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Incidence and predictors of stroke in patients discharged with the diagnosis of acute coronary syndrome

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ABSTRACT

Background: Stroke is one the most feared cardiovascular disease due to its high risk of disability and its incidence after an acute coronary syndrome (ACS) is not uncommon.
Methods: Retrospective study of all consecutive patients admitted for an ACS in two hospitals. Competing risk regression, taking all-cause mortality as a competing event, was used for the assessment of stroke incidence.
Results: We included 8771 patients, AF prevalence 12.4%. AF patients were older and presented higher prevalence of cardiovascular risk factors, previous cardiovascular disease, and lower glomerular filtration rate. Less than half of AF patients were receiving oral anticoagulation before admission. In-hospital mortality was 5.1% and it was more than two-fold higher in AF patients (10.2% vs. 4.4%; $p < 0.01$). Relevant differences on medical treatments were observed at discharge and oral anticoagulation was roughly <50% in AF patients. During a median follow-up was 58.7 months, 313 patients experienced at least one stroke (incidence 3.8%, 95% CI 3.4–4.2,) and it was 2-fold higher in patients with AF: 7.8% vs. 3.3% ($p < 0.01$). Median time to first stroke was 33.0 (30.1) months and it was shorter for AF patients compared to non-AF patients (28.2 ± 22.3 vs. 34.6 ± 31.1; $p < 0.01$). The adjusted competing risk regression identified AF, previous stroke and CHA_2DS_2-VASc score = 2 or ≥3 as independent predictors of stroke; CHA_2DS_2-VASc score = 2 was associated to higher risk of stroke only in AF patients.
Conclusions: The long-term incidence of stroke after an ACS was 3.8%, 7.8% in AF-patients and 3.3% in patients without any diagnosis of AF.

1. Introduction

Reductions of in-hospital mortality of patients admitted for acute coronary syndromes (ACS) has increased the number of patients with chronic coronary heart disease that are prone to have recurrent events [1,2]. Medical and invasive treatments of ACS survivors are directed to control cardiovascular risk factors and prevent recurrent events, mainly new ACS or heart failure [3]. Risk stratification has been focused on identifying patients at higher mortality risk [4] although some complications might be difficult to prevent based on currently available scales [5], specially stroke [1,6].

Strokes are one of the most feared cardiovascular events due to the risk of long-term disability [7]. Age, atrial fibrillation (AF), hypertension, diabetes and prevalent cardiovascular disease are the leading risk factors for stroke [8,9] and, therefore, its incidence in patients that survive an ACS might not be rare [1,7,9]. The objective of our study was describing the long-term incidence of stroke in a wide cohort of patients and the predictive role of AF and CHA2DS2-VASc score.

2. Methods

We designed a retrospective study of all consecutive patients admitted for ACS in two different centers. Methodology and results of our working group have been previously published [2,4,10]. ACS was defined by presence of typical clinical symptoms of chest pain and electrocardiographic changes indicative of myocardial ischemia/lesion and/or elevation of serum markers of myocardial damage [11]. A total of 8771 patients were admitted for ACS between November 2003 and December 2016. AF had been previously diagnosed in 759 (8.7%) patients and another 325 (3.7%) patients were diagnosed within the hospitalization; a total of 1084 (12.4%) patients were included in the AF group. According to current recommendations, stroke was defined as the new onset of focal neurological symptoms lasting >24 h or resulting in death [9,12], and classified as a stroke by the treating physician. Diagnoses were based on clinical reports only and patients were censored as a positive end-point when a medical doctor reviewed the medical report. Stroke events were further classified as ischemic, hemorrhagic or uncertain. ACS was classified as ST-elevation myocardial infarction (STEMI) and non-ST elevation ACS according

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to the electrocardiographic findings. Mortality risk was assessed by the GRACE score [11] and patients were categorized, according to current recommendations, into low (<108), intermediate (109–139) or high risk (>140). Bleeding risk was assessed by the CRUSADE risk score and high bleeding risk was defined as >50 [4,13].

