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ORIGINAL RESEARCH

Risk Factors for Ischemic Stroke After Acute Coronary Syndrome

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BACKGROUND: Stroke incidence is elevated after acute coronary syndromes (ACS). The aim of this study was to characterize risk factors related to ischemic stroke (IS) after ACS.

METHODS AND RESULTS: We conducted a retrospective registry study based on the data of 8049 consecutive patients treated for ACS between 2007 and 2018 in Tays Heart Hospital with a follow-up until December 31, 2020. Potential risk factors were identified by in-depth review of written hospital records and causes-of-death registry data maintained by Statistics Finland. The association between individual risk factors, early-onset IS (0–30 days after ACS, n=82), and late-onset IS (31 days to 14 years after ACS, n=419) were analyzed using logistic regression and subdistribution hazard analysis. In multivariable analysis, the most substantial risk factors for early- and late-onset IS were previous stroke, atrial fibrillation or flutter, and heart failure status depicted by the Killip classification. Left ventricular ejection fraction and coronary artery disease severity were significant risk factors for early-onset IS; age and peripheral artery disease were significant risk factors for late-onset IS. The risk of early-onset IS with ≥6 CHA_2DS_2-VASc score points (odds ratio, 6.63 [95% CI, 3.63–12.09]; P<0.001) was notable compared with patients with 1 to 3 points as well as the risk of late-onset IS with ≥6 points (subdistribution hazard, 6.03 [95% CI, 3.71–9.81]; P<0.001) in comparison with patients with 1 point.

CONCLUSIONS: Factors related to high thromboembolic risk also predict IS risk after ACS. CHA_2DS_2-VASc score and its individual components are strong predictors for both early- and late-onset IS.

Key Words: acute coronary syndrome ■ ischemic stroke ■ myocardial infarction ■ prevention ■ risk factors

Ischemic stroke (IS) is a serious and not uncommon complication after acute coronary syndrome (ACS; including acute myocardial infarction [AMI] and unstable angina pectoris) leading to neurological damage and disability, decreasing quality of life, and, at worst, increased death. The incidence is especially high during the first month after ACS, and the events further accumulate long term, with the cumulative incidence reaching almost 10% after 10 years.[1] Accurate risk prediction of IS among this high-risk patient group could lead to improvements in treatment results since there are potential interventions available.

Aside from atrial fibrillation (AF) or atrial flutter (AFL), which are linked to significantly increased risk of cardioembolic stroke and warrant anticoagulation, there are no established risk scores or risk identifiers that would unambiguously identify patients at high risk for IS after ACS. Common risk factors for IS following AMI include advanced age, previous stroke, or myocardial infarction (MI), diabetes, kidney deficiency, and AF.[2–7] Female sex, hypertension, and dyslipidemia are some of the more disputed factors.[2–4,6,8] Many of the above-mentioned general risk factors are incorporated into the CHA_2DS_2-VASc score and can be used to evaluate thromboembolic risk even in the absence of AF/AFL.[9–11]

Especially anterior wall MI localization has been considered to lead to left ventricular dysfunction, heart failure (HF) or both, thus increasing the risk of stroke by

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CLINICAL PERSPECTIVE

What Is New?

- This research on patients with acute coronary syndrome suffering ischemic stroke is based on unprecedented high-fidelity data with no loss to follow-up in a population of 8049 consecutive patients undergoing coronary angiography for acute coronary syndrome during a 12-year period (2007–2018).
- We included not only patients with myocardial infarction but also patients with unstable angina pectoris in the study and analyzed the risk factors for ischemic stroke both in early stages and later on to improve clinical understanding.

What Are the Clinical Implications?

- Our findings strongly indicate that factors related to high overall thromboembolic risk also predict ischemic stroke following acute coronary stroke as well as CHA_2DS_2-VASc score despite atrial arrhythmias in both early- and late-onset ischemic stroke.

Nonstandard Abbreviations and Acronyms

AFL	atrial flutter
IS	ischemic stroke
MADDEC	Mass Data in Detection and Prevention of Serious Adverse Events in Cardiovascular Disease
SDH	subdistribution hazard
TOAST	Trial of Org 10172 in Acute Stroke Treatment
VALIANT	Valsartan in Acute Myocardial Infarction

thrombosis formation.[2,3,8,12] In relation to this, evident decompensated HF status (Killip class III) has been shown to increase the in-hospital stroke risk notably.[4] Left ventricular thrombosis and cardioembolic stroke are especially common during the first 1 to 2 weeks after MI, and the risk stays increased for at least 3 months.[13] Before the widespread adaptation of double antiplatelet therapy, warfarin treatment combined with acetylsalicylic acid was proven to diminish the risk of left ventricular thrombosis and cardioembolic stroke after MI.[13–15] However, the elevated risk of bleeding is the obvious downside of universal anticoagulation with warfarin or by a novel (direct) oral anticoagulant in patients with recent MI, and it can exceed any possible advantages unless risk stratification is substantially improved.[12,14,16–20]

