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

Azmil H. Abdul-Rahim¹, Ana-Cristina Perez¹, Rachael L. MacIsaac¹, Pardeep S. Jhund¹, Brian L. Claggett², Peter E. Carson³, Michel Komajda⁴, Robert S. McKelvie⁵, Michael R. Zile⁶, Karl Swedberg⁷,⁸, Salim Yusuf⁵,⁹, Marc A. Pfeffer², Scott D. Solomon², Gregory Y.H. Lip¹⁰, Kennedy R. Lees¹, and John J.V. McMurray¹*, on behalf of the Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity-Preserved (CHARM-Preserved) and the Irbesartan in Heart Failure with Preserved Systolic Function (I-Preserve) Steering Committees

¹BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow G12 8TA, UK; ²Cardiovascular Division, Brigham and Women’s Hospital, Boston, MA, USA; ³Division of Cardiology, The VeteransAffairs Medical Center, Washington, DC, USA; ⁴Department of Cardiology, University Pierre and Marie Curie, Paris, France; ⁵Population Health Research Institute, McMaster University, Hamilton, ON, Canada; ⁶Division of Cardiology, Medical University of South Carolina, Charleston, SC, USA; ⁷Department of Molecular and Clinical Medicine, University of Gothenburg, Göteborg, Sweden; ⁸National Heart and Lung Institute, Imperial College, London, UK; ⁹Hamilton Health Sciences, Hamilton, ON, Canada; and ¹⁰University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, UK.

Received 29 March 2016; revised 13 June 2016; accepted 4 October 2016; online publish-ahead-of-print 13 November 2016.

Aims
The incidence and predictors of stroke in patients with heart failure and preserved ejection fraction (HF-PEF), but without atrial fibrillation (AF), are unknown. We described the incidence of stroke in HF-PEF patients with and without AF and predictors of stroke in those without AF.

Methods and results
We pooled data from the CHARM-Preserved and I-Preserve trials. Using Cox regression, we derived a model for stroke in patients without AF in this cohort and compared its performance with a published model in heart failure patients with reduced ejection fraction (HF-REF)—predictive variables: age, body mass index, New York Heart Association class, history of stroke, and insulin-treated diabetes. The two stroke models were compared and Kaplan–Meier curves for stroke estimated. The risk model was validated in a third HF-PEF trial. Of the 6701 patients, 4676 did not have AF. Stroke occurred in 124 (6.1%) with AF and in 171 (3.7%) without AF (rates 1.80 and 1.00 per 100 patient-years, respectively). There was no difference in performance of the stroke model derived in the HF-PEF cohort and the published HF-REF model (c-index 0.71, 95% confidence interval 0.57–0.84 vs. 0.73, 0.59–0.85, respectively) as the predictive variables overlapped. The model performed well in the validation cohort (0.86, 0.62–0.99). The rate of stroke in patients in the upper third of risk approximated to that with AF (1.60 and 1.80 per 100 patient-years, respectively).

Conclusions
A small number of clinical variables identify a subset of patients with HF-PEF, but without AF, at elevated risk of stroke.

Keywords
Heart failure with preserved ejection fraction • Stroke • Risk-factors

Corresponding author. Tel: +44 141 330 3479, Fax: +44 141 330 6955, Email: john.mcmurray@glasgow.ac.uk
© The Author 2016. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.
Introduction

Up to half of patients with heart failure have a preserved ejection fraction (HF-PEF).1–3 These patients differ from heart failure patients with reduced ejection fraction (HF-REF) in several aspects—they tend to be older, are more often women, and are more likely to have a history of hypertension and atrial fibrillation (AF); they are less likely to have coronary artery disease. Although, mortality rates may not be as high as in patients with HF-REF, the prognosis of HF-PEF patients is considerably worse than that of patients with hypertension, angina pectoris, AF, or diabetes in the same age range and gender distribution.4 The single most common cause of hospital admission in these patients is worsening heart failure and this, along with death, has been the focus of therapeutic interventions in HF-PEF.5 However, given the demographic profile and co-morbidity cluster characterizing these patients, stroke may also be a clinically important outcome in HF-PEF. Little is known about the incidence of stroke in HF-PEF, particularly in the absence of AF.

