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Hemorrhagic stroke the first 30 days after an acute myocardial infarction: Incidence, time trends and predictors of risk

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ABSTRACT

Background/objectives: Hemorrhagic stroke is a rare but serious complication after an acute myocardial infarction (AMI). The aims of our study were to establish the incidence, time trends and predictors of risk for hemorrhagic stroke within 30 days after an AMI in 1998–2008.
Methods: We collected data from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA). All patients with a myocardial infarction 1998–2008 were included, n = 173,233. The data was merged with the National Patient Register in order to identify patients suffering a hemorrhagic stroke. To identify predictors of risk we used Cox models.
Results: Overall the incidence decreased from 0.2% (n = 94) in 1998–2000 to 0.1% (n = 41) in 2007–2008. In patients with ST-elevation myocardial infarction the corresponding incidences were 0.4% (n = 76) in 1998–2000 and 0.2% (n = 21) in 2007–2008, and after fibrin specific thrombolytic treatment 0.6% and 1.1%, respectively, with a peak of 1.4% during 2003–2004. In total 375 patients (0.22%) suffered a hemorrhagic stroke within 30 days of the AMI. The preferred method of reperfusion changed from thrombolysis to percutaneous coronary intervention (PCI). Older age (hazard ratio (HR) >65- ≤ 75 vs ≤65 years 1.84, 95% confidence interval (CI) 1.38–2.45), thrombolysis (HR 6.84, 95% CI 5.51–8.48), history of hemorrhagic stroke (HR 12.52, CI 8.36–18.78) and prior hypertension (HR 1.52, CI 1.23–1.86) independently predicted hemorrhagic stroke within 30 days.
Conclusions: The rate of hemorrhagic stroke within 30 days of an AMI has decreased by 50% between 1998 and 2008. The main reason is the shift in reperfusion method from thrombolysis to PCI.
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1. Introduction

Hemorrhagic stroke is a relatively rare but very serious complication after an acute myocardial infarction (AMI). Previous research has mainly focused on the risk of intracranial hemorrhage (ICH) and major bleeding, both terms including but not separating hemorrhagic stroke [1–5]. The incidence of ICH ranges from 0.5% to 2.2% in different study populations with a mortality of 60–65% [1–3,5–12]. The incidence of hemorrhagic stroke after thrombolytic treatment of AMI has in general been estimated at between 0.4 and 0.9% with the lowest rates after treatment with streptokinase [7,13,14]. In patients with non ST-elevation myocardial infarction (NSTEMI) the incidence of hemorrhagic stroke has been reported to be 0.06% [12]. The majority of the data originates from clinical trials with patient populations with a fairly modest risk profile. Predictors of ICH including hemorrhagic stroke after AMI differ somewhat between studies. Older age, female sex, lower weight, hypertension, prior cardiovascular event, renal failure, diabetes and recent trauma have all been suggested to be of importance [2,3,5–8,10–12,15–18]. Little is known of time trends for hemorrhagic stroke after AMI, previous research is scarce and has not separated hemorrhagic stroke from other bleeding [4].

Our hypothesis was that, despite a more aggressive antithrombotic treatment, the incidence of hemorrhagic stroke after AMI has decreased due to a change in reperfusion methods, from thrombolysis to primary percutaneous coronary intervention (PCI), and to a change in AMI characteristics. Previous research has been based on relatively few events of hemorrhagic stroke after AMI, due to the rareness of the condition and fairly small study populations. In a global perspective thrombolysis remains the main method of reperfusion [19]. Knowledge about the relationship between different reperfusion methods, including thrombolysis, and hemorrhagic stroke in clinical praxis is therefore of considerable interest.

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The aims of our study were to establish reliable risk estimates, time trends and predictors of risk for hemorrhagic stroke within 30 days after an AMI during the period 1998–2008 by using a large, relatively unselected, Swedish study population.

