Title: Predicting stroke in heart failure and preserved ejection fraction without atrial fibrillation

Short title: Stroke risk in HFpEF without AF

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ABSTRACT

Background: The rate of stroke in patients with heart failure (HF) and preserved ejection fraction (HFpEF) but without atrial fibrillation (AF), is uncertain as is whether it is possible to reliably predict the risk of stroke in these patients.

Methods: We validated a previously developed simple risk model for stroke among patients enrolled in the I-Preserve and PARAGON-HF trials. The risk model consisted of three variables: history of previous stroke, insulin-treated diabetes and plasma N-terminal pro-B-type natriuretic peptide level.

Results: Of the 8,924 patients included in the pooled trial dataset, 5,126 patients did not have AF at baseline. Among patients without AF, 190 (3.7%) experienced a stroke over a median follow-up of 3.6 years (rate 10.5 per 1000 patient-years). The risk for stroke increased with increasing risk score: second tertile HR 1.78 (95%CI 1.17-2.71); third tertile HR 3.03 (2.06-4.47), with the first tertile as reference. For patients in the third tertile, the occurrence rate of stroke was 17.7 per 1000 patient-years, similar to that in patients with AF not receiving anticoagulation (20.7 per 1000 patient-years), and those with AF who were receiving anticoagulation (14.5 per 1000 patient-years). Model discrimination was good with a C-index of 0.81 (0.68-0.91) and a simple score could be created from the model.

Conclusions: A simple risk model can detect a subset of HFpEF patients without AF who have a higher risk for stroke. The balance of risk-to-benefit in these individuals may justify the use of prophylactic anticoagulation, but this hypothesis needs to be prospectively evaluated.

CLINICAL TRIAL REGISTRATION: https://www.clinicaltrials.gov. Unique identifier: NCT00095238 and NCT01920711.

Keywords: heart failure, stroke, atrial fibrillation, natriuretic peptides, risk-factors

Clinical Perspective

What is new?

The rate of occurrence of stroke in patients with heart failure and preserved ejection fraction (HFpEF) but without atrial fibrillation (AF) is unclear, as is how to reliably predict the risk of stroke in such patients. We validated the previously developed stroke risk model consisting of 3 variables: previous stroke history, insulin-treated diabetes, and N-terminal pro-B-type natriuretic peptide level. Patients in the highest tertile of this risk model had three times the risk of stroke compared to the lowest tertile.

What are the clinical implications?

This risk model reliably identified a subset of HFpEF patients without AF at a high risk of stroke. The model can be converted to a simple score ($S_2I_2N_{0-3}$) convenient for clinical use. Patients at high risk of stroke may have a risk-benefit balance that justifies the use of prophylactic anticoagulation, although this needs to be tested prospectively in a clinical trial.

Non-standard Abbreviations and Acronyms

AF = atrial fibrillation

CI = confidence interval

CIF = cumulative incidence function

HF = heart failure

HFpEF = heart failure and preserved ejection fraction

HFrEF = heart failure and reduced ejection fraction

HR = hazard ratios

I-Preserve = Irbesartan in Heart Failure With Preserved Systolic Function trial

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New Your Heart Association

PARAGON-HF = Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction trial

INTRODUCTION

Stroke is a catastrophic complication of heart failure (HF).[1–5] We have reported that stroke commonly occurs in patients with heart failure and reduced ejection fraction (HFrEF), even in individuals without atrial fibrillation (AF).[6–8] Less is known about the occurrence of stroke in patients with heart failure and preserved ejection fraction (HFpEF), especially those without AF.[9–11] Whereas the accurate mechanisms of thrombosis may be different between patients with HFrEF and HFpEF, these patients have many potential risk factors in common such as arterial disease (endothelial damage, atherosclerosis, fibrosis and stiffening), hypercoagulability induced by inflammation, and relevant co-morbidities such as diabetes and hypertension.[3-5] Two large randomized controlled trials (WARCEF and COMMANDER-HF) demonstrated that anticoagulants substantially reduced the occurrence of stroke in patients with HFrEF, although bleeding events increased.[12,13] These findings support a potential role of thromboembolism in stroke causation in this heart failure phenotype but no such studies have been carried out in HFpEF.

