Stroke Risk in post-Myocardial Infarction patients with Systolic Dysfunction and/or Heart Failure without Atrial Fibrillation

João Pedro Ferreira, MD, PhD[1,2]; Nicolas Girerd, MD, PhD[1]; John Gregson, PhD[3]; Ichraq Latar, MSc[1]; Abhinav Sharma, MD[4,5]; Marc A. Pfeffer, MD, PhD[6]; John J. V. McMurray, MD, PhD[7]; Azmil H. Abdul-Rahim, MD, MSc[8]; Bertram Pitt, MD, PhD[9]; Kenneth Dickstein, MD, PhD[10]; Patrick Rossignol, MD, PhD[1]; Faiez Zannad, MD, PhD[1]; for the High-Risk Myocardial Infarction database initiative.

[1]INSERM, Centre d'Investigations Cliniques Plurithématique 1433, INSERM U1116, Université de Lorraine, CHRU de Nancy, F-CRIN INI-CRCT, Nancy, France; [2]Department of Physiology and Cardiothoracic Surgery, Cardiovascular Research and Development Unit, Faculty of Medicine, University of Porto, Porto, Portugal; [3]Department of Biostatistics, London School of Hygiene & Tropical Medicine, London, UK; [4]Duke Clinical Research Institute, Duke University, Durham, North Carolina, USA; [5]Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada; [6]Division of Cardiovascular Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, U.S.A.; [7]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, United Kingdom; [8]Institute of Neuroscience and Psychology, University of Glasgow; [9]Department of Medicine, University of Michigan School of Medicine, Ann Arbor; [10]University of Bergan, Stavanger University Hospital, Department of Cardiology, Stavanger, Norway.

Address for correspondence:

Professor Faiez Zannad

Centre d'Investigations Cliniques-INSERM CHU de Nancy,

Institut Lorrain du Cœur et des Vaisseaux Louis Mathieu,

4 Rue du Morvan, 54500 Vandoeuvre lès Nancy, France.

Tel : +33 (0) 3 83 15 73 15

Fax : +33 (0) 3 83 15 73 24

E-mail: f.zannad@chru-nancy.fr

Abstract

Background: Stroke can occur after myocardial infarction (MI) in the absence of atrial fibrillation (AF).

Objectives: To identify risk factors (excluding AF) for the occurrence of stroke and developing a calibrated and validated stroke risk score in MI patients with heart failure (HF) and/or systolic dysfunction.

Methods: The datasets included in this pooling initiative are derived from four trials: CAPRICORN, OPTIMAAL, VALIANT, and EPHESUS (the latter used for external validation). A total of 22,904 patients without AF or oral anticoagulation were included in this analysis. The primary outcome was stroke and death was treated as a "competing risk".

Results: During a median follow-up of 1.9 (percentile$_{25-75}$=1.3-2.7) years, 660 (2.9%) patients had a stroke. These patients were older, more often female, smokers, hypertensive, had higher Killip class, lower estimated glomerular filtration rate (eGFR), higher proportion of MI, HF, diabetes, and stroke histories. The final stroke risk model retained older age, Killip class 3 or 4, eGFR≤45ml/min/1.73m^2, hypertension history, and previous stroke. The models were well calibrated and showed moderate/good discrimination (c-index =0.67). The observed 3-year event rates increased steeply for each sextile of the stroke risk score (1.8%, 2.9%, 4.1%, 5.6%, 8.3%, and 10.9%, respectively) and were in agreement with the expected event rates.

Conclusion: Readily accessible risk factors associated with the occurrence of stroke were identified and incorporated in an "easy-to-use" risk score. This score may help in the identification of patients with MI and HF and a high risk for stroke despite not presenting AF.

Key-words: myocardial infarction; heart failure; stroke; risk score.

