Incidence of stroke and mortality due to stroke after acute coronary syndrome

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Objectives: Stroke is a known complication after myocardial infarction (MI) and it is associated with increased mortality. We aimed to establish the true cumulative incidence of stroke and its subtypes and the associated mortality in a contemporary setting among patients treated for acute coronary syndrome (ACS). *Materials and methods:* A retrospective registry study based on the data of 8,049 consecutive patients treated for ACS in a sole provider of specialized cardiac and neurologic care for a catchment area of over 0.5 million residents between 2007 and 2018. Incident strokes and their subtypes were identified by in-depth review of written hospital records, hospital discharge registry data and causes of death registry data maintained by Statistics Finland up until December 31st 2020. *Results:* During a median follow-up of 5.8 years (IQR 3.2-9.0) 570 ACS patients suffered a stroke. The cumulative incidences of stroke for first week, first month, first year and at thirteen years were: 0.8 %, 1.1 %, 2.2 % and 10.3 %. In long-term, patients with different ACS subtypes had similar cumulative incidence of strokes, although the incidence of in-hospital strokes was highest among myocardial infarction patients. Stroke mortality rate was 32.5 % (n=185/570). The majority (88.8 %) of strokes were ischemic with the proportion being most substantial for in-hospital strokes (95.6 %). *Conclusions:* The risk of stroke among patients treated for ACS and the related mortality are still notable in a contemporary setting. A distinctive majority of strokes following ACS were ischemic especially early on after ACS.

Keywords: Stroke—Myocardial infarction—Acute coronary syndrome—Ischemic stroke—Intracranial haemorrhage

Abbreviations: ACS, acute coronary syndrome; MI, myocardial infarction; ICH, intracranial haemorrhage; AMI, acute myocardial infarction; IS, ischemic stroke; IHS, In-hospital stroke; CE, cardioembolism; LVD, large vessel disease; SVD, small vessel disease; HF, heart failure; AF, atrial fibrillation; UAP, unstable angina pectoris; EHR, electronic health record; ESC, European Society of Cardiology; ACC, American College of Cardiology; TIA, transient ischemic attack; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CT, computed tomography; AFL, atrial flutter; INR, international normalized ratio

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Introduction

Stroke is a known complication after acute coronary syndrome (ACS) and it is associated with increased mortality.[1,2] Especially stroke during the first year after myocardial infarction (MI) and intracranial haemorrhage (ICH) in general are related to increased risk of death.[3–5] Incidence of stroke after acute myocardial infarction (AMI) and the related mortality have decreased during the latest decades mainly due to more accurate secondary prevention and modern medical advances.[3,6,7] Accurate and updated epidemiological information is still ever more important due to the shift in the mean age of ACS patients and emerging therapies for stroke prevention. Especially modern usage of anticoagulation and antithrombotic therapies in secondary prevention could impact the proportion of ICH in stroke incidence compared to the more common ischemic stroke (IS), and thus impact general medical practices.

The incidence of stroke after MI is 0.5-2.1 % during hospitalization and 0.7-2.1 % during 30 days after MI based on observational data from previous decades.[4,5,7–14] The incidence is estimated to remain high especially during the first year, 1.1-4.1 %.[3–14] This heterogeneity in previously published reports may be due to historical shifts, improved secondary prevention of cardiovascular disease and different methodology for defining stroke. Furthermore, many studies have been based only on registry data, which has its limitations. After the first year, stroke risk has been observed to be increased but nearing that of the normal population, although the long-term risk for IS is considered to be elevated even 30 years after MI.[9] Overall mortality is significant among AMI patients, yet suffering a stroke increases it two- to three times.[7,15] Mortality after in-hospital stroke (IHS) is assessed to be 34-44 %, whereas one month mortality is estimated to be 25-34 %.[2,5,7,13]

In stroke with preceding MI, the role of IS is deemed greater (70-95 %) in comparison to ICH (5-29 %).[4,7,8,10,13,16,17] The most common subtype of IS is cardioembolic (CE) stroke, contributing up to 60 % of IHS, whereas a large number (36 %) of IS is still classified as cryptogenic.[5] In comparison, CE accounts for 20.0-25.6 %, large vessel disease (LVD) 23.3-26.0 %, small vessel disease (SVD) 11.8-23.7 % and cryptogenic 20.0 % of ischemic stroke in general.[15,18–23] Complications after MI such as heart failure (HF), left ventricular dysfunction and atrial fibrillation (AF) might lead to cardioembolisms.[9,24] There is a lot of variation in stroke incidence and mortality in past studies and little data on stroke risk following ACS instead of MI.

The aims of this retrospective registry study was to determine the true incidence and related mortality of stroke after ACS, estimate possible differences in stroke incidence between patients with unstable angina pectoris (UAP) and AMI, define the portion of ischemic stroke and its subtypes using in-depth review of written hospital records and causes of death data in a contemporary patient cohort. This data is useful when considering possibilities for improving prevention of stroke in ACS patient group.