Risk factors, clinical antecedents, treatments, complementary test and main diagnosis at discharge were collected from all patients by trained medical staff. The diagnostic and therapeutic ACS protocols in both centers include blood sample determinations in the emergency department and the first fasting state after hospital admission. Glomerular filtration rate was estimated from serum creatinine values with the Modification of Diet in Renal Disease Study equation. For the antecedent of previous coronary heart disease patients needed to have a clinical diagnosis of myocardial infarction, stable or unstable angina or angina-driven coronary revascularization. Previous heart failure was codified if patients had at least one hospitalization with such main diagnosis at discharge-medical report as well as those with typical signs and symptoms of heart failure that had a compatible imagine diagnosis (X-ray or echocardiogram). According to current guidelines [14] and previous reports [3], optimal medical treatment (OMT) at discharge was considered when patients received jointly these four treatments: antiplatelets, statins, betablocker and angiotensin-converter enzyme inhibitors or angiotensin receptor blockers.

The post-discharge follow-up of patients has a well-established protocol in each center and is made by phone calls, review of electronic medical reports and institutional databases. All health process is based on electronic resources in health areas of both centers. Patients´ death is always typed in patients´ the electronic database by the general practitioner responsible of out-of-hospital care or by a hospital clinical but the status in changed to "dead" only by the hospital staff responsible of diagnosis codification; therefore, vital status in certified by a double mechanism. Trained medical staff makes the collection and adjudication of clinical events in both databases. Moreover, and as stated above, we have included that bleeding events were collected according to the TIMI bleeding scale for non-CABG related major bleeding and those fitting definitions 3 or 5 of the BARC consortium. Previous results of major bleeding estimation have been previously published [10,15]. Both centers support and endorse the quality recommendations of the Spanish Society of Cardiology [16] and are integrated in the national network for biomedicine research (Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV)). Vital status was assured by phone calls in absence of medical reports. The ethics committee of the coordinator hospital approved the study protocol.

2.1. Statistical analyses

Quantitative variables are presented as mean (SD) and differences were assessed by t-Student and Chi-square tests. Qualitative variables are presented as percentages and differences were analyzed by ANOVA test. Positive and strong interactions between FA and stroke, age and left ventricle ejection fraction were observed and taken into account in all multivariate analysis. As expected, age, GFR, GRACE score and CRUSADE score obtained positive results colinearity and were modeled in categorical variables; nonetheless, none obtained positive results in the multivariate analyses. Survival analyses were performed after verifying the proportional risk assumption by the Schoenfied residuals test. All-cause mortality predictors were assessed by Cox regression models using all variables that obtained p values < 0.1 in the univariate analysis or could have plausible clinical implication; results are presented as hazard ratio (HR) and 95% confidence intervals (95% CI). The model's discriminative accuracy was assessed by the Harrell's C-statistic, while its calibration was tested by the Gronnesby and Borgan test. The incidence of stroke could be affected by patients' death and, therefore, the usual techniques for time-to-event analysis would provide biased or un-interpretable results due to the presence of competing risks and the Kaplan-Myer estimation will overestimate the real incidence of stroke [17]. With the aim of avoiding such effects we applied the model introduced by Fine and Gray [18] to test the competing events. The incidence of stroke is presented in cumuled incidence function graphs and results of the multivariate analysis as sub-hazard ratio (sHR) and corresponding 95% CI. Patients lost during follow-up were categorized as missing, as well as those who lacked any of the main variables for the analyses although these were very few.

Statistical difference was accepted at $p < 0.05$. All analyses were performed using STATA 14.2 (StataCorp. 2009. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

3. Results

The prevalence of AF was 12.4% (95% CI 11.7–13.1). As shown in Table 1, AF patients were older and had higher prevalence of cardiovascular risk factors, previous cardiovascular disease, including stroke, and lower glomerular filtration rate. Less than half of the AF patients were receiving oral anticoagulation before admission. AF patients presented less frequently as STEMI and angiography, revascularization and drug-eluting stent implantation were performed less frequently among them. In-hospital mortality was 5.1% (95% CI 4.6–5.6) and it was more than two-fold higher in AF patients (10.2% vs. 4.4%; $p < 0.01$). Relevant differences on medical treatments recommended at discharge were observed in AF vs. non-AF patients. The percentage of AF discharged with oral anticoagulation was roughly below 50% and the use of all antiplatelet treatments was lower in AF patients. Dual antiplatelet treatment (DAPT) was recommended in roughly >50% of AF patients. As both centers have similar ACS protocols, no differences in invasive strategy rate, medical treatments or outcomes were observed between both centers.