To investigate this further, we therefore combined and analysed patient-level data from two large HF-PEF trials, the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity–Preserved trial (CHARM-Preserved, ClinicalTrials.gov NCT00634712) and the Irbesartan in Heart Failure with Preserved Systolic Function trial (I-Preserve, NCT00095238),5 to provide a robust estimate of the current incidence of stroke in patients with HF-PEF, with and without AF. We also tested a simple clinical model, developed in HF-REF,7 for predicting the risk of stroke in patients without AF in this pooled dataset. Easy identification of those at highest risk of stroke coupled with the availability of new oral anticoagulants with a low risk of bleeding might allow for a stroke prevention strategy which has an acceptable benefit/risk balance in patients with HF without AF.

Methods

Trial patients

In order to have a sufficiently large number of HF-PEF patients without AF for analysis, we pooled data from the CHARM-Preserved (NCT00634712) and I-Preserve (NCT00095238) trials. Each was a randomized, double-blind, placebo-controlled, multicentre trial and was approved by the appropriate institutional review boards. CHARM-Preserved and I-Preserve enrolled 3023 and 4128 patients, respectively.5,6 Together, these trials included a broad spectrum of patients with chronic HF-PEF.

CHARM-Preserved enrolled patients aged ≥18 years in New York Heart Association (NYHA) functional class II–IV with a left ventricular ejection fraction (LVEF) >40% (although for the purposes of this study we included only patients with an LVEF ≥45%). I-Preserve enrolled patients aged ≥60 years in NYHA functional class II–IV with an LVEF ≥45% and corroborating ECG, echocardiographic or radiologic evidence. In addition, patients must have been hospitalized for heart failure in the preceding 6 months or, if not, had to be in NYHA functional class III or IV. N-terminal pro B-type natriuretic peptide (NT-proBNP) was measured at baseline in I-Preserve but not in CHARM-Preserved. In CHARM-Preserved, patients were randomly assigned to candesartan (target dose of 32 mg once daily) or matching placebo.5 In I-Preserve, patients were randomized to irbesartan (target dose 300 mg once daily) or matching placebo.6 The primary outcome in CHARM-Preserved was the composite of cardiovascular death or HF hospitalization1,8 and in I-Preserve it was the composite of all-cause mortality or cardiovascular hospitalization.5,8 The median follow-up in CHARM-Preserved was 3.1 years and in I-Preserve it was 4.1 years. Study treatment did not reduce the risk of the primary outcome or the risk of stroke in the either trial.5,6

Incident stroke

Incident strokes were centrally adjudicated by an independent endpoint committee in each trial using similar definitions and stroke was part of the primary or secondary composite cardiovascular outcomes in both trials.5,6,8,9 Stroke in both trials was defined as a persisting (≥24 h) disturbance of focal neurological function resulting in symptoms thought to be due to cerebral infarction, evidence of haemorrhage or for which there is no certain aetiology.5,6,8,9

Incident atrial fibrillation

The occurrence of AF was retrospectively collected in CHARM-Preserved during the trial close-out using a specifically designed case-report form. Incident AF was recorded prospectively in I-Preserve, using a specific case-report form.

Statistical methods

We included only patients with an LVEF of ≥45% (all 4128 patients in I-Preserve and 2573 of the 3023 in CHARM-Preserved). Patients with AF were defined as those with either AF confirmed on their baseline ECG or a history of AF. The remaining patients were defined as those ‘without AF’. Descriptive statistics were used to describe the pooled patient population from both trials and to compare these two subgroups, using means (standard deviation) or medians (interquartile range (IQR)) for continuous variables and count (percentage) for categorical variables.

The incidence rate of stroke (per 100 patient-years) was calculated over the trial follow-up period and was compared among the AF and no AF subgroups. We plotted Kaplan–Meier (KM) curves for the occurrence of stroke, according to AF status. To satisfy the assumption of the independence of stroke events, recurrent stroke events in a patient after randomization were not included in the analysis.