Condensed abstract

Stroke can occur after myocardial infarction (MI) in the absence of atrial fibrillation (AF). In a large (22,904) MI population with systolic dysfunction but without AF, 660 (2.9%) patients had a stroke during a median follow-up of 1.9 years. The final stroke risk model retained older age, Killip class 3/4, eGFR≤45ml/min/1.73m^2, hypertension, and previous stroke as independent stroke risk factors. The models were well calibrated and showed moderate/good discrimination (c-index=0.67). These readily accessible risk factors were incorporated in a risk score that may help in the identification of patients with a high risk for stroke despite not presenting AF.

Abbreviations

MI, myocardial infarction

AF, atrial fibrillation

HF, heart failure

eGFR, estimated glomerular filtration rate

OAC, oral anticoagulant

CRF, case report form

Introduction

Stroke may be potentially devastating for the patient and has important impact on their families, caregivers and society(1). Stroke can occur after myocardial infarction (MI) further complicating MI management and increasing associated death rates(2). The incidence rates of stroke after MI vary between ≈1% and 5%(3-6). The formation of areas of akinesia and/or dyskinesia in the left ventricle after MI may increase the risk for mural thrombi formation and subsequent peripheral thromboembolism and stroke(7). Nonetheless, these reports included patients with atrial fibrillation (AF) which is a major risk factor for stroke(8). Hence, whether is MI, akinesia, systolic dysfunction, heart failure (HF), AF or other factors that contribute to the occurrence of stroke in the post-MI setting is difficult to ascertain(9). Consequently, the risk of stroke in post-MI patients but without AF is poorly defined.

Myocardial infarction complicated with systolic dysfunction and/or HF (but without AF) may create a particularly thrombogenic environment *per se*, through fulfillment of the Virchow triad (stasis of blood flow, endothelial injury, and hypercoagulability)(10). Therefore, analyzing the incidence and risk factors for stroke in a "complicated" MI population without AF may help identify patients at high risk in whom an early intervention (e.g. oral anticoagulation) may be valuable for stroke prevention.

The high-risk MI initiate provides a unique opportunity to study the occurrence of stroke in patients with "complicated" MI but without AF in more than 20,000 patients and 600 stroke events. The present study aims to identify the characteristics of the patients who had a stroke during follow-up stroke and to develop a calibrated and validated stroke risk score in this population.

Methods

Study population

The high-risk MI initiative consists of a previously published cohort of pooled patient data derived from four clinical trials(11). Briefly, the main objectives of the project are to provide a comprehensive and statistically robust analysis of long-term clinical outcomes in high-risk survivors of MI. The datasets included in this pooling initiative were: the effect of Carvedilol on Outcome after Myocardial Infarction in Patients with Left Ventricular Dysfunction trial (CAPRICORN)(12, 13), the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)(14, 15), the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL)(16, 17) and the Valsartan in Acute Myocardial Infarction trial (VALIANT)(18, 19). Full details of total enrolled patients, the inclusion and exclusion criteria for each trial, the endpoints as well as the results have previously been published(11). Each trial enrolled patients with left ventricular systolic dysfunction, HF or both between 12 h and 21 days after acute MI. The information included in this pooled database does not include the treatment randomization assignments for each trial.

The respective chairpersons of the Steering Committees of the four trials initiated the pooling project.

The studies were all conducted in accordance with the Declaration of Helsinki and approved by site ethics committees. All participants gave written informed consent to participate in the studies.

For the present analysis, we selected patients without history of AF or AF present at randomization ECG or those treated with an OAC.

Outcomes

The primary outcome was stroke. Stroke was consistently defined as a focal neurologic deficit lasting more than 24 hours or resulting in death that was presumed to be related to stroke. All-cause death was considered the competing-risk event.

Endpoints were independently adjudicated in the respective trials.

Statistical methods

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as frequencies and proportions. For comparison of means and proportions, student t-test and chi-square test were used, respectively.