Table 1
Clinical features of the cohort according to the presence of atrial fibrillation (AF).

	Total	No AF	AF	p
N	8771	7587 (87.6%)	1084 (12.4%)	
Age	66.9 (12.9)	65.7 (12.9)	75.5 (9.2)	<0.01
Females	27.5%	26.6%	34.1%	<0.01
Diabetes	28.2%	27.5%	33.9%	<0.01
Hypertension	57.9%	55.7%	73.4%	<0.01
Current smokers	30.6%	32.4%	15.6%	<0.01
Dyslipidemia	48.0%	48.1%	47.7%	0.82
Previous HF	4.0%	2.7%	12.8%	<0.01
Previous CHD	21.3%	19.9%	31.4%	<0.01
Peripheral arterial disease	8.2%	7.8%	11.0%	<0.01
Previous stroke	6.4%	5.5%	13.4%	<0.01
Previous anticoagulation	5.8%	1.2%	38.9%	<0.01
COPD	9.6%	8.9%	15.0%	<0.01
STEMI	35.3%	36.9%	24.4%	<0.01
GFR ml/min/1.72m^2	79.7 (38.0)	81.7 (39.1)	65.9 (25.6)	<0.01
GFR < 60 ml/min/1.72m^2	23.5%	21.0%	41.1%	<0.01
GRACE score	143.2 (40.3)	139.9 (39.1)	166.1 (41.3)	<0.01
GRACE score > 140	48.5%	45.1%	72.0%	<0.01
CRUSADE score	21.7 (17.5)	20.3 (16.7)	31.3 (19.8)	<0.01
CRUSADE score > 50	10.6%	8.8%	23.7%	<0.01
CHAD2VASC2	2.9 (1.5)	2.8 (1.4)	4.0 (1.4)	<0.01
Charlson index	2.3 (2.2)	2.2 (2.2)	2.9 (2.6)	<0.01
Charlson index ≥4	19.6%	18.6%	26.9%	<0.01
LVEF (%)	54.6 (11.5)	54.9 (11.2)	52.4 (12.6)	<0.01
Angiography	90.3%	91.7%	80.6%	<0.01
Revascularization	75.8%	77.9%	61.9%	<0.01
DES implantation	34.6%	37.5%	13.8%	<0.01
Medical treatments at discharge				
Aspirin	90.9%	93.3%	72.8%	<0.01
Clopidogrel	63.3%	64.1%	57.3%	<0.01
Ticagrelor	6.3%	7.0%	0.7%	<0.01
Prasugrel	3.9%	4.4%	0.4%	<0.01
DAPT	70.9	73.2%	53.7%	<0.01
Oral anticoagulation	7.5%	2.34%	45.9%	<0.01
New oral anticoagulant	0.3%	0.1%	2.0%	<0.01
ACEI/ARB	66.7%	67.0%	64.1%	0.08
Beta-blockers	73.1%	74.4%	63.8%	<0.01
Diuretics	18.5%	16.0%	37.2%	<0.01
Statins	86.2%	87.4%	76.9%	<0.01
Insulin/Oral antidiabetics	19.0%	18.5%	23.1%	<0.01
Nitrates	10.9%	9.8%	19.7%	<0.01

ACEI: angiotensin-converter enzyme inhibitors; ARB: angiotensin receptor blocker; BMS: bare metal stent; CABG: coronary arterial bypass graft; CHD: coronary heart disease; DAPT: dual antiplatelet treatment; DES: drug-eluting stents; HF: heart failure; COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; LVEF: left ventricle ejection fraction; STEMI: ST-elevation myocardial infarction.