Previously, we created a stroke prediction model including N-terminal pro-B-type natriuretic peptide (NT-proBNP) for HFrEF patients without AF, using the CORONA and GISSI-HF trial datasets.[14] Recently, we validated this model using an external pooled dataset consisting of 3 large randomized more contemporary trials.[15] The performance of this model is unknown in patients with HFpEF. Therefore, we pooled and examined patient-level data from two large trials enrolling HFpEF patients in which NT-proBNP levels were measured at baseline: the Irbesartan in Heart Failure With Preserved Systolic Function trial (I-Preserve, NCT00095238),[16] and Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction trial (PARAGON-HF, NCT01920711).[17] The purpose of this study was to describe the rate of occurrence of stroke in patients with HFpEF and to validate our stroke prediction model as well as $S_2I_2N_{0-3}$ score which

is a more simple prediction score developed from our stroke prediction model for a clinical purpose, in HFpEF patients without AF, using this large pooled dataset.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Patients

Data from I-Preserve and PARAGON-HF were pooled to have a sufficient number of HFpEF patients without AF for analysis.[16,17] Each trial was approved by local Ethics Committees and written informed consent was obtained from each patient. The design and primary results of I-Preserve and PARAGON-HF are already published.[16–18]

Briefly, I-Preserve included 4,128 patients at least 60 years of age and with a left ventricular ejection fraction (LVEF) of 45% or higher.[16,18] Patients were required to have been hospitalized for HF during the previous 6 months and have New Your Heart Association (NYHA) class II, III, or IV symptoms. Or, if they had not been hospitalized, they were required to have NYHA class III-IV with corroborative evidence: chest X-ray (pulmonary congestion), electrocardiography (left ventricular hypertrophy, left bundle branch block), or echocardiogram (left ventricular hypertrophy, enlarged left atrium). NT-proBNP was not an inclusion criterion but NT-proBNP was measured at baseline in most patients (although the assay results were not known to investigators). Patients were randomly assigned in a 1:1 ratio to receive irbesartan 75 mg once daily (target dose 300mg) or a matching placebo. The median follow-up was 49.5 months.

PARAGON-HF included 4,796 patients at least 50 years of age and with an LVEF of 45% or higher.[17] Patients were required to have signs and symptoms of HF, NYHA class II-IV, evidence of structural heart disease, and diuretic therapy. For patients who were hospitalized for HF within 9 months, those in AF on screening electrocardiography were required to have an NT-proBNP concentration ≥600 pg/ml and those not in AF were required to have an NT-proBNP concentration ≥200 pg/ml. For patients without hospitalization for HF within 9 months, those

in AF on screening electrocardiography were required to have an NT-proBNP concentration ≥900 pg/ml and those not in AF were required to have an NT-proBNP concentration ≥300 pg/ml. Patients entered a single-blind run-in period of 1-2 weeks of treatment with valsartan 40 or 80mg twice daily followed by a period of 2-4 weeks of treatment with sacubitril/valsartan 49/51 mg twice daily. Thereafter, patients were randomly assigned in a 1:1 ratio to double-blind treatment with either sacubitril/valsartan 97/103 mg twice daily or matching valsartan 160 mg twice daily. The median follow-up was 35 months.

Stroke diagnosis

The occurrence of stroke was a secondary endpoint and was centrally adjudicated by a clinical events committee in both trials.[16–18] Stroke in both trials was defined as a focal neurological deficit of central origin lasting more than 24 hours (except for death within 24hrs), with or without imaging confirmation of cerebral infarction or intracerebral haemorrhage. However, categorization of stroke by etiology (ischaemic, haemorrhagic or other) was only available in the PARAGON-HF trial.

New-onset of AF

The new onset of AF was prospectively collected using a specific case report form in I-Preserve.[16,18] The new occurrence of AF was a prespecified secondary endpoint in PARAGON-HF.[17] However, there was no systematic ECG surveillance for AF in either trial.

Statistical methods

Patients with AF were defined as those with either AF confirmed on their baseline electrocardiogram or a prior history of AF and the remaining patients were defined as those without AF. Data regarding AF on electrocardiogram and a prior history of AF were missing in 18 cases and 4 cases, respectively, in PARAGON-HF. Descriptive statistics were used to describe the whole cohort and to compare these two sub-groups, with means±standard deviation, medians (interquartile range) for continuous variables, or number (percentage) for

categorical variables. We also compared the baseline characteristics of patients who developed stroke during the trial and those without. Continuous variables were compared using a t-test or Mann-Whitney's U-test, and categorical variables were compared using a chi-squared test.