Methods

Study population

This study is based on the data of 8,049 consecutive patients undergoing invasive evaluation for ACS in Tampere Heart Hospital and living in the region of Pirkanmaa Finland between January 1st 2007 and 31st of December 2018. Tays Heart Hospital is the sole provider of acute care in cardiology for patients suffering from ACS in the region of Pirkanmaa. Only the first ACS for each patient was recorded as a baseline event even if multiple ACS incidents were recorded during the observation period. Additional 2,260 patients permanently residing outside Pirkanmaa hospital district were also treated for ACS in the study centre but they were excluded from the analysis due to missing follow-up data for possible hospitalizations for stroke. The follow-up for incident strokes lasted from the first hospitalization (beginning from January 1st 2007) until 31st of December 2020.

This study aimed to evaluate only patients diagnosed invasively by a coronary angiography (which gave accurate diagnosis). However, to provide additional supporting data, the cumulative incidence of stroke among a subpopulation of patients treated and diagnosed conservatively for MI in years 2015 and 2016 (follow-up until the end of 2020) is also presented as secondary data.[25] These patients represent less than 10 % of all ACS patients. The reason for adopting a non-invasive strategy was usually based on poor overall prognosis.

Baseline phenotype data collection

Data was retrospectively collected from the MADDEC (Mass Data in Detection and Prevention of Serious Adverse Events in Cardiovascular Disease) database: a project launched 2016, which retrospectively combines data collected from 1990s onwards from different electronic databases used in specialized health care to create a comprehensive study registry focusing on high-risk cardiologic patients treated at Tays Heart Hospital.[26] This database combines electronic health record (EHR) data with prospectively collected and actively maintained KARDIO database data (data collection performed by physicians and nurses during the treatment of patients) and data gathered retrospectively by physicians using full-disclosure review of written health care records.[27] ACS and its subtypes were defined by European Society of Cardiology (ESC) and American College of Cardiology (ACC) criteria.[28,29]

Follow-up and end-point definitions

Incident strokes during follow-up were searched by a full disclosure review of all written patient records of specialized health care and complemented by a revision of causes of death data. Stroke was diagnosed using the International Classification of Diseases-Tenth Revision (I63 and I64) and the subtypes were classified based on the written medical reports made by neurologists following hospitalization. All incident strokes (up to three strokes for some patients) following ACS were recorded, but only the first incidental stroke was considered to contribute to the cumulative incidence of stroke. Patients who suffered only a transient ischemic attack (TIA), traumatic bleeding in the brain, other condition such as Moyamoya disease or brain cancer causing ICH were excluded from the analyses.

Due to the centralized structure of the health care in Finland, Tampere University Hospital is the only site providing care for neurological diseases in the region of Pirkanmaa. This combined with the fact that all deaths of those residing in Finland and of Finnish citizens residing abroad (causes of death data) are registered by Statistics Finland, ensured 100% coverage for the screening of incident strokes during follow-up.[30] Death due to stroke was defined by either the patient dying of stroke during the hospital stay for stroke or having a stroke diagnosis as a leading or secondary cause of death in the mortality register when the information of the hospitalization was not available (patient died before receiving medical treatment for stroke in specialized health care). Patients dying of stroke without hospitalization (n=33) had no specific identifiable incident date for stroke in the death certificate and therefore the time of death was used as the event time.

A full disclosure review of all written patient records was performed indicating 570 of 8,049 patients suffering a stroke after ACS. 33 patients with stroke as a cause of death without preceding hospitalization were retrieved from the mortality register.

Statistical analysis

Comparisons between different patient groups were performed by normal Chi-square testing for categorical variables, Student's t-test or ANOVA for normally distributed continuous variables and Kruskall-Wallis or Mann-Whitney U test of non-normally distributed continuous variables. Cumulative Incidence of stroke during the entire follow-up is modelled using subdistribution hazard models, which account for competing risk due to overall mortality. Comparisons between incidence rates between different categories is performed by log-rank test for unadjusted incidence. The analyses were perfomed by SPSS software (version 27, IBM) and by R software (version 4.1.3) (packages survival and cmprisk).

Results

Demographics of the study population

The mean age of the study population (n=8,049) was 68.7 years (± 11.8 SD) during hospitalization of ACS and 65.8 % (n=5,295) of patients were men. ACS was distributed as follows: UAP, 19.5 % (n=1,568), non-ST-elevation myocardial infarction (NSTEMI), 48.2 % (n=3,882) and ST-elevation myocardial infarction (STEMI), 32.3 % (n=2,599), the portion of MI thus being 80.5 % (n=6481). The majority, 64.6 % (n=5,197), of patients were treated with percutaneous coronary intervention (PCI), 9.0 % (n=728) with coronary artery bypass grafting (CABG), 1.2 % (n=100) with both procedures and 25.1 % (n=2,024) were treated conservatively. Over 85 % of STEMI patients were treated with primary PCI. The baseline characteristics of the study population are provided in Table 1.