Median follow-up was 58.7 months (interquartile range (IQR) 22.8–81.0) and only 4% of the patients were lost to follow-up. A total of 1738 (20.9%) patients died, and cardiovascular causes were attributed in 1174 (14.1%) cases; 3615 (48.8%) experienced at least one MACE; all three endpoints were significantly more frequent among patients with AF (Supl. Fig. 1). A total of 313 patients experienced at least one stroke after hospital discharge (incidence 3.8%, 95% CI 3.4–4.2,) and it was 2-fold higher in patients AF patients: 7.8% vs. 3.3% (Fig. 1). Patients that had a stroke through follow-up had higher mean age, were frequently females and had higher prevalence of cardiovascular risk factors and previous cardiovascular disease (Supl. Table 1); 17.9% of the patients that suffered a stroke had AF. The prevalence of AF was more than 2-fold higher in patients that had a stroke through follow-up. Patients that experienced a stroke were more frequently receiving oral anticoagulation. When we analyzed only AF patients the use of anticoagulation was the same in patients that experienced a stroke or

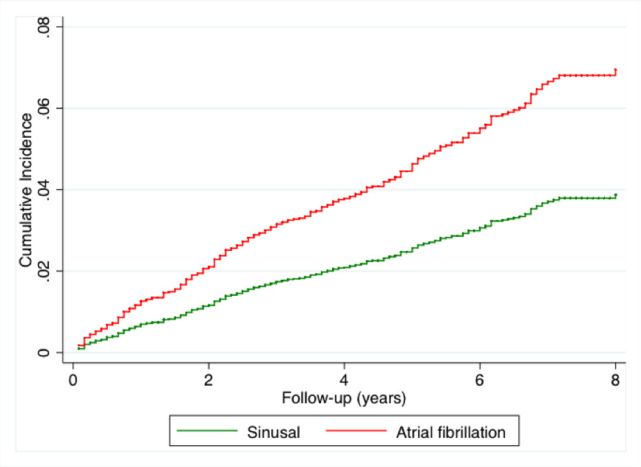

Fig. 1. Kaplan-Meyer curves for (A) cardiovascular mortality, (B) all-cause mortality and (C) first major cardiovascular event through follow-up in patients with or without AF.

not (43.9% vs. 45.4%; p = 0.82). Only 12.1% of the patients that had a stroke were receiving anticoagulants and 43.9% of the AF patients that experienced a stroke were discharged from the hospital with anticoagulants.

All-cause mortality was a competing event in 1368 patients. Ischemic stroke accounted for 92.0% of all strokes. Median time to first stroke was 27.0 (IQR 9.0–56.0) months and it was shorter for AF patients compared to non-AF patients (22.0 (IQR 4.0–46.0) vs. 29.0 (IQR 10.0–58.0); p < 0.01). The fractional polynomial graphs, adjusted for covariates, showed that the risk of stroke was increased at the level of CHA_2DS_2-VASc ≥ 3 for non-AF patients and remained the same, regardless of CHA_2DS_2-VASc score, in AF patients (Supl. Fig. 2). Incidence of stroke according to CHA_2DS_2-VASc score categories is presented in Fig. 2. The competing risk regression results, adjusted by age, gender, revascularization, previous cardiovascular disease, antiplatelets, anticoagulation and all medical treatments at discharge and Charlson index, are presented in Table 2. AF was associated to 82% higher risk of stroke and the leading risk factors for post-discharge stroke were the antecedent of previous stroke and CHA_2DS_2-VASc score = 2 or ≥3. Interestingly, CHA_2DS_2-VASc score = 2 was associated to higher risk of stroke only in AF patients.

4. Discussion

The long-term follow-up of two cohorts of patients discharged with the diagnosis of ACS showed a stroke incidence of 3.8% (95% CI 3.4–4.2), 7.8% in AF-patients, but also 3.3% in patients without any diagnosis of AF. Since clinical features and endpoints rates were similar to previous reports [5,6,9,19] we believe that our results might be representative of daily clinical practice. We also believe that our results have relevant implications in stroke prevention after an ACS, mainly in AF patients, that might be based on clinical characteristics, risk factors control and an optimized medical treatment, including anticoagulation.