Possible protective factors for IS after AMI include early revascularization, percutaneous coronary intervention (PCI), and the usage of statins.[8,21–24] Advanced treatment of hypertension with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers are related to diminished risk of stroke following AMI.[6,12]

The predictive factors for IS after ACS should be characterized in more detail. It is plausible that the risk factor profile of IS changes significantly after the acute phase when the incidence of IS is high compared with long-term follow-up when the cumulation of events has stabilized. Precise information of possible risk factors could help in designing and targeting new therapies to prevent IS in this high-risk patient population. The purpose of this research is to provide accurate data on the specific risk factors for IS immediately after and later on after ACS. The advantage of the present study is that all phenotype and end point information is based on unprecedented high-fidelity data with no loss to follow-up in a population of consecutive patients undergoing coronary angiography for ACS during a 12-year period (2007–2018).

METHODS

Due to the sensitive nature of the data collected for this research, they are not made widely available. This study is based on the retrospective registry study MADDEC (Mass Data in Detection and Prevention of Serious Adverse Events in Cardiovascular Disease) recording mass data of all patients with cardiac disease-treated in Tays Heart Hospital, which is a sole provider of specialized and tertiary health care for seriously ill patients in the region of Pirkanmaa (Finland).[25] Data for the registry are collected from multiple sources, including electronic health records, written patient records, and the prospectively updated KARDIO registry, which records structured data from all patients. The data of the KARDIO registry are maintained by treating nurses and physicians using an online tool. As a result, the MADDEC database comprises high-quality phenotype information of all patients treated for ACS.[25] The study design was approved by the scientific monitoring board of Pirkanmaa hospital district. Due the nature of the study, informed consent was not required. The study complies with the Declaration of Helsinki on the ethical principles for medical research. This study design and baseline phenotype data collection have been thoroughly described previously.[1,25]

All patients undergoing coronary angiography for ACS between January 1, 2007, and December 31, 2018, were followed up for incident strokes during

and after hospitalization. For the purpose of this study, only the first ACS for each patient was selected as the baseline/index event even if multiple events were recorded. A total of 10 314 patients were treated for ACS during this time period. Additionally, patients living permanently outside the hospital district of Pirkanmaa were excluded from the study due to no access to written medical records for the verification of all baseline data and end points during the follow-up. As a result, we analyzed the data of 8049 patients treated for ACS. We also collected data and analyzed the impact of the primary treatment modality of ACS (PCI, coronary artery bypass grafting [CABG], and conservative treatment) in early-onset IS risk.

CHA_2DS_2-VASc points were calculated on the basis of available risk factors (ie, age, sex, history of HF), hypertension, prior stroke, transient ischemic attack or thromboembolism history, vascular disease history (prior MI, peripheral artery disease, or aortic plaque), and type 2 diabetes data.[9,11,26] For early-onset IS, the first 3 CHA_2DS_2-VASc score categories were combined to 1 reference group for statistical analysis due to a low number of events. Killip classification (I–IV) for AMI (class I for no sign of congestion, class II for S3 [ventricular gallop] and basal rales on auscultation, class III for acute pulmonary edema, class IV for cardiogenic shock) was used as a covariate considering the development of HF in statistical modeling.[27]

Follow-Up and End Point Definitions

Patients were followed from the index event until the end of the year 2020, until patient suffered an IS (due to any cause), or death occurred before December 31, 2020. Only the first stroke for each patient was used in the analyses. Follow-up information of incident IS was collected by in-depth review of electronic health records containing hospital discharge diagnoses, all written medical records from specialized health care, and written death certificates detailing the cause of death and the circumstances leading up to the event. This thorough review was conducted for all 8049 patients to discover all the true IS events. Patients who suffered only a transient ischemic attack or other condition such as moyamoya disease were excluded from the analyses as well as IS occurring only before ACS. IS were subtyped by the TOAST (Trial of Org 10 172 in Acute Stroke Treatment) criteria and additional phenotypic data from the time of the incident stroke was also collected similarly by reviewing all possible medical records.

Statistical Analysis

For modeling the association between risk factors and the risk of IS in this population, strokes were classified as early-onset IS (occurring during the first 30 days after the diagnosis of ACS was made by coronary angiography) or late-onset IS (occurring 31 days to 14 years after ACS diagnosis). This division was made because the proportion of cardioembolic strokes has been shown to be higher in the acute phase when compared with later stages after ACS and controlling the proportionality assumption of hazard models.

The analysis of risk factors associating with early-onset IS was performed by logistic regression model. The analysis of risk factors associating with the late-onset IS was performed by subdistribution hazard (SDH) analysis accounting for competing risk of death due to high overall death in the population (32.3%, n=2599 patients died during the follow-up). All possible covariates associating with early- or late-onset IS with a P value of <0.05 in univariable analysis were included in the multivariable analysis. Results of the univariable models are presented in Tables S1–S2.