2. Methods

2.1. Study design

The Register of Information and Knowledge about Swedish Heart Intensive Care Admissions, RIKS-HIA, registers all patients admitted to a coronary care unit (CCU) in Swedish hospitals. It started in 1995 with 19 hospitals, coverage increased to 58 in 1998 and at the end of the study period in 2008, 74 out of 74 hospitals with CCU's participated, covering all Swedish CCU admissions [20,21]. Information regarding the patient history, medications, biochemical markers, procedures during hospitalization and diagnoses is recorded. In total over 100 variables are included [22].

The criteria for AMI are standardized and identical for all participating hospitals. From 1998 to 2001 the World Health Organization definition (WHO) was used [23]. Beginning in late 2001 the criteria set up by the European Society of Cardiology/American College of Cardiology/American Heart Association consensus document were adapted [24,25]. The validity of the entered data is examined yearly and shows 94–97% conformity between the RIKS-HIA data and patient records [21,26]. Full details of the registry have previously been published [21,22]. From this registry we included all patients with a first recording of myocardial infarction between 1 January 1998 and 31 December 2008, 173,233 cases in total. In order to identify patients suffering a hemorrhagic stroke we merged the RIKS-HIA registry with the National Patient Registry, NPR. The NPR includes dates for admission and discharge as well as diagnoses at discharge for all hospital stays in Sweden. We used the WHO definition of hemorrhagic stroke, including intracerebral- and subarachnoid bleeding but excluding subdural and epidural hematomas [27]. The NPR has been validated and a diagnosis of stroke has a positive predictive value of 98.6% [28]. Both registers are based on the entire population in Sweden. There are no criteria for exclusion. The RIKS-HIA registry is sponsored by the Swedish Health Authorities and does not receive any funding from commercial interests. The Regional Ethics Committee approved the merging of registries.

2.2. Statistical analysis

The significance levels of differences in the patient's baseline characteristics were evaluated with the chi square test for categorical variables and the *t*-test for continuous variables. The study period was divided into five time periods (January 1998–December 2000, January 2001–December 2002, January 2003–December 2004, January 2005–December 2006 and January 2007–December 2008), in order to study changes over time. Evaluation of a change in proportions over time was performed by the chi square test. Uni- and multivariable predictors of risks were assessed using Cox proportional hazards regression analysis. For our multivariable model we used previously established predictors of risk for intracranial hemorrhage and hemorrhagic stroke, and added the factors that were significant in our univariable analysis. All statistical analysis was performed using SPSS 20.0 software. A p-value less than 0.05 was considered significant.

3. Results

3.1. Patient characteristics and incidence

Baseline characteristics of the 173,233 patients are shown in Table 1, grouped by the occurrence of hemorrhagic stroke within 30 days of AMI. In total 375 patients (0.22%, 95% confidence interval (CI) 0.20–0.24%) suffered a hemorrhagic stroke. Patients suffering a hemorrhagic stroke were older (mean 73.3 vs. 71.9, $p < 0.001$), more often had a history of hypertension (47.5% vs 38.4% $p < 0.001$), and of hemorrhagic stroke (6.9% vs 0.7% $p < 0.001$) compared with patients without hemorrhagic stroke. Stroke patients tended to have higher systolic blood pressure on admission (149.5 mm Hg vs 145.0 $p = 0.08$) and a lower proportion of diabetes mellitus (15.7% vs 19.3% $p = 0.088$).

Pre-hospital and in-hospital thrombolysis was associated with 41 (1.0%) and 155 (0.7%) hemorrhagic strokes, respectively. Of these, 39/41 and 146/155 occurred in-hospital. In ST-elevation myocardial infarction (STEMI) and NSTEMI patients, 232 (93%) and 97 (77%) hemorrhagic strokes occurred in-hospital, respectively. Overall, 46 strokes occurred within 30 days but after discharge. The mean duration of the hospital stay was 6.3 days (standard deviation 5.2).

During the study period there were 11 events of other intracranial hemorrhages (subdural or epidural) within 30 days after admission. They were not included in the analyses in agreement with our inclusion criterion.

In the overall patient population the 30 day mortality rate was 11.4% in patients with STEMI and 9.2% in NSTEMI patients.

Table 1
Baseline characteristics of 173,233 patients with acute myocardial infarction 1998–2008 according to the 30 day occurrence of hemorrhagic stroke.