AF is the most prevalent sustained arrhythmia and its coexistence with coronary heart disease is common [2,4,7,20]. As opposed to ventricular tachycardia, AF does not cause ventricular fibrillation and has been classically considered as a benign rhythm disorder; nonetheless, long-term association with higher morbidity and mortality are clearly established [6]. Moreover, concomitant conditions, such as heart failure or previous stroke, have been outlined as main determinant of prognosis in AF patients. In a large registry of AF patients from 4 different hospitals, heart failure and chronic renal dysfunction were identified as main predictors of mortality [6]; of note, stroke accounted for <10% of

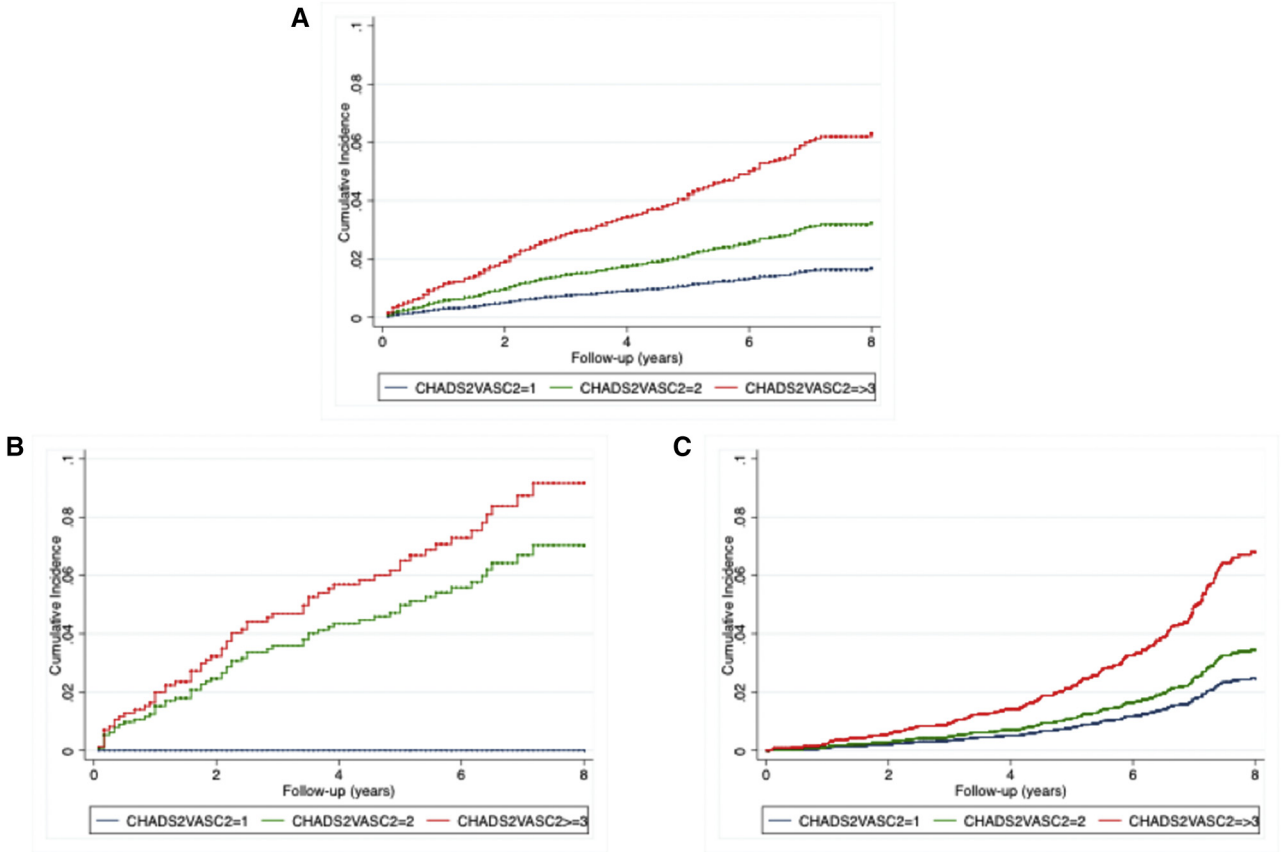

Fig. 2. Cumulative incidence function curves for stroke incidence in the whole cohort (A), in AF patients (B) and non-AF patients (C), according to the CHADS2VASC2 score.