The rate of occurrence of stroke (per 1000 patient-years) was calculated during the trial follow-up period and compared between the aforementioned sub-groups. Cumulative incidence function (CIF) plots were drawn for survival analyses. We estimated CIF for stroke occurrence considering the competing risk of death. To meet the assumption of the independence of stroke events, the first event in a patient after randomization was evaluated in the analysis.

We applied the previously published risk model for stroke occurrence derived from CORONA/GISSI-HF to the pooled data in patients without AF from the HFpEF trials.[14] The risk score was calculated by the following equation: (history of a previous stroke) × 6.53 + (insulin-treated diabetes) × 7.39 + [plasma NT-proBNP measurement at baseline (pmol/l) (in logarithmic transformation)] × 2.80. NTproBNP units pg/mL were converted to pmol/l, with 1 pg/ml = 0.1182 pmol/l. One-year, 2-year and 3-year rates of occurrence were estimated by the following equation: 1-year, 1-0.9971^exp(risk score/10); 2-year, 1-0.9945^exp(risk score/10); 3-year, 1-0.9908^exp(risk score/10).[14,15] As transient ischemic attack and stroke history were not collected separately in I-Preserve, the risk score was calculated by considering transient ischemic attack or stroke history as stroke history. Patients with a missing value for a history of previous stroke (n=4), insulin-treated diabetes (n=1), and NT-proBNP (n=457) were excluded from the model calculation, and complete case analyses were performed for the evaluation of the model and estimation of the rate of occurrence. Cox proportional hazard model was conducted to compute the hazard ratios (HR) and 95% confidence interval (CI) of the tertiles of the risk score. According to the tertiles, CIF plots for stroke occurrence were obtained.

We evaluated the model discrimination using the overall C-index for the risk model according

to the method of Pencina and D'Agostino, as outlined by Liu et al.[19,20] We also assessed the C-statistics of the model, using the traditional Harrell's C statistic.[21] The calibration of the model and its ability to separate the patient population into risk groups were assessed by observing the predicted and observed outcomes in the tertiles. Finally, discrimination of the $S_2I_2N_{0-3}$ score, which we previously proposed based on the aforementioned risk model, was evaluated.[15]

To examine the association between a stroke and subsequent mortality, Kaplan-Meier curves were plotted. At baseline, all patients were in the 'no stroke' group and changed exposure to stroke after a first stroke (or stayed in the 'no stroke' group). The hazard ratio (and 95% confidence interval) for mortality after a stroke (with the 'no stroke' group as a reference), adjusted for age, sex, NYHA functional class, body mass index, systolic blood pressure, heart rate, serum creatinine, NT-proBNP, coronary heart disease, diabetes, and history of stroke, was computed using the Cox proportional hazard models.

All analyses were undertaken using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA), STATA version 17.0 (Stata Corp., College Station, TX, USA), and R version 4.1.2.

RESULTS

Of the 4,128 patients in I-Preserve, 1,233 (29.9%) had either a history of AF or AF on their baseline electrocardiogram. The corresponding number was 2,565 (53.5%) of the 4,796 patients in PARAGON-HF. This generated a total of 3,798 patients (42.6%) with AF and 5,126 patients without AF in the pooled dataset.

Baseline characteristics

***Patients with and without AF*:** The baseline demographics of patients with and without AF are shown in **Table S1**. Patients without AF were younger and more often female and had a higher LVEF and worse NYHA functional class. Levels of serum creatinine and plasma NT-proBNP were lower in patients without AF than in those with AF. Regarding co-morbidity, a history of coronary heart disease was more commonly observed in patients without AF compared to those with AF. The two groups had a similar prevalence of diabetes, but those without AF were treated with insulin for their diabetes more frequently and more often had a history of stroke. A beta-blocker, mineralocorticoid antagonist, and digoxin were less frequently prescribed for patients without AF, and notable differences were observed in the use of antiplatelet therapy (40.3% of patients without AF vs. 21.3% in those with AF) and anticoagulant treatment (10.9% vs. 58.6%, respectively).

Patients without AF, with and without stroke, during follow-up: **Table 1** shows the baseline characteristics of patients without AF, according to whether or not patients developed a stroke after randomization. Patients without AF who experienced a stroke were slightly older than those who did not, but the proportion of females was similar in the two groups. Patients who developed a stroke were more often of Black race, had higher blood pressure at baseline, and higher creatinine and NT-proBNP levels than those who did not. A history of prior stroke was more common in patients who developed a stroke during follow-up. There was also a trend for

more insulin-treated diabetes in patients who developed a stroke during follow-up. The baseline characteristics according to the occurrence of stroke in patients with and without AF are shown in **Table S2**.