Left ventricular ejection fraction (LVEF) and Killip classification were not entered in the same multivariable models due to their high collinearity. LVEF was missing in 7.2% (n=577) of patients, and inadequate LVEF information was imputed by using multiple chained equations with Killip classification, age, and male sex covariates using the R package “mice” (R Foundation for Statistical Computing, Vienna, Austria). The risk associated with LVEF was thus analyzed after removing Killip classification form the multivariable models. Continuously distributed variables were standardized using a Z transformation for the regression analyses, and all the subsequent hazard and odds ratios (ORs) denote the risk associated with 1 SD increase in the continuous exposure variable. A P value of <0.05 was considered statistically significant. The analyses were performed by SPSS software version 27 (IBM, Armonk, NY) and by R software version 4.1.3 (packages mice, survival, cmprisk).

RESULTS

Demographics of the Study Population

The mean age of the study population (n=8049) was 68.7 years (±11.8 SD) during hospitalization for ACS, and 65.8% (n=5295) of patients were men. The median follow-up time was 5.8 years (interquartile range, 3.2–9.0). The majority (80.5% [n=6481]) of ACS was MI, and two-thirds (64.6%, n=5197) of ACS cases were treated with PCI and only 9.0% (n=728) with CABG. A total of 501 of 8049 patients with ACS suffered an IS during the follow-up time. The cumulative incidences of IS for the first month, first year, and at 13 years were 1.0%, 1.9%, and 9.0%, respectively. The total death rate of IS was significant (28.9% [n=145]), and it did not differ regardless of the onset time between ACS and IS. Baseline characteristics of the study population are provided in Table 1.

Table 1. Baseline Characteristics at the Index Event (Recorded During Hospitalization for Acute Coronary Syndrome)

	All patients (N=8049)
Age, y, mean±SD	68.7±11.8
Sex, male, n (%)	5295 (65.8)
Body mass index, kg/m^2 mean±SD	28.1±5.2
Diabetes (any type), n (%)	2090 (26.0)
Hypertension, n (%)	4958 (61.6)
Dyslipidemia, n (%)	4697 (58.3)
Chronic kidney disease, n (%)	568 (7.1)
Valvular heart disease, n (%)	509 (6.3)
Heart failure, n (%)*	2446 (30.4)
Atrial fibrillation or flutter, n (%)†	1419 (17.6)
Peripheral artery disease, n (%)	681 (8.5)
Cancer, n (%)‡	731 (9.1)
Dementia, n (%)	127 (1.6)
Smoking, n (%)§	3565 (44.3)
Previous stroke or transitient ischemic attack, n (%)	713 (8.9)
Previous myocardial infarction, n (%)	1409 (17.5)
Previous PCI, n (%)	846 (10.5)
Previous CABG, n (%)	647 (8.0)
Previous ICD, n (%)	29 (0.4)
Left ventricular ejection fraction, %, mean±SD	51.5±11.9
Status during admission, mean±SD	
Hemoglobin, g/L	130.2±16.0
Creatinine, μmol/L	88.8±60.8
Killip classification for heart failure, n (%)	
I	6239 (77.6)
II	1132 (14.1)
III	490 (6.1)
IV	176 (2.2)
Acute coronary syndrome subtypes, n (%)	
Unstable angina pectoris	1568 (19.5)
Non–ST-segment–elevation myocardial infarction	3882 (48.2)
ST-segment–elevation myocardial infarction, n (%)	2599 (32.3)
Treatment modality, n (%)	
PCI	5197 (64.6)
CABG	728 (9.0)
PCI and CABG	100 (1.2)
Conservative	2024 (25.1)

Percentages are valid percentages. Continuous variables are mean±SD. Categorical values are frequencies. CABG indicates coronary artery bypass grafting; ICD, implantable cardioverter-defibrillator; and PCI, percutaneous coronary intervention.

*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.

§Current or history of smoking.

There was no statistical difference between early- and late-onset IS subtypes regarding large-vessel disease (4.9% versus 6.7%) and small-vessel disease (9.8% versus 13.8%) especially considering the small number of cases in early-onset IS. On the other hand, the portion of IS due to cardioembolism without AF/AFL was notable, especially in early-onset IS (31.7% [n=26]), compared with late-onset IS (7.2% [n=30]; P<0.001). Similarly, cardioembolism with AF/AFL was clearly lower in early-onset IS (11.0% [n=9]) compared with late-onset IS (20.5% [n=86]; P<0.05). These findings are presented in Table 2.

Different Risk and Protective Factors for Early-Onset (0–30 Days) IS After ACS

Of the 8049 patients, 82 patients (1.0%) suffered IS during the first month after ACS. Most of these events (79.3%) occurred within the first week of angiography. The results of preliminary screening for significant risk factors in univariable model are presented in Tables S1. In multivariable analysis, significant predictors of early-onset IS were paroxysmal AF/AFL (OR, 2.05 [95% CI, 1.23–3.42]; P=0.006), history of stroke (OR, 3.46 [95% CI, 2.11–5.65]; P<0.001), occlusion of the left main coronary artery (OR, 1.75 [95% CI, 1.01–3.03]; P=0.048), severity of coronary artery disease, and high Killip class (Table 3). Advanced age was not a risk factor in multivariable analysis for early-onset IS.