		No hemorrhagic stroke n = 172,858	Hemorrhagic stroke n = 375	p-value
Demography				
Age,	≤65 years, %	31.1	21.3	<0.001
	>65 - ≤75 years, %	26.4	34.4	
	>75 years, %	42.4	44.3	
Age (mean)		71.9	73.3	<0.001
Female sex %		36.8 (n = 63,552)	40.5 (n = 152)	0.15
Weight (mean, kg)		77.6	75.5	0.11
Weight	≤65 kg, %	22.2 (n = 17,563)	28.1 (n = 39)	0.26
	>65–≤85 kg, %	51.0 (n = 40,260)	47.5 (n = 66)	
	>85 kg, %	26.8 (n = 21,184)	24.4 (n = 34)	
Risk factors				
Prior diabetes mellitus %		19.3 (n = 33,444)	15.7 (n = 59)	0.09
Prior hypertension %		38.4 (n = 66,460)	47.5 (n = 178)	<0.001
Current smoking %		20.6 (n = 35,665)	17.6 (n = 66)	0.17
Prior cardiovascular disease				
Prior myocardial infarction %		15.8 (n = 27,337)	12.3 (n = 46)	0.07
Prior heart failure %		12.0 (n = 20,686)	10.7 (n = 40)	0.49
Prior ischemic stroke %		8.5 (n = 14,671)	9.6 (n = 36)	0.50
Prior hemorrhagic stroke %		0.7 (n = 1284)	6.9 (n = 26)	<0.001
Medication on admission				
ASA %		37.4 (n = 64,729)	36.5 (n = 137)	0.76
P2Y12 inhibitors %		3.6 (n = 6216)	2.9 (n = 11)	0.60
Oral anticoagulants %		4.7 (n = 8205)	5.6 (n = 21)	0.52
Beta-blockers %		35.9 (n = 61,291)	40.4 (n = 150)	0.11
ACE-inhibitors/ARB %		22.1 (n = 38,128)	22.1 (n = 83)	1.0
Statins %		17.0 (n = 29,040)	15.6 (n = 58)	0.72
Characteristics on presentation				
STEMI %		37.7 (n = 63,526)	66.4 (n = 249)	<0.001
NSTEMI %		62.3 (n = 105,141)	33.6 (n = 126)	<0.001
Systolic BP (mean, mm Hg)		145.1 (n = 76,448)	149.5 (n = 142)	0.08
P-glucose (mmol/l)		8.2 (n = 92,752)	8.1 (n = 191)	0.9

n, number of cases; ASA, acetylsalicylic acid; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; STEMI, ST-elevation myocardial infarction; NSTEMI, no ST-elevation myocardial infarction.

3.2. Time trends

Table 2 and Table 3 display characteristics and treatment of the patients during the five consecutive time periods, respectively. The primary method of reperfusion for patients with ST-elevation myocardial infarction (STEMI) changed from thrombolysis to PCI. In 1998–2000 63.9% of the patients with STEMI received thrombolysis vs 22.3% PCI. The corresponding percentages were 39.0 vs 49.2 and 7.8 vs 73.6 during 2003–2004 and 2007–2008 respectively. The annual rate of thrombolysis versus primary PCI is shown in Table 4. For thrombolysis there was a shift from streptokinase toward fibrin-specific agents. Medication at discharge illustrates the introduction and the rapid increase in the use of clopidogrel, which dominates as a P2Y12 inhibitor. There was also an increased use of statins, beta-blockers and angiotensin converting enzyme (ACE) –inhibitors. In Figs. 1 and 2 trends over time for the proportion of hemorrhagic stroke according to type of myocardial infarction and reperfusion therapy are shown. In patients with STEMI the incidence of hemorrhagic stroke was 0.4% during 1998–2000 (n = 76). The incidence changed over time with a peak of 0.6% (n = 66) during 2003–2004 and decreased to 0.2% (n = 21) during 007–2008 ($p < 0.001$). The NSTEMI patients had a lower risk ($p < 0.001$) and the change over time was not significant ($p = 0.051$). In the thrombolysis group, the incidence of hemorrhagic stroke increased from 0.5%

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