Rates of stroke

The median follow-up in the pooled analysis was 3.4 years and 396 (4.4%) patients developed a stroke (13.1 per 1000 patient-years). In I-Preserve, 196 patients developed a stroke (11.9 per 1000 patient-years), and in PARAGON-HF 200 patients had a stroke (14.7 per 1000 patient-years).

Patients with AF: The median follow-up time in patients with AF was 3.1 years and 206 (5.4%) of these 3,798 patients developed a stroke (17.2 per 1000 patient-years). The 1-, 2-, and 3-year CIF rates of stroke were 1.8 (95%CI: 1.4-2.3), 3.5 (95%CI: 2.9-4.1), and 4.8 (95%CI: 4.2-5.6)%, respectively (**Figure 1A**). Among the patients treated with an anticoagulant at baseline, the rate of stroke was 14.5 per 1000 patient-years and among those not treated with an anticoagulant, it was 20.7 per 1000 patient-years. In patients receiving an anticoagulant, the 1-, 2-, and 3-year CIF rates of stroke were 1.5 (95%CI: 1.0-2.0), 2.9 (95%CI: 2.3-3.7), and 4.1 (95%CI: 3.3-5.0)%, respectively (**Figure 1B**); the corresponding CIF rates in patients not receiving an anticoagulant were 2.2 (95%CI: 1.6-3.0), 4.2 (95%CI: 3.3-5.2), and 5.9 (95%CI: 4.8-7.2)%, respectively (**Figure 1B**).

Patients without AF: The median follow-up in patients without AF was 3.6 years and 190 (3.7%) of these 5,126 patients developed a stroke (10.5 per 1000 patient-years). The 1-, 2-, and 3-year CIF rates of stroke were 1.1 (95%CI: 0.8-1.4), 2.0 (95%CI: 1.7-2.5), and 2.9 (95%CI: 2.5-3.5) %, respectively (**Figure 1**).

Incident AF and rate of stroke: Among 5,126 patients without AF at baseline, new onset of AF was observed in 444 patients (8.7%). Of the 190 patients without AF who experienced a

stroke, 17 patients (8.9%) developed new onset of AF before the occurrence of their stroke; the number of patients with a stroke without preceding AF was 173. Overall, 33 patients (17.4%) with incident stroke had new AF found before or after their stroke.

Validation of the stroke prediction model in patients without AF

The distribution of the stroke risk score is shown in **Figure S1**. The median value of the risk score was 11.4, and when patients were classified into 3 equally sized groups according to their risk score, it was 7.8 in tertile 1, 11.4 in tertile 2, and 17.0 in tertile 3. The CIF plots for stroke according to the tertile of the risk score are shown in **Figure 2**. The numbers of strokes in tertiles 1, 2, and 3 were 38, 53, and 83 respectively. The 1-, 2- and 3-year CIF rates of stroke in the highest tertile were 1.8 (95%CI: 1.3-2.6), 3.4 (95%CI: 2.6-4.5), and 4.6 (95%CI: 3.7-5.8)%, respectively. Patients in risk-tertile 3 had an overall stroke rate of 17.7 per 1000 patient-years. In Cox proportional hazard models, the risk of stroke increased as the risk score increased (**Table 2**): tertile 2, HR 1.78 (95%CI: 1.17-2.71); tertile 3, HR 3.03 (95%CI: 2.06-4.47), with tertile 1 as a reference.

Model calibration and discrimination

Observed and predicted probabilities of a stroke at 1, 2, and 3 years were compared with the patients divided by tertiles (**Figure 3**) and were acceptable. Hazard ratios according to tertiles were similar even when we took into account allocated treatment (**Table S3**). Model discrimination was good: the overall C-index was 0.81 (95%CI: 0.68-0.91). The Harrell's C statistic is available in the online-only supplement (**Table S4**).

The $S_2I_2N_{0-3}$ score

The number of patients, strokes observed, and the predicted incidence of stroke at 1 year according to $S_2I_2N_{0-3}$ score are shown in **Table 3 and 4**. The score discrimination for stroke occurrence was good with an overall C-index of 0.84 (95%CI 0.76-0.92) (**Table S5**).