The overall incidence of stroke during follow-up and by ACS subtypes

The median follow-up time was 5.8 years (IQR 3.2-9.0) during which 570 of 8,049 ACS patients suffered a stroke. Most patients (94.2 %, n=537/570) were hospitalized for stroke whereas 5.8 % (n=33) patients died of stroke before hospitalization. These included patients dying of stroke at home or at retirement facilities. Primary brain imaging results were available for 96.8 % (computed tomography (CT) scan n=504/570) patients and autopsies were performed for 33 patients without imaging. For 33 patients the diagnosis of stroke was based on a clinical diagnosis without further tests.

The cumulative incidence of stroke during the entire span of the follow-up time (up to fourteen years) exceeded ten percent (Fig. 1 A). The incidence of stroke increased rapidly during the first month of the follow-up and reached a steady rate thereafter as presented in Fig. 1 B.

The incidence of stroke was significantly different between patients treated for UAP, NSTEMI and STEMI only for in-hospital stroke (0-7 days). Incidence was highest for NSTEMI (1.1 %) and STEMI (0.7 %) compared to UAP (0.3 %), p=0.009. The comparison between ACS groups at any other time point or between UAP and MI (STEMI and NSTEMI) at any point in time did not reach statistical significance. One year risk was 2.4 % for NSTEMI, 2.2 % for STEMI and 1.6 % for UAP (p=0.168). Stroke incidence by different ACS subtypes can be seen in Fig. 2. Additionally, incidence of stroke by different age categories is presented in Fig. 3.

Different stroke subtypes and stroke rate during various time intervals

88.9 % (n=506) of incident strokes were ischemic and 11.2 % (n=64) haemorrhagic. The difference between ICH and IS incidence can be seen in Fig. 4. IHS risk was 0.8 % (n=68), of which 95.6 % were IS and one month overall

Table 1. *Baseline characteristics at the index event (recorded during hospitalization for acute coronary syndrome).*

	All patients (N = 8,049)
Age, years (SD)	68.7 ± 11.8
Sex, male % (N)	65.8 (5,295)
Body-mass index (kg/m^2)	28.1 ± 5.2
Diabetes (any) % (N)	26.0 (2,090)
Hypertension % (N)	61.6 (4,958)
Dyslipidemia % (N)	58.3 (4,697)
Chronic kidney disease % (N)	7.1 (568)
Valvular heart disease (any) % (N)	6.3 (509)
Heart failure % (N)*	32.6 (2624)
Atrial fibrillation or flutter % (N)**	21.1 (1,700)
Peripheral artery disease % (N)	8.5 (681)
Cancer % (N)***	9.1 (731)
Dementia % (N)	2.8 (223)
Smoking % (N)	44.3 (3565)
Previous stroke or transient ischemic attack % (N)	8.9 (713)
Previous myocardial infarction % (N)	17.5 (1,409)
Previous PCI % (N)	10.5 (846)
Previous CABG % (N)	8.0 (647)
Left ventricular ejection fraction % (SD)	51.5 ± 11.9
Status during admission	
Hb (g/l) (SD)	130.2 ± 16.0
Creatinine (μmol/l) (SD)	88.8 ± 60.8
Cardiac Arrest during hospitalization % (N)	7.4% (597)
Killip classification for heart failure	
I	77.6 (6239)
II	14.1 (1132)
III	6.1 (490)
IV	2.2 (176)
Acute coronary syndrome subtypes	
Unstable angina pectoris % (N)	19.5 (1,568)
Non-ST-elevation myocardial infarction % (N)	48.2 (3,882)
ST-elevation myocardial infarction % (N)	32.3 (2,599)
Treatment modality	
PCI % (N)	64.6 (5,197)
CABG % (N)	9.0 (728)
PCI or CABG % (N)	1.2 (100)
Conservative % (N)	25.1 (2,024)

*History of heart failure, Killip class II or greater during hospitalization or left ventricular ejection fraction below 50%.
**History of atrial fibrillation or flutter or atrial fibrillation or flutter observed during hospitalization.
***Data missing in 5% for cancer and <1% for all other variables. Percentages are valid percentages. Continuous variables are mean and ± is standard deviation. Categorical values are frequencies.Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

stroke risk was 1.1 % (n=88, 93.2 % IS). Incidence during the first year was 2.2 %, and thereafter it slowly increased an estimated 0.7 % per year up to 10.3 % at 13 years of follow-up. The cumulative incidence of stroke with subtypes for different time periods is presented in Table 2.