Continuous variables [e.g. body mass index (BMI), ejection fraction, and creatinine level] were assessed by visual inspection of restricted cubic splines to identify potential non-linear effects. Uni- and multivariable predictors of the risk for stroke were evaluated using Cox proportional hazards regression analysis in patients without AF. Two separate multivariable analyses for stroke were created. First, an ‘HF-PEF stroke model’ was created using established predictors of ischaemic stroke10–15 with the addition of variables that were significant (P < 0.05) in univariable analysis of our dataset. The final list of variables included was age, sex, LVEF, NYHA class III/IV, BMI, creatinine level, systolic blood pressure, history of stroke, hypertension, and diabetes treated with insulin. Second, we applied a recently published multivariable predictive model for stroke in patients with HF-REF (HF-REF stroke model) in our HF-PEF cohort.7 The five variables included in this model were age, BMI, NYHA class, history of stroke, and diabetes treated with insulin. There were no data missing for the baseline variables used either model. We calculated the hazard ratio and corresponding 95% confidence intervals (95% CI) to
express the hazard rate of stroke. The statistical contribution of each variable to the predicted risk of stroke was assessed by the $\chi^2$ statistic. In order to be consistent with our previous publication, we compared each model’s discrimination ability using estimates of overall c-index for the Cox regression models according to the method of Pencina and D’Agostino, as outlined by Liu et al. We pre-determined that we would proceed using only the HF-REF stroke model if the overall c-indexes for the two models were not meaning-
differently.

The coefficients from statistically significant variables in the final multivariable model were used to calculate an individual patient’s risk score for stroke. The KM curves for occurrence of stroke according to tertiles of risk score were plotted.

Final model calibration and the ability to separate patients into risk groups were assessed by observing predicted compared with observed outcomes in tertiles, and by using the Hosmer–Lemeshow goodness-of-fit test. The model’s discrimination abilities were evaluated by the overall c-index.

We also conducted a sensitivity analysis to compare the cumulative incidence function for stroke estimated using competing risk technique (to account for the competing risk of death) with the rates of stroke described from the traditional KM curves above. We also compared the overall c-index of the model with the traditional Harrell’s c-statistic.

Finally, we validated the preferred risk model in a third HF-PEF trial: the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) (NCT00094302). TOPCAT included patients aged ≥50 years with at least one symptom and sign of heart failure, an LVEF ≥45% and either a hospitalization with heart failure in the preceding 12 months or an elevated NT-proBNP or BNP.

All analyses were undertaken using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Of the 6701 patients with an LVEF ≥45%, 2025 (30%) had a history of AF or AF on their baseline ECG and 4676 patients (70%) had no AF.

Baseline characteristics

The baseline characteristics of patients with and without AF are shown in the Supplementary material online, Table S1. The baseline characteristics of patients without AF, according whether or not they experienced a subsequent stroke, are shown in Table 1.

Patients with and without atrial fibrillation

Patients without AF were younger and were more likely to have a history of coronary artery disease and hypertension, compared with patients with AF. Patients without AF also had a slightly higher systolic blood pressure but had a lower mean serum creatinine and much lower median NT-proBNP level than patients with AF. There were also notable differences in medical therapy, particularly in use of anti-platelet therapy (69% of patients without AF vs. 39% of those with AF) and anticoagulant treatment (6% vs. 57%, respectively), but also in relation to diuretics, mineralocorticoid receptor antagonists, anti-arrhythmic agents, and digoxin.

Patients without atrial fibrillation—with and without incident stroke during follow-up

Among patients without AF, those who experienced a stroke (compared with those who did not) were older, more likely to have a history of diabetes, hypertension, and stroke and had worse NYHA functional class. Patients experiencing stroke also had a higher systolic blood pressure, creatinine, and NT-proBNP level. Compared with those not experiencing stroke, those who did were less likely to be treated with lipid lowering therapy but more likely to be taking nitrates, anti-platelet therapy, and insulin. Very few patients in either group were treated with an oral anticoagulant (263 in total, 6%). LVEF did not differ between patients with and without stroke.

Rates of stroke

Patients with atrial fibrillation

The median follow-up time in patients with AF was 3.4 (IQR: 2.8–4.4) years and 124 of these 2025 patients (6.1%) experienced a stroke (1.80 per 100 patient-years). The 1, 2, and 3 year KM rates for stroke were 1.5 (95% CI: 1.0–2.1)%, 3.5 (95% CI: 2.7–4.4)%, and 5.5 (95% CI: 4.5–6.6)%, respectively (Figure 1). The stroke rate in patients treated with an anticoagulant was 1.51 per 100 patient-years; and in those not treated with an anticoagulant it was 2.19 per 100 patient-years (yearly rates shown in the Supplementary material online, Figure S1).