Table 2
Independent predictors of stroke after hospital discharge.

Variables	All patients	Non atrial fibrillation	Atrial fibrillation
Previous stroke	1.92 (1.35–2.74); p < 0.01	2.40 (1.62–3.56); p < 0.01	0.97 (0.45–2.08); p = 0.94
CHA_2DS_2-VASc score = 2	1.95 (1.02–3.75); p = 0.04	1.76 (0.90–3.43); p = 0.10	3.06 (2.05–12.3); p < 0.01
CHA_2DS_2-VASc score ≥ 3	3.86 (1.93–7.70); p < 0.01	3.39 (1.68–6.86); p < 0.01	4.05 (2.16–16.6); p < 0.01
Atrial fibrillation	1.82 (1.26–2.63); p < 0.01		

mortality and three leading causes of dead were heart failure, infections and cancer that explained nearly 2 thirds of fatality. A recent community-based study from Spain found similar results and highlighted the role of age and heart failure on both mortality and stroke incidence [21]. The CHA_2DS_2-VASc [8] has been widely accepted as the gold-standard scale for individual risk of stroke assessment and, also, correlates with coronary lesions burden and MACE incidence in ACS patients [5,19]. Main predictors of stroke in our study were AF, previous stroke and CHA_2DS_2-VASc ≥ 2. Patients without previous diagnosis of AF had an increased risk of stroke if they had CHA_2DS_2-VASc ≥ 3 or previous stroke. These findings could be explained by the effect of carotid or cerebral atherosclerosis and, also, incident AF [22].

The addition of a low-dose of oral anticoagulation, with 2.5 mg/12 h of rivaroxaban, to aspirin reduced mortality, myocardial infarction and stroke in patients with chronic coronary heart disease and sinus rhythm in the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) study and such reduction was mainly achieved by protection against stroke [23]. Similarly, the addition of ticagrelor to aspirin more than 1 year after an ACS also reduced the incidence of stroke in the PEGASUS trial [24]. On the contrary, studies evaluating antithrombotic treatment in the early phase after an ACS have not found benefits in stroke protection [25] probably reflecting the complexity of reducing events beyond the strong protection that is already conferred by the standard therapy that includes double antiplatelet therapy, statins and ACE inhibitors. It is noteworthy that doses of anticoagulation could be determinant, especially when added to DAPT. For example, in the ATLAS trial [25] the arm of 5 mg/12 h of rivaroxaban had a significantly higher increase in bleeding complications that penalized the net clinical benefit of rivaroxaban; in contrast, the 2.5 mg/12 h of rivaroxaban used in the COMPASS trial [23] obtained a clear net clinical benefit despite the increase of non-fatal bleeding. The stroke incidence among patients in sinus rhythm in our study, which represented the majority of the population, did not increase significantly and the stroke survival curves did not diverge, until the second year of follow-up after de ACS. We believe that such findings highlight the complexity of stroke prevention and lack of long-term preventive medication under current medical practice.

The stroke incidence in our study was 3.8%, after 4 years follow-up, similar to other publications. For example, a retrospective analysis using administrative data from California yielded a stroke incidence of 2.7% after 2 years of follow up [26] and a metanalysis revealed a one-year incidence of 2.14% [1]. More recently, a subanalysis of the IMPROVE-IT trial showed a stroke incidence of 3.5%, during a median follow-up of 6 years, in population of patients stabilized after an ACS [9]. In the same manner as the results of our study, prior stroke, age > 75 years and atrial fibrillation were the leading risk factors but we believe that the analysis performed by the Bohula et al. [9] had several weakness because they did not take under consideration the effect of competing events [10]. The conventional analysis of "time to first event" can be biased by the concurrence of other events, especially death, and could overestimate the results. The competing risk regression was developed for situations when the occurrence of one type of event changes the ability to observe the event of interest [18]. The incidence of intermediate end-points in the cardiology field, such as stroke, heart failure or hemorrhages, can be altered by death and this is key issue for statistical analyses. Many studies have been previously published without taking competing risk under consideration but more recent and reliable publications have incorporated this methodology [2,17,27]. Overall stroke incidence, follow-up and clinical features are very similar in our study and the one from Bohula et al. [9] but we strongly believe that our results are largely more representative of actual predictors of stroke.