The distribution of ischemic stroke subtypes was the following: CE with AF or atrial flutter (AFL) 19.0 % (n=96), SVD 13.0 % (n=66), CE without AF/AFL 11.1 % (n=56), LVD 6.3 % (n=32), unspecified 0.8 % (n=4) and cryptogenic stroke 49.8 % (n=252). The portion of IS due to cardioembolism without atrial fibrillation or flutter was significant especially in IHS (32.3 %) and during the first month (31.7 %) and first year (21.7 %). Afterwards, it slowly decreased to the level of 9.8 % during the follow-up time whereas CE with AF or AFL slowly increased after the first month (11.0 %) to 18.8 % during thirteen years follow-up (Table 2). Yet, there was no statistical significance for cardioembolic stroke risk (with or without AF/AFL) at one week, month or year when comparing UAP and MI patient groups. The CE stroke incidence was thus similar regardless whether a patient suffered an UAP or MI.

Interestingly, when looking into all cardioembolic strokes, anticoagulant treatment was functional only for 22.4 % of patients. It was not used in 42.1 % of cases, it was unclear or unmentioned in 21.1 % instances and

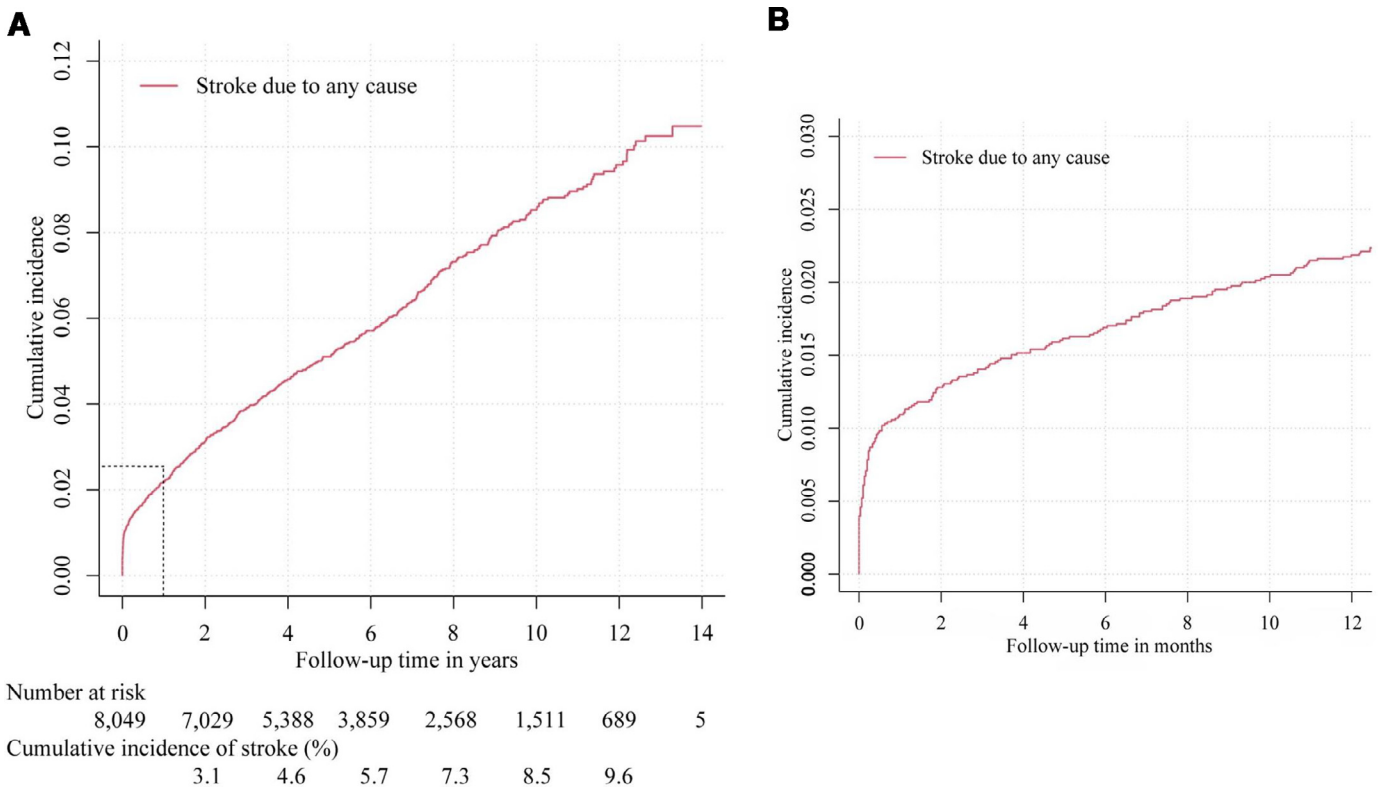

Fig. 1. *(A) Cumulative incidence function for stroke during the whole follow-up time. Dashed line marks the 12 months incidence presented in Fig. 1 B. (B) Cumulative incidence function for stroke during the first 12 months.*