The association between a stroke and subsequent mortality

In participants without AF, compared to patients with no stroke, the risk of death markedly increased after a stroke: all-cause mortality rate 4.0 (95%CI 3.7-4.3) per 100 patient-years in patients with no stroke versus 27.8 (95%CI 22.1-35.0) per 100 patient-years in patients after a stroke - giving a HR of 6.90 (95%CI 5.32-8.95) (**Figure S2**). The difference in risk of death was large over the initial 30 days after a stroke but remained significant beyond 30 days.

DISCUSSION

In the present study, we confirmed that a simple model consisting of two clinical variables (history of previous stroke and insulin-treated diabetes) and a routinely measured biomarker (NT-proBNP) successfully predicted the stroke risk in HFpEF patients without AF; the discrimination of this model for stroke risk was good and the predictive probability was accurate. The rate of occurrence of stroke among patients without AF in the highest tertile of risk (17.7 per 1000 patient-years) was close to that of individuals with AF and not treated with an anticoagulant (20.7 per 1000 patient-years) and higher than in those with AF who were treated with an anticoagulant (14.5 per 1000 patient-years). Few strokes were preceded by clinically recognized AF. Finally, the risk of death increased considerably after a stroke.

Little epidemiological information on the occurrence of stroke in HFpEF patients without AF is available.[3] One of the few such sources is the Swedish Heart Failure Registry, which showed that the rate of occurrence of ischaemic stroke or transient ischaemic attack (TIA) in these patients was 17.9 per 1000 patient-years, which is considerably higher than the rate in our study (10.5 per 1000 patient-years).[11] However, the Swedish population was older, had higher NT-proBNP levels, and included some individuals with a LVEF between 40 and 45%; the composite outcome also included TIA, and all of these may explain the different event rates. Two recent reports have provided the rate of stroke in the TOPCAT trial but did not differentiate between patients with and without AF.[22,23] Therefore we analyzed the TOPCAT dataset (Americas only) to differentiate between patients with and without AF. Among the 1007 patients not in AF at baseline, 36 strokes occurred during a median follow-up of 2.6 years, giving a stroke rate of 12.4 (9.0-17.3) per 1000 patient-years, consistent with our findings (and lower than the rate among the 760 patients in TOPCAT with AF in whom the stroke rate was 18.7, 13.8-25.3, per 1000 patient-years).

A comparison with HFrEF patients who do not have AF is also of interest. In a recent analysis using a pooled dataset integrating data from three trials (ATMOSPHERE, PARADIGM-HF,

and DAPA-HF), we observed a rate of stroke of 11.7 per 1000 patient-years.[15,24–26] The similar stroke rate in the two major HF phenotypes is notable given the previously reported relationship between LVEF and stroke occurence.[27] Prior concepts of blood stasis associated with reduced left ventricular contractility leading to thrombosis and embolism may be too simplistic and do not explain the similar rate of stroke in HFrEF and HFpEF. Prior stroke is expected to be predictive of future stroke and type 2 diabetes requiring insulin is usually long-standing and often associated with widespread endothelial dysfunction, atherosclerosis and abnormalities of coagulation and fibrinolysis, as well as nephropathy, all of which are associated with a higher risk of stroke.[28–30] The association with higher NT-proBNP is perhaps less obvious but this may reflect atrial enlargement/myopathy and even occult paroxysmal atrial fibrillation.[31–34]

The obvious therapeutic question raised by our findings is whether the risk of stroke in patients with HFpEF can be reduced. Specifically, might anticoagulation play such a role? In WARCEF, the risk of ischaemic stroke was reduced by almost half with warfarin (29 versus 55 strokes; hazard ratio 0.52, 0.33-0.82) in HFrEF patients in sinus rhythm; however, there was a small excess of intracerebral haemorrhage (5 versus 2 cases). In similar patients in COMMANDER-HF, the number of ischaemic strokes was smaller in the rivaroxaban group compared with the placebo group (41 versus 63; hazard ratio 0.64, 0.43-0.95) but there was no excess of intracranial bleeding. A recent systematic review of randomized controlled clinical trials assessing oral anticoagulants versus placebo or antiplatelet agents in patients with heart failure or ventricular systolic dysfunction/cardiomyopathy without clinical heart failure, and sinus rhythm found a total of seven trials which included 15,794 patients.[35] In that report, oral anticoagulation reduced the rate of stroke or systemic embolism compared to control (odds ratio 0.57, 95% CI: 0.39, 0.82). Collectively, these reports suggest an important role for thrombosis or thromboembolism in the causation of stroke, at least in HFrEF. However, in unselected patients, the benefit-to-risk balance is not sufficiently favourable to recommend