The association between CHA_2DS_2-VASc score and early-onset IS was strong, with the risk of IS increasing significantly with higher points. IS incidence was 0.4% (n=16) among patients with 1 to 3 CHA_2DS_2-VASc points, whereas it was 2.6% (n=33) for patients with ≥6 points (OR, 6.63 [95% CI, 3.63–12.09]; P<0.001). The absolute and relative occurrence and the occurrence rate of IS by CHA_2DS_2-VASc score in different categories are detailed in Table 4.

Table 2. Early-Onset (0–30 Days After ACS) and Late-Onset (31 Days to 14 Years After ACS) Ischemic Stroke Subtypes

Subtype of IS	Early-onset IS (N=82), n (%)	Late-onset IS (N=419), n (%)	*P* value
LVD	4 (4.9)	28 (6.7)	0.541
SVD	8 (9.8)	58 (13.8)	0.317
Cardioembolism without AF/AFL	26 (31.7)	30 (7.2)	<0.001
Cardioembolism with AF/AFL	9 (11.0)	86 (20.5)	0.044
Cryptogenic	33 (40.2)	215 (51.3)	0.067
Unspecified	2 (2.4)	2 (0.5)	0.068

P values are calculated by chi-square. AF indicates atrial fibrillation; AFL, atrial flutter; IS, ischemic stroke; LVD, large-vessel disease; and SVD, small-vessel disease.

Table 3. Risk Factors Associated With Early-Onset (0–30 Days After ACS) Ischemic Stroke

	Multivariable odds ratio (95% CI)	*P* value
Age, y (per 1 SD)	1.26 (0.97–1.64)	0.090
Previous stroke	3.46 (2.11–5.65)	<0.001
Left ventricular ejection fraction (per 1 SD), %†	0.78 (0.63–0.98)	0.033
Cardiac arrest during hospitalization	1.19 (0.58–2.41)	0.635
Killip classification		0.015*
I	Reference	
II	1.37 (0.77–2.43)	0.291
III	2.25 (1.18–4.28)	0.013
IV	1.91 (0.64–5.68)	0.246
Atrial fibrillation or flutter		0.284*
No atrial arrythmias	Reference	
Paroxysmal	2.05 (1.23–3.42)	0.006
Persistent or chronic	0.94 (0.41–2.14)	0.883
Severity of coronary artery disease		0.026*
No occlusion	Reference	
1-vessel disease	1.60 (0.55–4.65)	0.509
2-vessel disease	1.79 (0.61–5.29)	0.292
3-vessel disease	2.59 (0.89–7.52)	0.080
Occlusion of the left main coronary artery	1.75 (1.01–3.03)	0.048

Only variables with a $P<0.05$ in the univariable model were included in the multivariable model. ACS indicates acute coronary syndrome.

*P value calculated for linear trend.

†Not in the same model concurrently with Killip classification due to collinearity. Odds ratio estimate calculated by replacing Killip classification with left ventricular ejection fraction in the model.

The Association Between Treatment Modality and Early-Onset IS

The association between IS and treatment modality of ACS (CABG, PCI, and conservative) was analyzed separately. Patients who were treated by CABG suffered early-onset IS more often (2.3% [n=19/828]) when compared with patients treated by PCI (0.8% [n=42/5198]) or conservatively (1.0% [n=21/2023]). Overall, this corresponds to an unadjusted OR of 2.67 (95% CI, 1.59–4.48; $P<0.001$) when comparing the risk of early-onset IS in patients with CABG with patients treated with either PCI or conservative treatment. However, when the analysis was adjusted with the other significant risk factors for early-onset IS (paroxysmal AF/AFL, history of stroke, severity coronary artery disease and high Killip class), the association became nonsignificant (OR, 1.46 [95% CI, 0.81–2.61]; $P=0.206$).

Different Risk and Protective Factors for Late-Onset (31 Days to 14 Years) IS After ACS

After the acute phase (30 days after ACS), 419 ISs were observed during the follow-up. In the multivariable models, advanced age (SDH, 1.02 [95% CI, 1.01–1.03]; $P<0.001$), peripheral artery disease (SDH, 1.39 [95% CI, 1.03–1.89]; $P=0.034$), previous stroke (SDH, 1.38 [95% CI, 1.03–1.85]; $P=0.033$), high serum creatinine levels (SDH, 1.12 [95% CI, 1.05–1.20]; $P<0.001$), and paroxysmal (SDH, 1.32 [95% CI, 1.01–1.74]; $P=0.045$) or persistent/chronic AF/AFL (SDH, 1.75 [95% CI, 1.28–2.39]; $P<0.001$) were associated significantly with the risk of IS. Notably, unlike in early-onset IS, persistent/chronic AF/AFL was associated with statistically significant risk of IS in addition to paroxysmal AF/AFL. Combined Killip classes II and III for HF at the time of ACS associated significantly with the risk for late-onset IS (Table 5). The results of univariable analyses are presented in Table S2.