Patients without atrial fibrillation

The median follow-up time in patients without AF was 3.5 (IQR: 3.0–4.6) years and 171 of these 4676 patients (3.7%) experienced a stroke (1.00 per 100 patient-years). The 1, 2, and 3 year KM rates of stroke were 1.0 (95% CI: 0.8–1.4)%, 2.0 (95% CI: 1.7–2.5)%, and 3.0 (95% CI: 2.5–3.5)%, respectively (Figure 1).

Incident AF and risk of stroke

In CHARM-Preserved, 1781 patients did not have AF at baseline. Out of 1781, 59 patients (3.3%) experienced a stroke. Of these 59 patients, 10 (17%) developed new AF before the occurrence of their stroke; the number of patients with a stroke without preceding AF was 49 (83%). Development of AF reported was not reported in any patient following a stroke.

In I-Preserve, 2895 patients did not have AF at baseline. Out of 2895, 112 patients (4%) experienced a stroke. Of these 112 patients, 18 (16%) developed new AF before the occurrence of their stroke; the number of patients with a stroke without preceding AF was 94 (84%). Twenty patients (18%) with an incident stroke had new AF reported before or after their stroke.

Predictors of stroke in patients with heart failure and preserved ejection fraction without AF

Figure 2 and Supplementary material online, Table S2 show the relationship between baseline variables and risk of stroke (univariable analysis). Supplementary material online, Table S3 shows an adjusted analysis using the four independent predictors identified in a multi-variable stroke model developed in the present HF-PEF cohort.
| Demographics, n (%) | Patients without AF (N=4676) | Non-stroke (n=4505) | Stroke (n=171) |
|---------------------|-------------------------------|---------------------|----------------|
| **Age, year**       | 69 ± 9                        | 69 ± 9              | 71 ± 8         |
| <65                 | 1400 (30)                     | 1366 (30)           | 34 (20)        |
| 65 to <75           | 2032 (43)                     | 1956 (43)           | 76 (44)        |
| ≥75                 | 1244 (27)                     | 1183 (26)           | 61 (36)        |
| **Race**            |                               |                     |                |
| Caucasians          | 4273 (91)                     | 4116 (91)           | 157 (92)       |
| Afro-American/Afro-Caribbean | 155 (3)          | 148 (30)           | 4 (7)          |
| Other               | 248 (5)                       | 241 (5)             | 7 (4)          |
| **Female sex**      | 2542 (54)                     | 2459 (55)           | 83 (49)        |
| **NYHA class**      |                               |                     |                |
| II                  | 1657 (35)                     | 1612 (36)           | 42 (26)        |
| III                 | 2918 (62)                     | 2799 (62)           | 119 (70)       |
| IV                  | 101 (2)                       | 94 (2)              | 7 (4)          |
| **Duration of heart failure, year** |                     |                     |                |
| <2                  | 2778 (59)                     | 2673 (59)           | 105 (61)       |
| 2–5                 | 1110 (24)                     | 1076 (24)           | 34 (20)        |
| >5                  | 764 (16)                      | 734 (16)            | 30 (18)        |
| **LV ejection fraction, %** | 58 ± 9                       | 58 ± 9              | 57 ± 8         |
| **Baseline vital signs** |                           |                     |                |
| BMI, kg/m²           | 30 ± 6                        | 30 ± 6              | 29 ± 5         |
| BP, mmHg             |                               |                     |                |
| Systolic             | 137 ± 16                      | 137 ± 16            | 140 ± 15       |
| Diastolic            | 79 ± 10                       | 79 ± 10             | 79 ± 9         |
| Pulse pressure       | 58 ± 14                       | 58 ± 14             | 61 ± 14        |
| Heart rate, b.p.m.   | 71 ± 11                       | 71 ± 11             | 71 ± 10        |
| **Laboratory measurements** |                       |                     |                |
| Serum creatinine, μmol/L | 88 ± 29                      | 88 ± 29             | 96 ± 33        |
| Haemoglobin, g/dL    | 14 ± 2                        | 14 ± 2              | 14 ± 1         |
| NT-proBNP*, pg/mL (median ± IQR) | 230 (104–537) | 225 (104–525) | 426 (170–1121) |
| **Medical history, n (%)** |                           |                     |                |
| Coronary heart disease | 2960 (63)                    | 2855 (63)           | 105 (61)       |
| Myocardial infarction | 1599 (34)                    | 1534 (34)           | 65 (38)        |
| Angina pectoris      | 2517 (54)                     | 2429 (54)           | 88 (51)        |
| CABG or PCI          | 1078 (23)                     | 1044 (23)           | 34 (20)        |
| Hypertension         | 3779 (81)                     | 3632 (81)           | 147 (86)       |
| Diabetes mellitus    | 1313 (28)                     | 1245 (28)           | 68 (40)        |
| Stroke               | 379 (8)                       | 343 (8)             | 36 (21)        |
| ICD                  | 11 (0.2)                      | 11 (0.2)            | 0 (0)          |
| Current smoker       | 2597 (56)                     | 2502 (56)           | 95 (56)        |
| **Medication, n (%)** |                           |                     |                |
| Diuretic (loop or thiazide) | 3392 (73)                   | 3266 (73)           | 126 (74)       |
| Loop diuretic        | 2278 (49)                     | 2195 (49)           | 83 (49)        |
| Thiazide diuretic    | 1481 (32)                     | 1430 (32)           | 51 (30)        |
| ACE inhibitor        | 1020 (22)                     | 982 (22)            | 38 (22)        |
| Aldosterone antagonist | 788 (17)                     | 753 (17)            | 35 (20)        |
| Beta-blocker         | 2761 (59)                     | 2663 (59)           | 98 (57)        |
| Digitalis glycoside  | 405 (9)                       | 391 (9)             | 14 (8)         |
| Calcium channel blocker | 1809 (39)                   | 1747 (39)           | 62 (36)        |
| Antiarrhythmic drug  | 179 (4)                       | 173 (4)             | 6 (4)          |
| Long-acting nitrate  | 1476 (32)                     | 1410 (31)           | 66 (39)        |
| Lipid lowering therapy | 1786 (38)                   | 1734 (38)           | 52 (30)        |