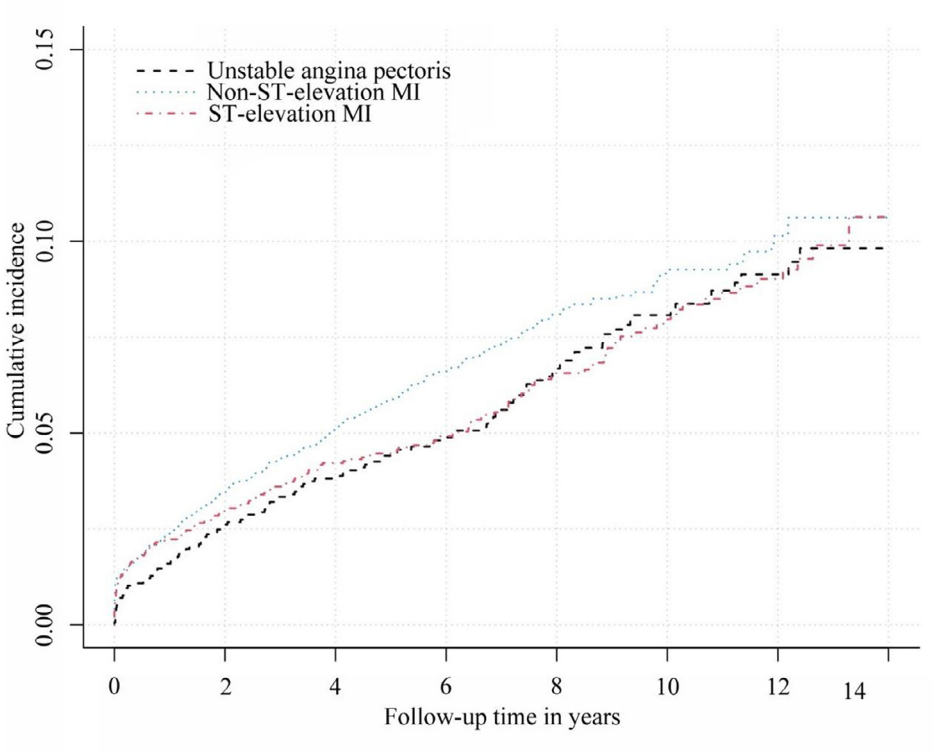

Fig. 2. *Cumulative incidence function for stroke with different ACS subtypes.*
MI, myocardial infarction.