Table 4. Association Between CHA_2DS_2-VASc Score and the Risk of Early-Onset (0–30 Days After ACS) IS

CHA_2DS_2-VASc score	Group size (N)	Occurrence of IS, n (%)	Odds ratio (95% CI)	*P* value
1–3*	4048	16 (0.4)	Reference	
4	1479	14 (0.9)	2.42 (1.18–5.00)	0.016
5	1214	19 (1.6)	4.02 (2.06–7.85)	<0.001
≥6	1292	33 (2.6)	6.63 (3.63–12.09)	<0.001

ACS indicates acute coronary syndrome; and IS, ischemic stroke.

*First 3 CHA_2DS_2-VASc score categories are combined into 1 reference group for statistical analysis due to low number of events (occurrence rate of IS in patients with 1, 2, and 3 CHA_2DS_2-VASc score points were 0.2% [n=2/1040], 0.4% [n=6/1496], and 0.5% [n=8/1528], respectively).

CHA_2DS_2-VASc score was notably associated with late-onset IS, especially among patients with ≥6 points compared with patients with only 1 point (SDH, 6.03 [95% CI, 3.71–9.81]; $P<0.001$). Subdistribution hazard and cumulative incidence functions for late-onset IS regarding CHA_2DS_2-VASc score are presented in the Figure. As previously mentioned, AF/AFL was significantly associated with the long-term risk of IS (and showed unchanged SDHs) despite adjusting for CHA_2DS_2-VASc score (SDH, 1.44 [95% CIl, 1.14–1.84]; $P=0.002$ for paroxysmal AF/AFL type; and SDH, 1.61 [95% CI, 1.20–2.15]; $P=0.001$ for persistent/chronic AF/AFL type).

Preexisting Anticoagulation Therapy in Patients With IS

We examined the prevalent use of anticoagulation (warfarin, novel oral anticoagulants, and low-molecular-weight heparin) at the time of IS (early- or late-onset) to analyze the proportion of patients possibly benefiting from better risk stratification and targeted use of anticoagulation. These data were available in 334 of 501 (66.6%) patients. At the incident time of IS, 53.3% (n=178/334) of these previously mentioned patients had no anticoagulative medication, and the rest (46.7% [n=156/334]) were anticoagulated. Also, for 30 patients, the anticoagulation was in the subtherapeutic range (warfarin treatment with international normalized ratio <2.0).

Table 5. Risk Factors Associated With Late-Onset (31 Days to 14 Years After ACS) Ischemic Stroke (n=419)

	SDH (95% CI)	*P* value
Age, y (per 1 SD)	1.32 (1.17–1.49)	<0.001
Sex, male	1.16 (0.93–1.44)	0.138
Smoking		0.242*
Never	Reference	
Ex-smoker	0.93 (0.72–1.20)	0.541
Active smoker	1.08 (0.82–1.42)	0.609
Diabetes (any type)	1.04 (0.83–1.30)	0.672
Hypertension	1.13 (0.90–1.41)	0.268
Peripheral artery disease	1.39 (1.03–1.89)	0.034
Previous myocardial infarction	1.16 (0.91–1.48)	0.189
Previous stroke	1.38 (1.03–1.85)	0.033
History of kidney failure (acute or chronic)	1.12 (0.85–1.48)	0.413
Creatinine (per 1 SD)†	1.12 (1.05–1.20)	<0.001
Killip classification		0.100*
I	Reference	
II‡	1.22 (0.94–1.58)	0.140
III‡	1.35 (0.94–1.95)	0.100
IV	0.78 (0.25–2.44)	0.671
Atrial fibrillation or flutter		<0.001*
No atrial arrythmias	Reference	
Paroxysmal	1.32 (1.01–1.74)	0.045
Persistent or chronic	1.75 (1.28–2.39)	<0.001
Severity of coronary artery disease		0.650*
No occlusion	Reference	
1-vessel disease	1.16 (0.82–1.64)	0.443
2-vessel disease	1.28 (0.90–1.84)	0.177
3-vessel disease	1.10 (0.76–1.60)	0.610

Patients who died or suffered ischemic stroke within the first month after acute coronary syndrome were excluded from the analysis, and only variables with a $P<0.05$ in the univariable model were included in the multivariable model. Subdistribution hazard (SDH) ratios were calculated with SDH modeling accounting for deaths as competing events.

*P value calculated for linear trend.

†Mean serum creatinine value during hospitalization, not in the same model with history of kidney failure.

‡SHD, 1.26 (95% CI, 1.02–1.56); $P=0.033$ for combined Killip II and Killip III classes.