Stroke and ACS share atherosclerosis as the common physiopathology and also have many risk factors in common [28]; however, individual risk associated with each factor is variable. Dyslipidemia and diabetes are the most determinant risk factors for ACS [29]; in contrast, hypertension and obesity have higher impact on stroke [30] and both diseases are highly influenced by smoking [29,30]. Hypertension, as well as age and prevalent cardiovascular disease, increase the risk of AF and, therefore, the risk of stroke. ACS can also predispose to stroke through different mechanisms that can also induce AF, such as left ventricle dysfunction, heart failure or sinus dysfunction. Almost two thirds of the ACS patients in our study were hypertensive. Hypertension was the most prevalent risk factor, what added to a mean age of >65 years and a recent ACS generate population with an increased risk of stroke. Median time to first stroke was more than one year after hospital discharge and <25% occurred within the first year. Anticoagulation was not associated to lower stroke incidence in our study and this might highlight two relevant issues: 1) stroke after ACS might be more related to atherosclerosis than AF or; 2) anticoagulation drugs and the doses that were used were inefficient for stroke prevention. Protocols of both institutions recommended dual antiplatelet treatment for only 12 months after hospital discharge and oral anticoagulation was prescribed according to physicians´ criteria.

The low rate of anticoagulation at discharge in our study might highlight the unmet need of safe and effective strategies with antiplatelet and anticoagulants in the setting of ACS. A recent subanalysis of the ARISTOLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial showed that the use of antiplatelet therapies and anticoagulants varied widely between centers [20]. Moreover, the presence of previous stroke modified the effect of apixaban on post-ACS patients, demonstrated by a significant interaction [31], in the APPRAISE-2 (Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome) trial. The so-called triple therapy, DAPT plus anticoagulation, has been proven to reduce mortality but with higher rates of bleeding [32]. The WOEST trial demonstrated the safety of a dual therapy, with clopidogrel and anticoagulation [33]. Most recently, two clinical trials [34,35] and several metanalyses [36,37] have proven the efficacy of dual therapy, with clopidogrel and NOACs, for AF patients treated with PCI; nonetheless, no more than 50% of patients in these last two trials were included in the setting of ACS. Interestingly, and in accordance with previous studies, benefits did not include reduction in the stroke incidence.

Our study has some limitations that should be addressed. Firstly those inherent to observational retrospective studies, the lack of randomization and the lack of active search for stroke may be the most relevant. Recent studies have changed the standard of care and recommendations for treatment of patients with ACS and concomitant AF and also for patients with stable CHD [34,35] that have not been translated into daily clinical practice jet. As any observational study associations between various treatments and outcomes may be confounded by unmeasured variables and there could also have been limitations for medical treatments or invasive procedures that were not collected in our databases. Several unmeasured confounders or details

about physician or patient decision-making might not be available in our collection data protocol and could account for some of paradoxes observed. This could explain the lower-than-expected use of DAP or anticoagulation according to the rate of revascularization and AF prevalence. Moreover, doses of oral anticoagulation were not collected in our database and, therefore, we could not assess whether there were prescribed properly or not; the lower-than-expected use of DAPT or anticoagulation according to the rate of revascularization and AF prevalence may have influenced the incidence of outcomes in the present study. Our study adds relevant information about the incidence, the time relationship between MI and stroke and prognostic factors in the scenario of current common practice. There are also strengths that must be highlighted, like the meticulous statistical analysis including competing events consideration and the long follow-up in a large population, with a high number of events particularly among patients in sinus rhythm.

We conclude that stroke incidence after an ACS is considerable, as expected it is higher in patients with AF, but the risk is not neglectable among patients in sinus rhythm. Previous stroke and CHA_2DS_2-VASc were also independently associated with the stroke risk, which could be of relevance at the time of the medical treatment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.082.

Disclosures

Authors declare that there are no potential conflicts of interest related to the results of this article.

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