treating all HFrEF patients with an anticoagulant. For example, in COMMANDER-HF, there were 8 more patients per 1000 patient-years of treatment with major bleeding but only 5 fewer patients with stroke per 1000 patient-years of treatment with rivaroxaban, compared with placebo. Hence, we have argued that anticoagulation should be targeted at patients at the highest risk of stroke, assuming such patients can be easily and reliably identified. We believe that our prediction model fulfils this goal, now having been validated in both HFpEF and HFrEF. The simple $S_2I_2N_{0-3}$ score we have created enables this model to be used easily in clinical practice. Since the components of this score change over time, it may be appropriate to reassess the score during a patient's follow-up. The recent emergence of factor XI inhibitors potentially strengthens the approach we have suggested because these novel agents seem to carry a very low risk of bleeding and targeted to patients at higher risk of stroke may further tip the benefit-to-risk balance in a favourable direction. [36–39] While questions remain regarding the relative roles of thrombosis and thromboembolism in HFpEF versus HFrEF, in patients with AF, anticoagulant therapy is equally effective in individuals with HFrEF and HFpEF.[32] Clearly, this hypothetical strategy of stroke risk-stratification and targeted anticoagulation needs to be tested in a prospective randomized controlled trial.[3,40]

Finally, our results emphasize the importance of primary and secondary prevention of stroke given not only the disability that results from this event but also because of the greatly elevated risk of death occurring after stroke. Since several risk factors for the development of stroke, including diabetes and hypertension, also risk factors for the development of HFpEF (and comorbidities targeted in the management of HFpEF), these deserve special attention in the older population at risk of stroke and HFpEF as well as in people who have developed HFpEF or experienced stroke.[1,6,8,11,14]

There are several limitations to our study. First, the two large clinical trials used in our analyses

have specific inclusion/exclusion criteria and likely included patients at lower risk than in the "real world", including lower risk of stroke (for example, patients with prior disabling stroke may not have been enrolled).[11] Second, we could not distinguish between type 1 and type 2 diabetes although the majority of HFpEF patients have type 2 rather than type 1 diabetes. Third, although the new occurrence of AF was collected prospectively in each study, systematic electrocardiographic monitoring was not performed. Thus, the reported incidence of AF is likely lower than would have been detected by electrocardiographic monitoring. However, screening for AF is currently not recommended or feasible for all patients with HFpEF. In any case, because a stroke may occur at the time of or shortly after the onset of AF, an AF-detection strategy is likely to be less effective at reducing the risk of stroke than prophylactic anticoagulation. Finally, we could not differentiate between ischemic and haemorrhagic stroke, although haemorrhagic stroke is thought to be relatively uncommon, as has been shown in the HFrEF anticoagulation trials.[11] Moreover, in our previous HFrEF analyses, the risk model described here was as effective at predicting the occurrence of ischaemic stroke as overall stroke.[15]

In conclusion, we confirmed that patients with HFpEF can have a substantial risk of stroke even in the absence of AF and validated a risk model for stroke in HFpEF patients without AF. This simple risk model can detect a subset of HFpEF patients without AF who have a high rate of occurrence of stroke. The balance of risk-to-benefit in these individuals may justify the use of prophylactic anticoagulation. This hypothesis needs to be evaluated in a prospective randomized controlled trial.

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CONFLICT OF INTEREST

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Singapore; has received research support from AstraZeneca, Bayer, Boston Scientific, and Roche Diagnostics; has served as a consultant or on the advisory board/steering committee/executive committee for Actelion, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc, Us2.ai, Janssen Research & Development LLC, Medscape, Merck, Novartis, Novo Nordisk, Radcliffe Group Ltd, Roche Diagnostics, Sanofi, and WebMD Global LLC; and serves as the co-founder and non-executive director of Us2.ai. A.P.M. has received fees for serving on a study committee from Bayer, Novartis and Fresenius. F.A.M has received research grants and/or honoraria from Novartis, AstraZeneca, Bayer, Pfizer, Bristol-Myers Squibb, Gador, Baliarda, and Boehringer Ingelheim. M.P reports consulting fees from AbbVie, Akcea, Actavis, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, Novo Nordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance. M.C.P is supported by the British Heart Foundation (BHF) Centre of Research Excellence Award (RE/13/5/30177 and RE/18/6/34217þ); has received research funding from AstraZeneca, Boehringer Ingelheim, Boston Scientific, Medtronic, Novartis, Novo Nordisk, Pharmacosmos, Roche, and SQ Innovations; and has served as a consultant and on Clinical Trials Committees for Abbvie, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Medtronic, Novartis, Novo Nordisk, Pharmacosmos, Siemens, and Takeda. M.A.P reports research grant support through Brigham and Women's Hospital from Novartis; and consulting fees from AstraZeneca, Boehringer Ingelheim and Eli Lilly Alliance, Corvidia, DalCor, GlaxoSmithKline, National Heart, Lung, and Blood Institute (NHLBI) CONNECTs (Master Protocol Committee), Novartis, Novo Nordisk, Peerbridge, and Sanofi; and has equity in DalCor. J.L.R reports grants and consulting fees from Novartis and consulting fees from Abbott, AstraZeneca, MyoKardia, and Sanofi. K.S. reports honoraria from AstraZeneca,Boehringer Ingelheim and Novartis. D.J.V.V has received fees for serving on a steering committee and travel support from ARCA biopharma and Corvia