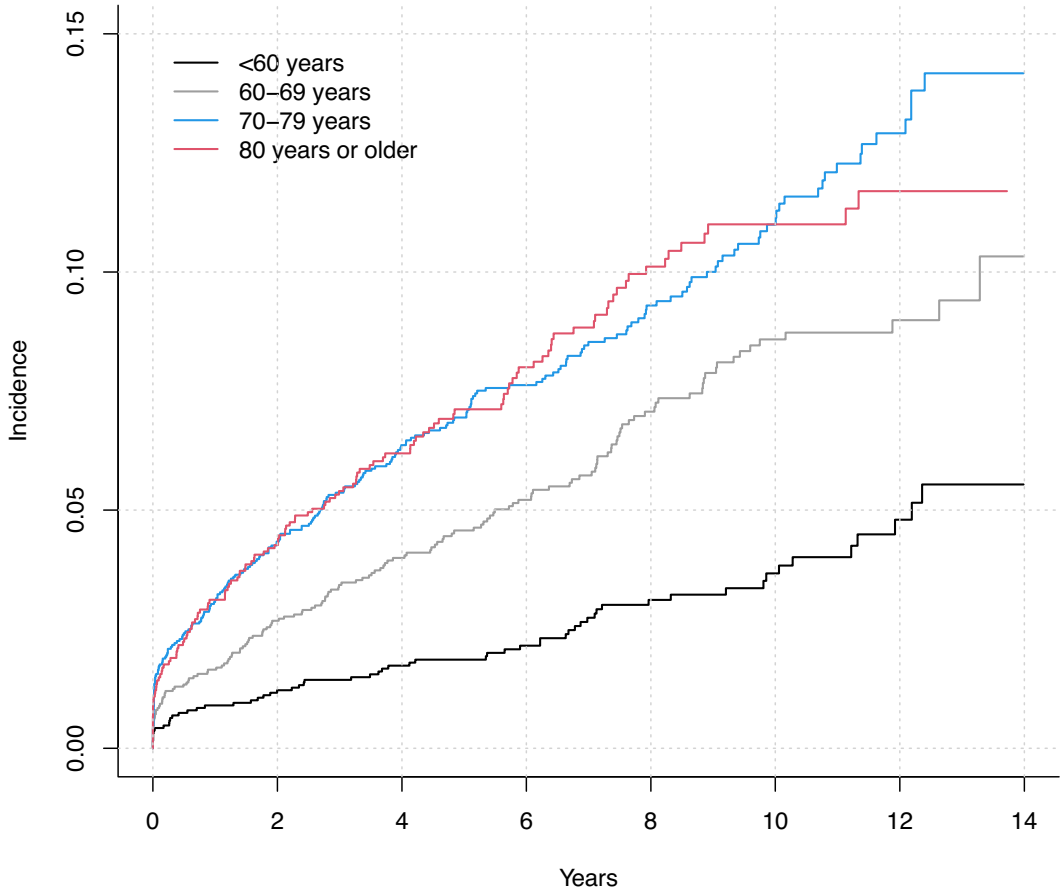

Fig. 3. *Cumulative incidence function of strokes by age. The cumulative incidence reached 3.67 %, 8.59 %, 10.99 % and 11.00 % at twelve years in age categories <60 years, 60-69 years, 70-79 years of age and among 80 years or older patients at the time of the acute coronary syndrome.*

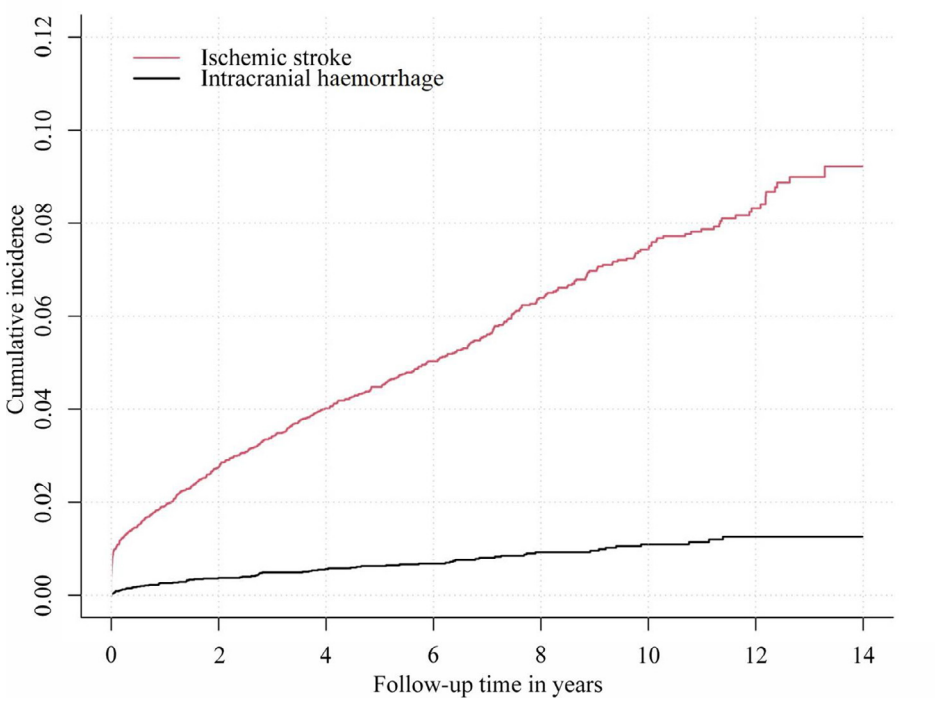

Fig. 4. *Cumulative incidence function for ischemic and haemorrhagic stroke.*

warfarin treatment was insufficient (international normalized ratio, INR < 2) in 14.5 % of cases.

Stroke mortality

Stroke with preceding ACS caused death in 32.5 % (n=185/570) of patients. Mortality was significant during the first month after stroke (20.0 %, n=114/570), counting for 61.6 % of all stroke related deaths in this study. For comparison, mortality was only 4.8 % at one month and 32.3 % during the whole follow-up time in the entire study group. Stroke mortality after ACS stayed constant despite the onset time from ACS. Majority of strokes, 78.4 % (n=145), leading to death