Time-to-event analysis was conducted using a competing-risk model as described by Fine and Gray(20), with stroke as outcome event and death as competing-risk. Log-linearity was checked by testing the functional forms of the covariable by the Kolmogorov-type supremum test and by visual inspection by plotting the beta estimates versus the mean across deciles. Covariables were entered in the multivariable model in a stepwise regression analysis with p-value to enter and stay in the model set to p =0.15 and p =0.05, respectively. Covariables considered to be of potential prognostic impact were age, gender, body mass index, smoking status, systolic blood pressure, heart rate, Killip class, estimated glomerular filtration rate (eGFR, calculated using the CKD-EPI formula(21)), previous myocardial infarction, history of heart failure, peripheral artery disease, hypertension, diabetes mellitus, previous stroke, and medications (use of angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, statins and aspirin). These variables had a small proportion of missing values (<10%) and no multiple imputation was performed. We assessed interactions with the *Log* of time, age, sex, systolic blood pressure, and diabetes but none were significant (all p >0.10).

Discrimination of the competing-risk regression model was assessed by calculating the C-statistics. Assessment of the calibration was performed by visually

plotting the cumulative incidence of observed versus expected stroke events derived from the competing risk model across sextiles of the predicted risk. Internal validation of the model was performed by bootstrapping (50x) and external validation was performed in the EPHESUS trial dataset.

In order to create a simple integer risk score, continuous variables included in the chosen model, were categorized into either two or three groups using a combination of established clinical cut-points and graphical examination of rates across quintiles. To simplify the risk score, integer points were assigned to each prognostic factor based upon the log-hazard ratio estimates. The total risk score for each patient was calculated by summing the points across all chosen prognostic variables. From the overall distribution of the risk score we formed six categories of risk, containing approximately equal number of events. Within each risk category and by treatment group we calculated the number of events, person-years at risk, and the overall event rate. Kaplan–Meier plots were drawn showing the cumulative incidence curves by treatment group and risk category.

All analysis was performed with STATA® software (version 14). A p-value <0.05 was considered as statistically significant.

Results

Population characteristics

From the initial 28771 patients included in the high-risk MI pooled dataset(11), 3754 were excluded from the analysis due to the presence and/or history of AF, and 2113 patients were additionally excluded for being prescribed OAC leaving 22904 patients included in the current analysis.

The mean age was 64 (SD=11) years and 30% of patients were female. Patients who had a stroke during follow-up were older, more often female, smokers, and had

higher systolic blood pressure, were more often on Killip class 3 or 4, had lower eGFR, had higher proportion of previous MI events, HF history, hypertension, diabetes, and previous stroke. **Table 1**.

During a median follow-up of 1.9 (percentile $_{25\text{-}75}$ 1.3-2.7) years, 660 (2.9%) patients had a stroke. The stroke incidence rate was 4.1 (95%CI 3.9-4.5) per 1000 patient-years. **Table 1**.

Risk models

The covariates retained in the final stroke risk model are depicted in **Table 2**. Older age, Killip class 3 or 4, eGFR ≤45 ml/min/1.73m^2, hypertension history, and previous stroke were independently associated with increased risk of stroke.

The models were well calibrated: a steep gradient in risk by sextiles of predicted risk was observed (**Figure 1**, **Supplemental Table 1**, and **Figure 2**), and showed moderate/good discrimination (c-index =0.67). The integer risk score derived from these covariates ranges from 0 to 11 points. **Table 2**.

The model calibration remained good when patients with previous stroke were excluded from the analysis. **Supplemental Table 2**.

The external validation was performed in the EPHESUS dataset also with good calibration and discrimination. **Supplemental Table 3** & **Table 3.**

Event rates

The 1, 2, and 3-year observed cumulative incidence rates of stroke were 1.3% (95%CI =1.2–1.4), 1.5% (95%CI =1.4–1.6), and 1.6% (95%CI =1.5–1.7), respectively.