Medical. F.Z has served on the advisory board/steering committee/executive committee for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cardior, CEVA, CVRx, GE Healthcare, Janssen, KBP biosciences, LivaNova, Novartis, Novo Nordisk, Merck, Mundipharma, Quantum Genomics, Relypsa, Roche, Vifor Fresenius; and is co-founder of CardioRenal, CVCT, and Eshmoun. M.R.Z reports research funding from Novartis and has been a consultant for Novartis, Abbott, Boston Scientific, CVRx, EBR, Endotronics, Ironwood, Merck, Medtronic, and Myokardia V Wave. S.D.S has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellPro-Thera, Moderna, American Regent, and Sarepta. J.J.V.M has received payments through Glasgow University from work on clinical trials, consulting and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, Dal-Cor, GSK, Ionis, KBP Biosciences, Novartis, Pfizer, Theracos Personal lecture fees: the Corpus, Abbott, Hikma, Sun Pharmaceuticals, Medscape/Heart.Org, Radcliffe Cardiology, Servier Director, Global Clinical Trial Partners (GCTP).

SUPPLEMENTAL MATERIALS

Figure S1-S2

Table S1-S5

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FIGURE LEGENDS

Figure 1. Cumulative incidence function plots for stroke (with death as a competing risk) in (A) patients with and without AF at baseline; and (B) patients with AF, according to anticoagulant treatment at baseline.
AF indicates atrial fibrillation.

Figure 2. Cumulative incidence function plot for stroke by tertiles of the risk score in patients without AF
AF indicates atrial fibrillation.

Figure 3. Comparison of observed and predicted stroke rates after 1 to 3 years for patients categorized by tertiles of risk score.
The dark grey bar indicates observed stroke rates and the light grey bar indicates predicted stroke rates for 1-year (A), 2-year (B), and 3-year (C).

Table 1. Baseline characteristics according to the occurrence of stroke during follow-up in patients without AF

	All patients without AF n=5,126	Patients without AF	
		No stroke n=4,936	Stroke n=190
Demographics, n (%)			
Age, years	70.9±7.8	70.9±7.8	72.0±7.8
≥65	3,973 (77.5)	3,819 (77.4)	154 (81.1)
≥75	1,734 (33.8)	1,665 (33.7)	69 (36.3)
Race			
White	4,378 (85.4)	4,222 (85.5)	156 (82.1)
Black	135 (2.6)	125 (2.5)	10 (5.3)
Asian	365 (7.1)	348 (7.1)	17 (8.9)
Others	248 (4.8)	241 (4.9)	7 (3.7)
Female sex	2,992 (58.4)	2,892 (58.6)	100 (52.6)
NYHA functional class			
I	78 (1.5)	76 (1.5)	2 (1.1)
II	2,281 (44.5)	2,206 (44.7)	75 (39.5)
III	2,682 (52.3)	2,574 (52.2)	108 (56.8)
IV	83 (1.6)	78 (1.6)	5 (2.6)
Time from diagnosis of HF			
≤1 year	2,327 (45.5)	2,233 (45.3)	94 (49.5)
>1 years	2,788 (54.5)	2,692 (54.7)	96 (50.5)
LV ejection fraction, %	58.9±8.8	58.9±8.8	57.5±8.1
Body mass index, kg/m2	29.8±5.2	29.9±5.2	29.2±4.7
Ischemic cause of heart failure	1,730 (33.8)	1,650 (33.4)	80 (42.1)
Baseline vital signs			
Systolic BP, mmHg	135±15	135±15	138±16
Diastolic BP, mmHg	77±10	77±10	77±10
Pulse pressure, mmHg	58±13	58±13	61±15
Heart rate, beats/min	70±10	70±10	69±10
Laboratory measurements			
Serum Creatinine, µmol/l	89.5±28.5	89.2±28.4	96.6±30.5
NT-proBNP, pg/ml	403 (186-806)	399 (183-787)	563 (285-1188)
Medical history, n (%)			
Coronary heart disease	2,746 (53.6)	2,646 (53.6)	100 (52.6)
Myocardial infarction	1,415 (27.6)	1,360 (27.6)	55 (28.9)
Angina pectoris	2,082 (40.6)	2,005 (40.6)	77 (40.5)