Table 2. *Cumulative incidence of stroke and subtypes in ACS patients.*

Follow-up time	Total (N)	Incidence* %	IS % (N)	CE without AF/AFL % (N) portion of IS	CE with AF/AFL % (N) portion of IS	ICH % (N)
1 week	68	0.8	95.6 (65)	32.3 (21)	13.8 (9)	4.4 (3)
2 weeks	78	1.0	96.2 (75)	30.7 (23)	12.0 (9)	3.8 (3)
3 weeks	84	1.0	95.2 (80)	31.3 (25)	11.3 (9)	4.8 (4)
1 month	88	1.1	93.2 (82)	31.7 (26)	11.0 (9)	6.8 (6)
2 months	103	1.3	93.2 (96)	29.2 (28)	10.4 (10)	6.8 (7)
3 months	113	1.4	92.0 (104)	27.9 (29)	10.6 (11)	8.0 (9)
6 months	136	1.7	89.7 (122)	26.2 (32)	13.1 (16)	10.3 (14)
9 months	158	2.0	89.2 (141)	23.4 (33)	14.2 (20)	10.8 (17)
1 year	177	2.2	88.7 (157)	21.7 (34)	15.9 (25)	11.3 (20)
2 years	253	3.1	88.9 (225)	17.8 (40)	15.6 (35)	11.1 (28)
4 years	361	4.6	88.9 (321)	13.4 (43)	16.8 (54)	11.1 (40)
6 years	430	5.7	89.5 (385)	12.7 (49)	16.9 (65)	10.5 (45)
8 years	503	7.3	88.9 (447)	11.9 (53)	17.7 (79)	11.1 (56)
10 years	542	8.5	88.7 (481)	11.6 (56)	17.9 (86)	11.3 (61)
12 years	562	9.6	87.7 (498)	11.2 (56)	19.4 (95)	11.4 (64)
13 years	569	10.3	88.8 (505)	11.1 (56)	18.8 (95)	11.2 (64)
Total	570		88.8 (506)	9.8 (56)	16.8 (96)	11.2 (64)

*Cumulative incidence is calculated by subdistribution hazard.IS, ischemic stroke; CE, cardioembolism; AF, atrial fibrillation; AFL atrial flutter; ICH, Intracranial haemorrhage.

were ischemic and 21.6 % (n=40) were haemorrhagic. ICH mortality was significant, since only 11.1 % of strokes in total were haemorrhagic.

Incidence of stroke among patients diagnosed conservatively

Among MI patients diagnosed and treated conservatively (n=163) in 2015−2017 and followed up until the end of 2020 (median follow-up of 2.0 years (IQR 0.1-4.5)), 66.9% (n=109) died and the cumulative incidence of stroke reached 3.68% (n=5). The relatively short median follow-up for these patients is explained by high mortality.

Discussion

This retrospective cohort study outlines the risk of stroke and the related mortality of patients treated for ACS in a contemporary setting with all modern secondary prevention and medical advances available. Our findings suggest a slightly smaller in-hospital stroke risk after ACS than what has been demonstrated in recent literature.[5,7] Up to one year our results are more in line with prior studies.[3,5,6,8,9,12,16,31] However, information regarding the long-term cumulative incidence is scarce in previous literature. According to our observations, the cumulative incidence of stroke is high with over one in ten patients afflicted in the span of thirteen years. It is important to note, that previous studies tend to focus on solely MI and ischemic stroke without further subtyping.[3,6,11,12,32] This leaves a gap in understanding the effect of UAP in stroke risk as well as the incidence of ICH and CE with or without atrial arrhytmias (atrial fibrillation or flutter) in ACS patients considering the general usage of anticoagulation and antithrombotic medication.[3,5,6,9,11,12]

In a previous retrospective registry study by Hachet et al. researching AMI patients with following strokes in 2001-2010 found the IHS (0-5 days in contrast to our 0-7 days) incidence to be 1.4 %, which is higher than the risk in our study (0.8 %).[5] This might be in part explained by the usage of Kaplan-Meier estimator, which leads to an upwards-biased cumulative incidence in the presence of competing events.[5] In a similar setting with data collected in 1986-2005, Saczynski et al. estimated the risk of stroke after AMI to also be 1.4 % during hospitalization, but when looking into only the latest year of 2005, it reduced to 1.1 %.[7] In line with this, a prospective registry study by Albaker et al with data gathered in 2006-2007 found the IHS risk to be similar to ours, 0.9 %.[13]

A cohort study by Sundboll et all. based on Danish medical registries from 1980 to 2009 established one month risk of stroke to be 1.1 % after MI, which corresponds to our similar finding of 1.1 % risk including UAP.[9] Interestingly, in studies conducted by Nikolsky et al (data collected before 2008) focusing on AMI patients and Myint et al with quite modern data from 2006 to 2013 looking into NSTEMI patients, the one month stroke risk was estimated as lower, 0.7 %, possibly because UAP was ruled out.[8,31] In contrast, a prospective study conducted by Sampson et al., found that MI with LV dysfunction, HF or both, had a one month stroke risk of 3.2 % suggesting that the risk is dependent on the previous incident and patient risk profile.[16] Our results seem be cohesive with previous literature and confirm the reduction in this serious complication in recent years. One possible factor in reducing the incidence of stroke is the improved treatment of STEMI patients by PCI. In our study population over 85 % of the STEMI patients were treated with primary PCI, which reduces mortality and serious complications when compared to fibrinolytic therapy.[25,33]

One year risk of stroke after AMI has been estimated to be between 1.1-2.0 % in recent literature whereas some studies focusing on only IS suggest the risk to be even greater, 2.1 %.[3,5,12] These findings are in line with our one year risk of 2.2 %. A retrospective registry study by Ulvenstam et al. recorded the one year incidence to be even greater, 4.1 %, but it also concluded that stroke risk declined by 20 % from 1998 to 2008.[6] The stroke incidence with preceding AMI after one year is variably recorded in literature, the two year risk being estimated as 1.5 %, the subsequent three year incidence as 1.8 %.[5,8] In contrast, our findings indicate a greater and continuously increasing risk (0.7 % per year) as high as over ten percent in 13 years.