**Continued**
using the HF-REF model (P-value for difference = 0.415). Thus, we proceeded using the previously validated HF-REF model. This model can be used to calculate an individual’s risk of stroke as described in the Supplementary material online, Supplementary material.

Figure 3 shows the distribution of the risk score for stroke and illustrates the risk of stroke for a given score. A score of approximately 12 predicts a risk of stroke similar to that which was seen among patients with AF in the current cohort. Figure 4 shows KM curves for stroke with patients classified into three equal-sized groups according to risk score. The number of strokes in tertiles 1, 2 and 3 were 37, 45 and 89, respectively. The 1, 2 and 3 year KM rates of stroke in the two higher risk tertiles were tertile 2: 1.1 (95% CI: 0.7–1.7)%, 1.6 (95% CI: 1.1–2.4)%, and 2.4 (95% CI: 1.7–3.3)% respectively; and tertile 3: 1.4 (95% CI: 1.0–2.2)% 3.2 (95% CI: 2.4–4.2)% and 4.9 (95% CI: 3.9–6.2)% respectively (Figure 4). Patients in risk-tertile 3 had an overall stroke rate of 1.60 per 100 patient-years.

Figure 5 shows the model’s goodness-of-fit by comparing observed and expected probabilities of stroke at 3 years with the patients divided into tertiles. The calibration was also assessed using the Hosmer–Lemeshow test, which was \(P = 0.761\).

### Validation of stroke risk model

We tested the predictive model in TOPCAT, which included 1240 patients with and 2205 patients without AF. The mean follow-up was 3.5 years. There were 65 strokes in the patients with AF and 52 strokes in those without AF, giving stroke rates in patients with and without AF 1.64 and 0.71 per 100 patient-years, respectively.