DISCUSSION

This contemporary retrospective registry study brings forth the most common risk factors for IS after ACS, which also predict overall high cardiovascular risk. Our results are based on an unprecedented series of consecutive patients in a limited geographic area in which there is no other cardiac care for patients with ACS. Our findings stress the importance of AF/AFL, high CHA_2DS_2-VASc score despite atrial arrhythmias, and Killip classification in IS risk evaluation. Our results are in line with previous literature, and they deepen the understanding of different relevant factors in IS risk prevention. To the best of our knowledge, there are no prior studies disclosing the role CHA_2DS_2-VASc score with or without AF/AFL has on IS risk after ACS. Additionally, it is important to note that previous research tends to focus on solely MI, leaving out unstable angina pectoris, which undermines the widespread comprehension of IS risk factors in the ACS population.[2–6]

A previous retrospective meta-analysis by Witt et al[3] based on studies published in 1978 to 2004 suggests the most substantial risk factors for IS after MI to be advanced age, diabetes, hypertension, previous stroke or MI, anterior location of index MI, atrial fibrillation, HF, and non-White race in general. Although these results are based on somewhat outdated research, focusing on in-hospital strokes and not accounting for unstable angina pectoris, our findings are very similar. The only striking difference was that Witt et al found Killip class to have no impact on IS risk, even though HF was a strong indicator for stroke. Also, our study was conducted in Finland, with most patients being White, and therefore no stand can be taken on what impact race and ethnicity has on stroke risk.

Our other major findings relating to increased risk of especially late-onset (after 30 days) stroke after ACS include previous stroke, peripheral artery disease, history of kidney failure, and severity of coronary artery disease, which corresponds with recent literature.[2,4,6,28] Female sex, on the other hand, has previously been often linked to higher risk of stroke, yet our results suggest there to be no difference between sexes in early-onset IS and the risk to the opposite in late-onset IS risk, although it was not evident in multivariable analyses.[2,6,21] A prospective trial by Sampson et al[8] with 14 703 patients also found female sex not to be a risk factor for early- (<45 days) or late-onset (>45 days) stroke.

High CHA_2DS_2-VASc score has been proven to increase the risk of stroke despite AF/AFL in earlier literature, and we demonstrated similar and strong impact also after ACS in both early- and late-onset IS.[9–11] Notably, patients with low scores (1–3) have only a minor risk of early-onset IS (0.4% occurrence rate), and, conversely, patients with ≥6 points have a >6-fold risk in comparison. Similar magnitude difference was observed in the risk of late-onset IS when comparing patients with only 1 CHA_2DS_2-VASc point and patients with ≥6 points. These findings can be deemed significant and, especially combined with serum creatinine levels, could be valuable in IS risk evaluation for patients with ACS in the future.

A prospective VALIANT (Valsartan in Acute Myocardial Infarction) study by Szummer et al[4] demonstrated Killip class III to have a 1.5 times higher in-hospital stroke risk after MI compared with class I, whereas class II had a similar risk as that of patients without HF. Similarly, we found the Killip class III to have an impact in early-onset

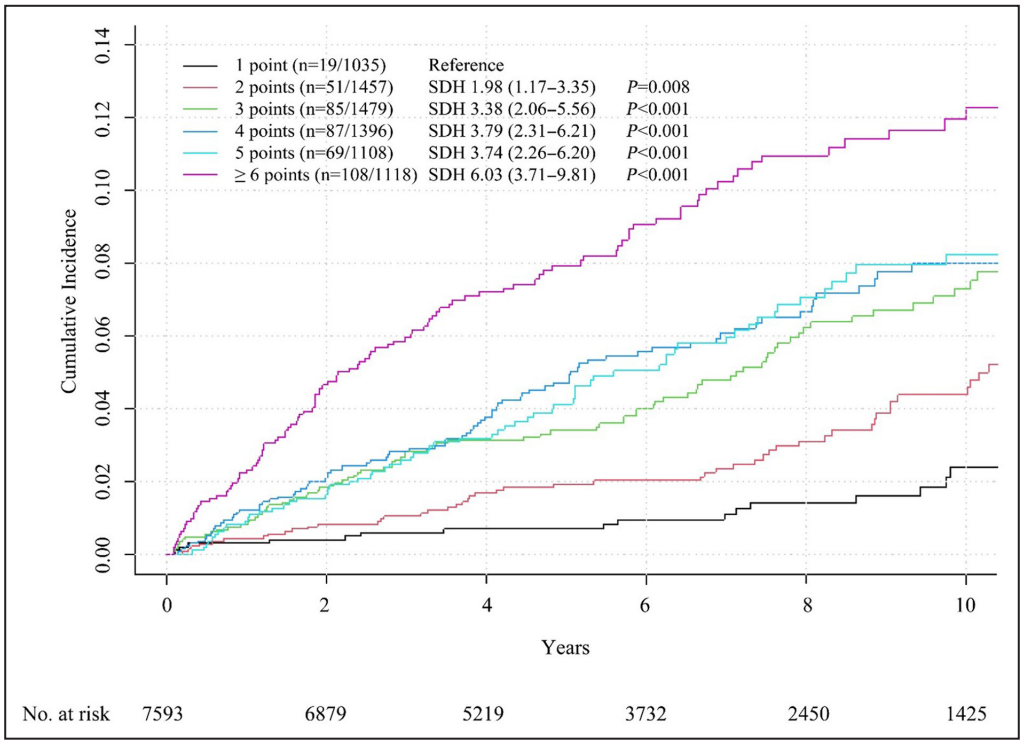

Figure. Cumulative incidence of ischemic stroke in different CHA_2DS_2-VASc score categories. The relative risk of ischemic stroke was calculated using subdistribution hazard (SDH) modeling accounting for deaths as competing events. The numbers in parentheses refer to the number of cases with ischemic stroke during follow-up and the group size at baseline.