The observed 3-year stroke event rates increased steeply for each category of the risk score (1.8%, 2.9%, 4.1%, 5.6%, 8.3%, and 10.9%, respectively) and were in agreement with the expected event rates. **Figure 1** and **Supplemental Table 1**.

An on-line calculator for stroke risk prediction in each individual patient (with the characteristics of those included in the present study) is available in the **Supplemental Calculator**.

Event rates in patients with atrial fibrillation

Among the 3754 patients with AF at baseline, 215 (5.7%) had a stroke during a median follow-up of 1.7 (percentile $_{25-75}$ 1.0-2.4) years. The stroke incidence rate was 9.5 (95%CI 8.3-10.8) per 1000 patient-years. The cumulative incidence at 1, 2, and 3 years was 2.9% (95%CI =2.7–3.1), 3.3% (95%CI =3.0–3.6), and 3.4% (95%CI =3.1–3.7), respectively.

Discussion

Our study identifies readily available clinical risk factors associated with stroke in a population with MI complicated by systolic dysfunction and/or HF but without AF (or OAC treatment). These risk factors were computed in an easy-to-use risk score that provides useful prognostic information to clinicians and may serve to ascertain "risk enhancement strategies" in future trials for stroke prevention in populations with these characteristics. However, practical decisions regarding anti-coagulation in this population warrant prospective and randomized evidence before any such advice is provided.

Overall, post-MI patients with systolic dysfunction but without AF may have a higher risk of stroke than individuals without MI. However, this risk may still vary considerably among MI survivors, and be low (<2% at 3-years) for patients in the bottom sextile of our risk score or high (>10%) in patients with several risk factors (e.g., older age, impaired renal function, hypertension, previous stroke or Killip class 3/4) in the top sextile of the risk score.

The overall stroke rate in our pooled data analysis overlapped that reported in other post-MI cohorts. In the Survival and Ventricular Enlargement trial(6) including 2231 post-MI patients who had left ventricular systolic dysfunction and were followed for ≈42 months, 4.6% (n=103) had a stroke during the study (1.5% event rate per follow-up year). However, 16% of patients with stroke had AF vs. 10% of patients without stroke; p =0.03. Similarly, older age was also an independent risk factor for stroke. Reports derived from population-data show a ≈4% stroke incidence at 1-year post-MI and describe similar independent risk factors for stroke, such as age and previous stroke(5). A meta-analysis(22) reported lower rates of stroke in the post-MI setting (≈1-2%), but also found older age, hypertension and history of prior stroke (plus anterior MI, HF, diabetes, and AF) as independent risk factors for stroke. Although, these reports reinforce the external validity of our results, one should notice that the population included in our pooled dataset is a "high-risk" population i.e., all patients had MI complicated with systolic dysfunction and/or HF (or diabetes in the EPHESUS trial), hence is not surprising that we found higher stroke rates than those reported in "population-derived data". However, when looking at patient-populations with similar characteristics (as in the Survival and Ventricular Enlargement trial) we find overlapping stroke rates (despite not having patients with AF in our cohort). Of note, although lower left ventricular ejection fraction has been reported as a risk factor for stroke,(6) this that was not the case in our analysis. This may be due to the overall low ejection fraction of our patient-population, where an ejection fraction <35% was an entry criterion for these trials.

In patients with AF the risk of stroke (and also the strategies to avoid stroke) are much better developed. Readily accessible risk scores are available for use in clinical practice. For instance the CHA_2DS_2-VASc [Congestive heart failure, Hypertension, Age

≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female)](23) is recommended by the current guidelines and its use has been extensively validated(24, 25) (although the c-index of this score does not exceed 0.6 in most populations(23)). Notwithstanding, in daily practice most patients with AF and a CHA_2DS_2-VASc score of 1 or greater (according to the ESC guidelines) or ≥2 (according to the AHA/ACC/HRS guidelines) should be treated with anticoagulant therapy (unless contra-indicated or counter balanced by a high bleeding risk)(24, 25). In our patient-population, the incidence rates for stroke in patients with AF were ≈2-fold higher compared to patients without AF. Patients without AF and with a risk score of 3 or higher had similar (for stroke risk score =3) or higher (for stroke risk score >3) stroke rates. These data provide an idea of the magnitude of the problem. Patients without AF and with the characteristics depicted herein, that have a stroke risk score ≥3 may also benefit from oral anticoagulation as their AF counterparts.