PCI or CABG	1,169 (22.8)	1,121 (22.7)	48 (25.3)
Hypertension	4,743 (92.5)	4,565 (92.5)	178 (93.7)
Diabetes	1,824 (35.6)	1,748 (35.4)	76 (40.0)
Insulin treated diabetes	617 (12.0)	589 (11.9)	28 (14.7)
Stroke	440 (8.6)	413 (8.4)	27 (14.2)
Current smoker	731 (14.3)	694 (14.1)	37 (19.6)
Medical history, n (%)			
Beta blocker	3,448 (67.3)	3,318 (67.2)	130 (68.4)
Mineralocorticoid antagonist	893 (17.4)	860 (17.4)	33 (17.4)
Diuretic	4,407 (86.0)	4,246 (86.0)	161 (84.7)
Digoxin	155 (3.0)	151 (3.1)	4 (2.1)
Lipid lowering therapy	2,534 (49.4)	2,450 (49.6)	84 (44.2)
Antiplatelet agent	2,365 (46.1)	2,262 (45.8)	103 (54.2)
Anticoagulant agent	232 (4.5)	226 (4.6)	6 (3.2)
Antiarrhythmic agent	173 (3.4%)	168 (3.4%)	5 (2.6%)

Data are presented as mean±standard deviation, median (interquartile range), or number (percentage).
AF indicates atrial fibrillation; CABG, coronary artery bypass graft; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; LV, left ventricular: PCI, percutaneous coronary intervention.
NYHA class was missing in 2 cases, time from diagnosis of HF 11 cases, LV ejection fraction 1 case, body mass index 8 cases, heart rate 1 case, serum creatinine 56 cases, and N-terminal pro-B-type natriuretic peptide 457 cases, history of stroke 4 patients, current smoker 19 patients, and medical history including insulin 1 patient.

Table 2: Validation of stroke model in Cox proportional hazard model for patients without AF (n=5,584)

	Number of strokes (%)	Stroke rate (1000 patient-years)	Hazard ratio (95% CI)	p-value
Tertile 1	38 (2.4)	5.9	reference	
Tertile 2	53 (3.4)	10.4	1.78 (1.17-2.71)	0.007
Tertile 3	83 (5.3)	17.7	3.03 (2.06-4.47)	<0.001

AF indicates atrial fibrillation; CI, confidence interval.

Table 3. The $S_2I_2N_{0-3}$ score

Stroke history	2 points
Insulin for DM	2 points
NT-proBNP	0 points if NT-proBNP 100 - 499 pg/mL 1 points if NT-proBNP 500 - 1499 pg/mL 2 points if NT-proBNP 1500 - 4999 pg/mL 3 points if NT-proBNP 5000 - 20000 pg/mL

The $S_2I_2N_{0-3}$ score is a simplified scoring method, created by assigning points to each component based on the risk model.

DM indicates diabetes mellitus; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 4. Number of patients, and the predicted and observed rates of stroke according to the $S_2I_2N_{0-3}$ score.

Total points	Number of patients	Predicted incidence rate at 1 year	Observed Kaplan-Meier rate at 1 year
0	1,743 (43.3%)	0.6-0.9%	0.8%
1	1,061 (26.4%)	0.9-1.2%	1.2%
2	671 (16.7%)	1.1-1.9%	1.4%
3	361 (9.0%)	1.7-2.6%	1.7%
4	135 (3.4%)	2.3-3.6%	3.2%
5	45 (1.1%)	3.3-5.2%	5.1%
6	7 (0.2%)	4.9-6.7%	-
7	2 (0.1%)	6.7-9.8%	-