IS (>2-fold risk). When considering long-term IS risk, patients with Killip II or III had also notably higher risk of IS, but the magnitude was attenuated (SDH, 1.26 [95% CI, 1.02–1.56]). In turn, the class IV was not associated with the risk of IS in either early- or late-onset IS in multivariable analyses. This might be explained by the high death rate of patients with Killip class IV HF and the resulting survival bias.

Low LVEF has been linked to increased in-hospital stroke risk in a retrospective registry study by Hachet et al,[2] whereas a similar research by Podolecki et al[6] found low LVEF (<35%) not to be a risk factor for stroke in the long term. Our results suggest the role of low LVEF increasing IS risk, especially in the short term, since higher LVEF was the strongest protective factor in early-onset IS. Thus, it could be concluded that low LVEF is a protective factor for IS risk, specifically during the first month after ACS. More comprehensive studies regarding the role of LVEF and the cause of such stroke is still needed, especially since the number of early-onset cardioembolic strokes was too low for analysis in our study. Additionally, the effect of the proportion of IS due to cardioembolism without AF/AFL being considerably higher compared with cardioembolism with AF/AFL in early-onset IS and vice versa in late-onset IS has been thoroughly demonstrated with multiple time points in our previously published research based on the same data.[1]

Treatment of ACS by CABG compared with PCI has previously been linked to increased IS risk, and we had similar findings.[29,30] However, when AF/AFL status and the extent of coronary artery disease (factors also influencing the selection of the treatment modality itself) were included in the risk analysis, the association did not persist. Similarly, Head et al[31] demonstrated in their research how the long-term prognosis was significantly better when patients with multivessel disease were treated by CABG instead of PCI. Therefore, the risk of IS depending on the treatment modality of ACS is multifactorial and treatment by PCI instead of CABG does not always lead to better results and, depending on the patient, is not necessarily even preferable.

One clear limitation in our study was the deficiencies of specific information on, in particular, anticoagulant medication at the time of the incident stroke events. This is partly due to the fact that many patients died of stroke before reaching the hospital or the information was not reliably extractable or unambiguous despite having access to all written medical records from specialized health care at the time of the event (patients unable to give an accurate account of medical treatments or medication poorly described by treating neurologists). For this reason, it is hard to draw conclusions on the efficiency of these medications in IS prevention. However, we can estimate that over two-thirds

of patients who suffered IS were not anticoagulated at the time of the event and could therefore perhaps benefit from more aggressive anticoagulative therapy if correctly identified beforehand. Further research in this regard is, without fail, still needed.

Another disadvantage is the fact that even though the phenotype data was collected by treating physicians in the prospectively updated KARDIO registry, a majority of the data were collected retrospectively, and our results are based on post hoc analyses of the MADDEC database. For this reason, despite the strong observations, our results could benefit from independent replication. Furthermore, we also included only patients who underwent invasive evaluation (ie, coronary angiography) for ACS and thus left out conservatively diagnosed and treated patients with ACS.[1] However, in our study center, only 8.4% of patients are ruled out of invasive evaluation due to poor general condition and functional status, and have a very high overall death rate, which reduces the clinical impact of possible secondary preventive measures in any case.[32] An additional factor to consider is the causal relationship between serious risk factors and death. For example, risk factors such as cardiogenic shock (Killip class IV), which is almost always due to systolic HF, was seen to associate less significantly with the risk of IS in the analyses. This is likely to be caused by 2 phenomena: the overall high death rate related to cardiogenic shock, leaving fewer patients alive to suffer an IS, and strong selection bias, leaving only the most otherwise fit to recover and survive.

CONCLUSIONS

Our research establishes the most common risk (and protective) factors for early- (0–30 days after ACS) and late-onset (31 days to 14 years after ACS) IS and demonstrates the significant role of AF/AFL, high CHA_2DS_2-VASc score despite AF/AFL, and Killip classification II to III in IS risk evaluation. These findings enable improving secondary prevention of this serious complication not just in patients with MI but all patients with ACS alike in the future.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Risk factors associating with early-onset (0-30 days after ACS) ischemic stroke risk in univariable logistic regression model (n=82).