Despite observational data showing that some populations may also be at high risk for stroke despite not having AF(9), oral anticoagulation is not currently recommended as routine strategy for stroke prevention in patients without AF. A strategy of OAC was tested in patients with chronic HF in sinus rhythm (a different setting from that described herein) in the WARCEF trial(26). The rate of stroke was similar to that described in our report (≈1.4% at 3 years). As compared to aspirin warfarin did not reduce the primary composite outcome of ischemic stroke, intracerebral hemorrhage, or death from any cause. However, warfarin was associated with a lower rate of ischemic stroke (0.72 events per 100 patient-years vs. 1.36 per 100 patient-years; p =0.005) but increased the rate of major hemorrhage (1.78 events per 100 patient-years vs. 0.87; p <0.001), without differences in intracranial hemorrhage rates.

More recently, the COMPASS (Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease) trial(27) evaluated whether rivaroxaban (2.5 mg twice daily) alone or in combination with aspirin (100 mg once daily) would be more effective than aspirin alone for secondary cardiovascular prevention in patients with stable atherosclerotic vascular disease. Approximatively 62 % and 22% of patients presented with a history of MI and HF at baseline, respectively. The primary outcome of CV death, stroke, or myocardial infarction occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (4.1% vs 5.4%; HR =0.76; 95%CI =0.66-0.86; p <0.001), but major bleeding events occurred in more frequently in the rivaroxaban-plus-aspirin group, without difference in fatal or intracranial bleeding. It should be noted that the rate of ischemic stroke was lower in the rivaroxaban-plus-aspirin and rivaroxaban alone groups compared to the aspirin-alone group, suggesting that low-dose rivaroxaban may prevent the occurrence of stroke even in the absence of AF.

The COMMANDER-HF trial(28) is underway to assess whether rivaroxaban (2.5 mg twice daily) may prevent morbidity and mortality in patients with HF-REF plus coronary artery disease and without AF. The primary outcome is a composite of death, MI or stroke. The COMMANDER-HF trial may help to determine if low-dose rivaroxaban may prevent stroke in HF patients without AF. Downstream of COMPASS and COMMANDER-HF, whether the score we designed herein may further help identifying an even higher-stroke risk subgroup warrants a dedicated testing, along with the effect of antithrombotic strategies in this subgroup.

A particular strength of this study is the validation of our predictive model in another data set. Consequently, our findings may have clinical implications - with a small number of

routinely collected clinical variables it is possible to identify patients with MI (plus systolic dysfunction and/or HF) but without AF who are at risk of stroke. Patients with a stroke risk score ≥3 have similar or higher stroke rates than patients with AF. To date there is no trial evidence to justify anticoagulant treatment in this population, but our findings may help in the identification of patients for such a trial. Of the five variables retained in our final stroke risk model, two variables were also found in HF-REF and HF-PEF populations(9, 29, 30) - older age and previous stroke, however lower eGFR, hypertension history and Killip class 3 or 4 are specific of MI patients with reduced left ventricular ejection fraction.