Using the same analytical approach (see Supplementary material online, Table S4, Figures S2 and S3), the 1, 2 and 3 year KM rates of stroke in patients without AF, in the two higher risk tertiles were tertile 1: 1.3 (95% CI: 0.6–2.4)% 1.3 (95% CI: 0.6–2.3)% and 1.7 (95% CI: 0.9–2.9)%, respectively; and tertile 3: 1.5 (95% CI: 0.8–2.7)% 1.7 (95% CI: 0.9–2.9)% and 2.6 (95% CI: 1.6–4.1)% respectively. Patients in risk-tertile 3 of the validation model derived from TOPCAT cohort had an overall stroke rate of 1.06 per 100 patient-years. The overall c-index for the model was 0.86 (95% CI: 0.62–0.99).

Sensitivity analysis that evaluated the cumulative incidence functions of stroke for the corresponding KM curves reported above is available in the Supplementary material online, Figures S4–S7. There is little difference between the two types of curves. The comparison for the ‘stroke in HF-REF’ model’s discrimination ability within the

### Table 1 Continued

| Variables                        | Patients without AF (N=4676) | Non-stroke (n=4505) | Stroke (n=171) |
|----------------------------------|------------------------------|---------------------|---------------|
| Antiplatelet therapy             | 3204 (69)                    | 3080 (68)           | 124 (73)      |
| Anticoagulant therapy            | 263 (6)                      | 255 (6)             | 8 (5)         |
| Any antithrombotic (antiplatelet or anticoagulant therapy) | 3408 (73) | 3278 (73) | 130 (76) |
| Antiabetic therapy               | 1096 (23)                    | 1040 (23)           | 56 (33)       |
| Insulin therapy                  | 438 (9)                      | 409 (9)             | 29 (17)       |
| Placebo arm in the original trial | 2322 (50)                    | 2231 (50)           | 91 (53)       |

All continuous values are given in mean ± standard deviation unless stated otherwise. AF, atrial fibrillation; n (%), number of observations (percentage of observations within the group); BMI, body mass index; BP, blood pressure; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type natriuretic peptide; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; ICD, implantable cardioverter defibrillator; ACE, angiotensin converting enzyme.

*Available in 2453 patients.
HF-PEF cohort using the overall c-index and the traditional Harrell’s c-method is available in the Supplementary material online, Table S5.

**Discussion**

In this analysis, HF-PEF patients with AF were at a high risk of stroke, with an average incidence rate of 1.8% per year which is similar to that recently reported in HF-REF patients with AF (1.6% per year).\(^7\)

HF-PEF patients without AF in this study had a lower risk of stroke compared with those with AF. However, the overall rate of stroke in HF-PEF patients without AF (1.0% per year) was similar to the rate we recently reported in HF-REF patients without AF (1.2% per year).\(^6\) Moreover, as in HF-REF, a small number of demographic and clinical variables identified a subset of HF-PEF patients without AF who were at greater risk of stroke than the remainder. Specifically, in our pooled analysis, patients in the upper third of the risk score had a rate of stroke (1.6% per year) which was higher than in HF-PEF patients with AF receiving an anticoagulant (1.5% per year), although not as high as in similar patients not treated with an anticoagulant (2.2% per year).

We have been unable to find other reports of the risk of stroke in HF-PEF patients without AF although in patients in the same age range in clinical trials for hypertension (i.e. with a similar co-morbid phenotype to HF-PEF) have a stroke risk of around 1% per year or less.\(^22–26\)

In HF-PEF patients with AF randomized to warfarin in ARISTOTLE\(^27\) the rate of stroke was 1.4% per year which was similar to the rate in anticoagulant-treated AF patients in our study (1.5% per year). In AF patients with HF and an LVEF >40% in RELY-AF\(^28\) the rate of stroke or systemic embolism was 2.07% per year in the warfarin group; in ROCKET-AF\(^29\) the rate of the same outcome in similarly defined patients was 2.06% per year. The higher event rates in the latter two trials are due to broader composite outcome (which included non-cerebral systemic embolism) and the requirement for patients in these trials to have additional risk factors for stroke.