	Odds ratio (95% Cl)	P-value
Age (per 1 SD)	1.65 (1.29-2.11)	<0.001
Sex, male	1.05 (0.67-1.65)	0.825
Body-Mass Index (kg/m²)	0.89 (0.71-1.12)	0.330
Smoking		0.184*
Never	Reference	
Ex-smoker	1.08 (0.64-1.81)	0.782
Active smoker	0.58 (0.31-1.10)	0.096
Diabetes (any type)	1.47 (0.93-2.33)	0.088
Hypertenstion	1.30 (0.81-2.08)	0.179
Hyperlipidemia	0.95 (0.63-1.53)	0.948
Peripheral Artery Disease	0.70 (0.28-1.73)	0.439
Valvular Heart Disease	1.57 (0.78-3.15)	0.207
Cancer	1.64 (0.86-3.12)	0.135
Previous Myocardial Infarction	1.14 (0.66-1.98)	0.632
Previous CABG	1.42 (0.71-2.84)	0.328
Previous PCI	0.92 (0.44-1.91)	0.823
Previous Stroke	4.92 (3.07-7.86)	<0.001
History of Kidney Failure (Acute or Chronic)	1.23 (0.68-2.22)	0.505
Creatinine (per 1 SD)**	0.92 (0.70-1.22)	0.573
Left Ventricular Ejection Fraction (per 1 SD)%	0.68 (0.55-0.85)	<0.001
Cardiac Arrest During Hospitalization	2.16 (1.11-4.22)	0.024
Acute Coronary Syndrome Subtypes		0.241
Unstable Angina Pectoris	Reference	
Non-ST-Elevation Myocardial Infarction	1.79 (0.90-3.56)	0.099
ST-Elevation Myocardial Infarction	1.70 (0.82-3.50)	0.153
Killip Classification		<0.001*
I	Reference	
II	2.01 (1.15-3.51)	0.014
III	3.88 (2.12-7.09)	<0.001
IV	3.06 (1.10-8.60)	0.033
Atrial Fibrillation or Flutter		<0.001*
No Atrial Arrythmias	Reference	
Paroxysmal	3.28 (2.02-5.33)	<0.001
Persistent or Chronic	1.65 (0.75-3.66)	0.216
Severity of Coronary Artery Disease		<0.001*
No Occlusion	Reference	
One-Vessel Disease	1.79 (0.62-5.18)	0.218
Two-Vessel Disease	2.38 (0.81-6.95)	0.113
Three-Vessel Disease	4.53 (1.60-12.82)	0.004
Occlusion of the LMCA	3.12 (1.86-5.24)	0.001

*P-value calculated for linear trend.
**Mean serum creatinine value during hospitalization.
SD, standard deviation; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LMCA, left main coronary artery.

Table S2. Risk factors associating with late-onset (31 days to 14 years) ischemic stroke in univariable subdistribution hazard (SDH) model.

	SDH (95% Cl)	P-value
Age (per 1 SD)	1.52 (1.38-1.68)	<0.001
Sex, male	1.33 (1.09-1.56)	0.004
Body-Mass Index	0.94 (0.86-1.02)	0.140
Smoking		0.015*
Never	Reference	
Ex-smoker	0.87 (0.68-1.11)	0.250
Active smoker	0.72 (0.56-0.93)	0.011
Diabetes (any type)	1.30 (1.05-1.60)	0.015
Hypertension	1.44 (1.17-1.77)	<0.001
Hyperlipidemia	1.07 (0.88-1.31)	0.470
Peripheral Artery Disease	1.90 (1.44-2.52)	<0.001
Valvular Heart Disease	1.31 (0.94-1.84)	0.086
Cancer	1.25 (0.92-1.70)	0.150
Previous Myocardial Infarction	1.48 (1.18-1.85)	<0.001
Previous CABG	0.94 (0.67-1.35)	0.740
Previous PCI	0.99 (0.73-1.36)	0.970
Previous Stroke	1.91 (1.44-2.53)	<0.001
History of Kidney Failure (Acute or Chronic)	1.76 (1.38-2.25)	<0.001
Creatinine (per 1 SD)	1.16 (1.10-1.23)	<0.001
Left Ventricular Ejection Fraction (per 1 SD) %	0.93 (0.84-1.03)	0.160
Cardiac Arrest During Hospitalization	1.18 (0.79-1.76)	0.427
Acute Coronary Syndrome Subtypes		0.830
Unstable Angina Pectoris	Reference	
Non-ST-Elevation Myocardial Infarction	1.21 (0.96-1.53)	0.101
ST-Elevation Myocardial Infarction	1.02 (0.79-1.32)	0.894
Killip Classification		<0.001*
I	Reference	
II	1.63 (1.28-2.08)	<0.001
III	1.95 (1.38-2.76)	<0.001
IV	0.90 (0.29-2.84)	0.861
Atrial Fibrillation or Flutter		<0.001
No Atrial Arrythmias	Reference	
Paroxysmal	1.71 (1.32-2.21)	<0.001
Persistent or Chronic	2.48 (1.86-3.32)	<0.001
Severity of Coronary Artery Disease		0.005*
No Occlusion	Reference	
One-Vessel Disease	1.18 (0.84-1.66)	0.350
Two-Vessel Disease	1.51 (1.06-2.14)	0.021
Three-Vessel Disease	1.48 (1.04-2.12)	0.031
Occlusion of the LMCA	0.79 (0.53-1.16)	0.231

*P-value calculated for linear trend.
SD, standard deviation; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LMCA, left main coronary; SDH, Subdistribution hazard model.