Limitations

Several limitations should be acknowledged in this analysis. First, this is a non-prespecified retrospective study of a pooled dataset from randomized clinical trials. Although the end-points have been independently adjudicated in each trial, no causality can be established and the associations reported herein are subject to the same potential bias of observational studies. Second, although an ECG was routinely performed at randomization we cannot ascertain which patients developed AF after randomization or even patients that had paroxysmal AF without being reported in the CRF. Hence many patients included in this analysis may actually have (or have developed AF). The fact that no time-interaction was observed may suggested that this did not have a substantial influence, as the risk factors present at short-time after MI did not vary significantly across follow-up. Third, the findings here reported cannot be generalized to other populations without these characteristics, particularly post-MI patients with preserved ejection fraction. Fourth, the type of stroke is not reported in the dataset. We assume that the great majority of strokes were ischemic but hemorrhagic strokes might also

have occurred(31). Fifth, there are clinically relevant differences between the derivation cohort (EPHESUS trial) and the other cohorts (OPTIMAAL, CAPRICORN, and VALIANT trials). Differences as previous HF history (13% in EPHESUS vs. 44% in the other cohorts) and diabetes (32% in EPHESUS vs. 23% in the other cohorts) could have influenced the risk model discrimination. However, the discrimination ability of the developed stroke risk model is similar in validation and derivation cohorts (0.67 vs. 0.66). Sixth, patients without AF but treated on OACs were excluded from the present analysis that is tailored for MI populations with reduced ejection fraction and without AF or OACs treatment. Moreover, we could not ascertain the reasons for anticoagulation in this population, that could vary widely (e.g. pulmonary embolism, deep venous thrombosis, LV thrombus) and affect the validity of the stroke risk model. Lastly, the discrimination of the best stroke risk model developed herein was moderate/good (c-index≈0.7). A higher (>0.7) model discrimination would provide more accurate predictions in discriminating between patients with and without stroke. Nonetheless, a higher discrimination would not change clinical practice either. In order to change/guide patients` treatment adequately powered, randomized and controlled evidence is required.

Conclusion

In a large population with MI complicated by systolic dysfunction or HF but without AF, readily accessible risk factors were identified and incorporated in an "easy-to-use" risk score. This risk score may help in the identification of patients with a high stroke risk despite not having AF.

Disclosures

Clinical competencies and translational outlook

We identified readily available risk factors for the occurrence of stroke in a population with myocardial infarction and left ventricular ejection fraction ≤35% without atrial fibrillation. The stroke risk score developed herein may help in the identification of patients with a high stroke risk (despite not having AF) and aid as "risk-enhancement" strategy for patient selection in future clinical trials targeting populations with the same characteristics of those described in the present study.

Bibliography

1.   Feigin VL, Mensah GA, Norrving B, Murray CJ, Roth GA. Atlas of the Global Burden of Stroke (1990-2013): The GBD 2013 Study. Neuroepidemiology. 2015;45(3):230-6.
2.   Budaj A, Flasinska K, Gore JM, et al. Magnitude of and risk factors for in-hospital and postdischarge stroke in patients with acute coronary syndromes: findings from a Global Registry of Acute Coronary Events. Circulation. 2005;111(24):3242-7.

3.   Maggioni AP, Franzosi MG, Santoro E, White H, Van de Werf F, Tognoni G. The risk of stroke in patients with acute myocardial infarction after thrombolytic and antithrombotic treatment. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico II (GISSI-2), and The International Study Group. N Engl J Med. 1992;327(1):1-6.

4.   Behar S, Tanne D, Abinader E, et al. Cerebrovascular accident complicating acute myocardial infarction: incidence, clinical significance and short- and long-term mortality rates. The SPRINT Study Group. Am J Med. 1991;91(1):45-50.

5.   Ulvenstam A, Kajermo U, Modica A, Jernberg T, Soderstrom L, Mooe T. Incidence, trends, and predictors of ischemic stroke 1 year after an acute myocardial infarction. Stroke. 2014;45(11):3263-8.

6.   Loh E, Sutton MS, Wun CC, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. N Engl J Med. 1997;336(4):251-7.

7.   Lamas GA, Vaughan DE, Pfeffer MA. Left ventricular thrombus formation after first anterior wall acute myocardial infarction. Am J Cardiol. 1988;62(1):31-5.