We found the one month mortality for stroke after ACS to be 20.0 % despite the onset time of stroke following ACS. In turn, mortality was only one fourth (4.8 %) without stroke during the first month after ACS. This vast difference has also been noted in previous literature.[2,7] A study by Westerhout et al. focusing on strokes occurring during the first month after NSTEMI found the one month mortality to be 3.4 % without and 25 % with stroke.[2] Moreover, with data collected during a similar time period (1986-2005), Saczynski et al. estimated the one month mortality to be higher, 34.1 %, which concludes there to be some dispersion in previous studies.[7] Although the development has been positive during recent years, the impact of acute mortality is notable even with modern treatment modalities.

There is little to no previous studies including UAP in stroke risk evaluation and the related time frame to this extent. One study by Shoji et al recorded the one month risk of stroke to be 0.3 % for all patients treated with PCI (including elective) and 0.5 % for ACS patients, which is only one half of our result of 1.1 %.[34] This contradicting result by Shoji et al is considerably lower than the common one month incidence of stroke after MI (0.7-2.1 %) and thus can be questioned.[8,9,11−13] Also, 80.5 % of ACS in our study were MI. Despite the fact that we found the risk of stroke to be higher among MI patients when compared to UAP patients during the first week following ACS, after that there was no significant difference in the cumulative incidence of stroke between different ACS

patient groups. Our observations highlight the importance of stroke prevention among all ACS patients. In addition, there was no statistical significance for cardioembolic stroke risk (with or without AF/AFL) when comparing UAP and MI patient groups. It can be argued, that all ACS patients might be at risk for CE stroke especially early on after ACS possibly due to ACS causing left ventricular dysfunction.

Regarding sufficient anticoagulation among patients with increased CE stroke risk, we did not observe any indications that ICH would be more represented compared to IS immediately after ACS. On the contrary, the proportion of IS declined during follow-up compared to ICH since the portion of IS was 95.6 %, 93.2 % and 88.7 % at hospitalization, one month and year, respectively. These results are reliable since 94.2 % of patients went thorough precise examinations (imaging such as CT scan or autopsy) prior diagnosis. In literature, most strokes after AMI are ischemic, and consequently the in-hospital and one-month portions of IS are estimated to be 68.0-86.2% and after one year it increases to 92.1-95.6%.[2,4,5,7,8,13,17] Unfortunately, more detailed evaluation of medical therapy immediately after ACS or during follow-up years was out of scope for this study.

Further subtypes of stroke are mostly missing in previous literature. Hachet et al. estimate the portion of CE in in-hospital ischemic strokes to be 60.4 %.[5] In our study this estimate was somewhat lower 46.2 %. In turn, Hachet et al found the one year percentage to be 34.9 %, which corresponds with our result, 37.6 %.[5] Our study found the portion of CE without AF/AFL to be significantly increased in strokes occurring shortly after ACS (31.7 % during the first month) and decreasing slowly during the follow-up time whereas the proportion of CE with atrial arrhythmias did the opposite.

One clear disadvantage of our study is the fact that stroke subtyping is based on retrospective data. Although we had access to all written medical records, a prospective setting would probably lead to a more accurate endpoint definition and also to a smaller proportion of cryptogenic strokes overall. Another limitation is the fact that our study did not include patients who did not undergo invasive evaluation (i.e. coronary angiography) for ACS. However, in our study centre, only 8.4 % of patients are ruled out of invasive evaluation due to poor overall condition, functional status and general prognosis due to other conditions.[35] This could have a modest impact on the cumulative incidence, since it is possible that patients who do not undergo invasive evaluation have a higher incidence of stroke. In addition, overall mortality (i.e. the risk of competing event) among these patients is very high which also reduces the cumulative incidence of strokes and, because to their poor prognosis, secondary preventive measures have less clinical impact. In additional data, we concluded that patients diagnosed (and treated) conservatively have a significant overall mortality and thus, the cumulative incidence of stroke was moderate.

Our study, based on high-fidelity data, establishes the cumulative incidence of stroke with a preceding ACS in a contemporary patient cohort. Cumulative incidence is still very notable during the first months, first year and over one of every ten patients will suffer a stroke 13 years after ACS. There is no significant difference in cumulative incidence of stroke long term between patients with UAP or MI which stresses sufficient stroke prevention for all ACS patients.

Declaration of Competing Interest

None.

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