemic stroke, advanced age, and decreased renal function (GFR <60 mL/min) were also significant factors, which is also consistent with findings from earlier studies.[5,8,9] Hypertension is an important risk factor for ICH. A history of hypertension was close to reach significance (P=0.058) in our study. A lack in the database of actual blood pressure values could possibly explain part of this modest association. Possibly also, good blood pressure control in these post-AMI patients weakened the importance of a previous diagnosis of hypertension. We found that female gender was associated with decreased risk of ICH, in contrast to a previously report.[1] One possible explanation for this discrepancy is that we did not include patients with ICH during the hospital stay, which is often associated with thrombolytic treatment. Furthermore, our study included a fairly unselected cohort of AMI patients.[17,35,36]

We did not find statin treatment to be associated with any increased risk of ICH. The hypothesis that the 2 are related, based on the SPARCLE (Stroke Prevention by Aggressive Reduction of Cholesterol Levels) trial, does not seem to be valid, at least in our AMI patient population.[19,21]

Limitations

The RIKS-HIA data set includes patients with AMI who were hospitalized in CCUs. Therefore, very old patients or patients with extensive comorbidity may not be included.[23] This might

lead to an underestimation of the ICH rate because, based on previous studies and our results, older patients are expected to have a higher risk of ICH than younger patients.

In our analyses, there was a low number of valid cases to include for the examination of some of the variables, especially in the early time period during which some of the variables were yet to be included in the RIKS-HIA database. This was true for heart rate, blood pressure, P-glucose, and ARB, early in the study. It was an issue throughout the entire period with respect to BMI, P-cholesterol, and P-low-density lipoprotein. Furthermore, when trying to establish independent risk factors with multivariate analysis, there is always the risk of confounding factors that are not taken into account because they were not recorded as variables in the database.

Concerning the risk associated with antithrombotic therapy over the long term, we had no information regarding the intended duration of therapy or the actual persistence of patients' therapy. During the study period, the recommended length of DAPT was 3 to 12 months after the AMI.

Conclusions

Despite the marked increase in use of dual antiplatelet treatment over the course of the study, the incidence of ICH within 1 year of discharge after AMI was stable, at ≈0.35%, which is approximately 2 times higher than the incidence measured in a matched reference population. Advanced age, decreased renal function, previous ischemic stroke, and, most important, previous hemorrhagic stroke are all predictors of increased ICH risk, and therefore they need to be taken into account when making decisions regarding antithrombotic therapy upon hospital discharge. A previous ischemic stroke is associated with a higher risk of ICH when anticoagulant therapy, and possibly dual antiplatelet therapy, is used. Further research is needed to clarify the impact on ICH risk of the length of delay between onset of stroke and initiation of antithrombotic therapy.

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Disclosures

None.

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