8.   Lip GY, Tse HF, Lane DA. Atrial fibrillation. Lancet. 2012;379(9816):648-61.

9.   Abdul-Rahim AH, Perez AC, et al. Risk of Stroke in Chronic Heart Failure Patients Without Atrial Fibrillation: Analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials. Circulation. 2015;131(17):1486-94.

10.   Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. J Am Coll Cardiol. 1999;33(5):1424-6.

11.   Dickstein K, Bebchuk J, Wittes J. The high-risk myocardial infarction database initiative. Prog Cardiovasc Dis. 2012: 362-6.

12.   Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet. 2001: 1385-90.

13.   Dargie HJ. Design and methodology of the CAPRICORN trial - a randomised double blind placebo controlled study of the impact of carvedilol on morbidity and mortality in patients with left ventricular dysfunction after myocardial infarction. Eur J Heart Fail. 2000: 325-32.

14.   Pitt B, Williams G, Remme W, et al. The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. Cardiovasc Drugs Ther. 2001;15(1):79-87.

15.   Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003: 1309-21.

16.   Dickstein K, Kjekshus J. Comparison of the effects of losartan and captopril on mortality in patients after acute myocardial infarction: the OPTIMAAL trial design. Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan. Am J Cardiol. 1999: 477-81.

17.   Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet. 2002: 752-60.

18.   Pfeffer MA, McMurray J, Leizorovicz A, et al. Valsartan in acute myocardial infarction trial (VALIANT): rationale and design. Am Heart J. 2000: 727-50.

19.   Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003:1893-906.

20.   Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk.   J Am Stat Assoc. 1999;94 :496–509.   .

21.   Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009: 604-12.

22.   Witt BJ, Ballman KV, Brown RD, Jr., Meverden RA, Jacobsen SJ, Roger VL. The incidence of stroke after myocardial infarction: a meta-analysis. Am J Med. 2006;119(4):354.

23.   Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72.

24.   Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31(19):2369-429.

25.   January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21).

26.   Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012;366(20):1859-69.

27.   Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017.

28.   Zannad F, Greenberg B, Cleland JG, et al. Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial. Eur J Heart Fail. 2015;17(7):735-42.

29.   Abdul-Rahim AH, Perez AC, MacIsaac RL, et al. Risk of stroke in chronic heart failure patients with preserved ejection fraction, but without atrial fibrillation: analysis of the CHARM-Preserved and I-Preserve trials. Eur Heart J. 2017;38(10):742-50.

30.   Freudenberger RS, Cheng B, Mann DL, et al. The first prognostic model for stroke and death in patients with systolic heart failure. J Cardiol. 2016;68(2):100-3.

31.   Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP. Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. Stroke. 2009;40(6):2068-72.

Figure 1. Model calibration plot: % of observed vs predicted events at 3-years by categories of stroke risk score.
Legend: the models were well calibrated: a steep gradient in risk by sextiles of predicted risk was observed.

Figure 2. Kaplan-Meier failure estimates curve by stroke risk score categories for the outcome of stroke with death as competing risk.
Legend: stroke event rates increase by stroke risk score categories.

Table 1. Characteristics of the patients without atrial fibrillation and no oral anticoagulants

Characteristics	n	No stroke (n=22244)	Stroke (n=660)	p-value
Age, years	22904	64.1 ± 11.4	68.7 ± 10.0	<0.0001
Female gender, n (%)	22904	6570 (29.5 %)	224 (33.9 %)	0.015
BMI, Kg/m^2	22368	27.5 ± 4.9	27.2 ± 4.2	0.064
Current smoker, n (%)	22882	6730 (30.3 %)	244 (37.0 %)	<0.0001
SBP, mmHg	22863	121.8 ± 16.8	125.1 ± 18.6	<0.0001
Heart rate, bpm	22850	75.3 ± 12.4	76.0 ± 13.4	0.15
LVEF, %	15578	34.7 ± 8.8	34.4 ± 9.4	0.60
Killip 3 or 4, n (%)	22819	3876 (17.5 %)	162 (24.6 %)	<0.0001
eGFR, ml/min/1.73m^2	21974	71.3 ± 38.8	66.5 ± 31.9	0.002
Hemoglobin, g/L	10298	133.7 ± 15.9	133.1 ± 14.6	0.55
Sodium, mmol/L	10550	139.4 ± 3.8	139.1 ± 3.5	0.14
Potassium, mmol/L	10497	4.3 ± 0.5	4.2 ± 0.5	0.16
Previous MI, n (%)	22902	5537 (24.9 %)	207 (31.4 %)	0.0002
CABG, n (%)	22904	1117 (5.0 %)	31 (4.7 %)	0.71
PCI, n (%)	22904	4673 (21.0 %)	82 (12.4 %)	<0.0001
HF history, n (%)	22904	8215 (36.9 %)	270 (40.9 %)	0.037
PAD, n (%)	22903	1694 (7.6 %)	63 (9.5 %)	0.066
Hypertension, n (%)	22904	11890 (53.5 %)	407 (61.7 %)	<0.0001
Diabetes mellitus, n (%)	22904	5576 (25.1 %)	202 (30.6 %)	0.001
COPD, n (%)	22904	1769 (8.0 %)	56 (8.5 %)	0.62
Previous stroke, n (%)	22904	1522 (6.8 %)	115 (17.4 %)	<0.0001
Aspirin, n (%)	22904	19791 (89.0 %)	592 (89.7 %)	0.56
ACEi/ARBs, n (%)	18283	9951 (55.8 %)	240 (52.1 %)	0.11
Beta-blockers, n (%)	21282	13908 (67.4 %)	391 (61.7%)	0.003
Diuretics, n (%)	22904	9415 (42.3 %)	323 (48.9 %)	0.0007
Statins, n (%)	22904	7654 (34.4 %)	167 (25.3 %)	<0.0001
Stroke, n (%)	22904	0 (0.0 %)	660 (100.0 %)	<0.0001
ACM, n (%)	22904	3372 (15.2 %)	281 (42.6 %)	<0.0001

Legend: BMI, body mass index; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; HF, heart failure; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; ACM, all-cause mortality.

Table 2. Multivariate competing risk model for Stroke

Final model	HR (95%CI)	Coef.	P-value	Integer
Age < 60 yr	Ref.	-	-	
Age ≥60 to 75	1.82 (1.48-2.25)	0.60	<0.001	+2
Age >75	2.12 (1.65-2.73)	0.75	<0.001	+3
Killip class 3 or 4	1.31 (1.09-1.57)	0.27	0.004	+1
eGFR >60 ml/min/1.73m^2	Ref.	-	-	
eGFR >45 to 60	0.91 (0.74-1.11)	-0.09	0.37	-
eGFR ≥30 to ≤45	1.29 (1.02-1.63)	0.26	0.031	+1
Hypertension	1.18 (1.00-1.40)	0.17	0.045	+1
Previous stroke	2.21 (1.78-2.74)	0.80	<0.001	+3

Model C-index (Harrell`s C) =0.67

Final report after 50x bootstrap.

Legend: eGFR, estimated glomerular filtration rate.

Table 3. External validation of the risk model in the EPHESUS dataset

Stroke risk score (6 categories)	n. (%)	n. events	% observed	% expected
0 or 1	1,789 (35.5)	17	1.5	1.8
2	689 (13.7)	14	3.7	3.0
3	1,217 (24.2)	31	3.8	3.6
4	734 (14.6)	24	4.2	4.1
5	277 (5.5)	12	6.7	5.0
≥6	332 (6.6)	12	7.0	8.2

C-index of the stroke risk model in the EPHESUS dataset =0.66