---

**Figure 2** The relationship between baseline variables and risk of stroke in patients with heart failure and preserved ejection fraction without atrial fibrillation. Variables are divided by quintiles. BMI, body mass index; BP, blood pressure; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
The similar risk of stroke in patients with HF-PEF and HF-REF, without AF, is also of interest. We previously reported that LVEF was not predictive of stroke in HF-REF patients without AF. Neither was LVEF an independent predictor of stroke risk in this study although we examined only patients with an LVEF \( \leq 45\% \). This finding is consistent with observations in three recent trials comparing non-Vitamin K antagonist oral anticoagulants with warfarin in patients with AF. In those trials, the risk of stroke and systemic embolism was similar, irrespective of LVEF category, in patients with AF and concomitant HF. A similar conclusion was reached by the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) in AF patients not treated with an oral anticoagulant where the risk of stroke was similar in patients with concomitant HF-REF or HF-PEF.30

As in HF-REF, we found that neither systolic blood pressure nor history of hypertension was independent predictor of stroke. Although this contrasts with the findings in other patient cohorts, it is consistent with the ‘reverse epidemiology’ of heart failure and the known association between higher blood pressure and better outcomes in this condition.31–33 Likewise, we saw an association between lower BMI and higher risk of stroke, another feature of the ‘reverse epidemiology’ in heart failure.31–33

A particular strength of this study is the validation of our predictive model in another dataset (TOPCAT). Consequently, our findings have clear clinical implications. With a small number of routinely collected clinical variables it is possible to identify patients with HF-PEF, but without AF, who may be at sufficiently high risk of stroke to potentially justify anticoagulation. Clearly, there is as yet no trial evidence to justify such treatment but our findings suggest a means of identifying patients for such a trial. Consistent with this hypothesis, prior trials in patients with heart failure and reduced ejection fraction collectively suggest that anticoagulation can reduce the risk of stroke in patients in sinus rhythm. However, in the largest of these, the Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction trial (WARCEF), although warfarin was effective in reducing ischaemic stroke this benefit was offset by major bleeding. With non-vitamin K oral anticoagulants, the risk-to-benefit balance might be more favourable, especially as the target International Normalized Ratio (INR) in WARCEF was 2.75 (range 2.0–3.5).34–37

Limitations
Each of the two trials included had specific inclusion and exclusion criteria and, hence, our findings may not be generalizable to all patients with HF-PEF. Notably, few patients were in NYHA class IV and worse functional class was a predictor of higher risk of stroke. Hence, the risk of stroke may be higher in ‘real world’ patients than in the cohort studied. Although our data suggest that only the minority of strokes is related to incident AF, systematic detection of new onset AF was insensitive, e.g. continuous ambulatory monitoring was
not performed. It is widely recognized that silent AF is frequent in heart failure and undetected AF may have accounted for more strokes than realized. However, waiting for the development of clinically recognized AF before employing anticoagulant therapy may not be the ideal preventive strategy and the best and most cost-effective way to screen for silent AF in HF-PEF is unknown. In addition, these patients may have other reasons to develop thromboembolic and other types of ischaemic stroke, e.g. endothelial dysfunction and blood stasis. Therefore, we believe that our findings support a potential preventive role for anticoagulant therapy in HF-PEF patients in sinus rhythm, particularly as new agents with a lower risk of bleeding are available. Of course, this hypothesis needs to be tested prospectively in a randomized trial and it may be too simplistic to assume that an anticoagulant can substantially reduce the risk of stroke in those with HF-PEF at highest risk.

CHARM-Preserved and I-Preserve were randomized controlled heart failure trials, rather than stroke trials, and used definitions of stroke consistent with other heart failure trials conducted during the same period. Although the definition may not be identical to that used in contemporary stroke trials, it was applied consistently by adjudicators blind to treatment allocation and thus gave an unbiased estimate of treatment effect. Unfortunately, classification of stroke subtype was not carried out in both trials. When the trials were conducted, neuroimaging was not standard in patients with suspected stroke in many, if not most countries, involved. Therefore, we are unable to distinguish between ischaemic and haemorrhagic strokes.

In conclusion, we found that a relatively high-risk subset of a third of HF-PEF patients without AF have a risk of stroke similar to that in HF-PEF patients with AF. This higher-risk subset can be identified using five simple clinical variables. The risk of stroke is similar in HF-PEF and HF-REF patients without AF and is predicted by the same variables. The risk of stroke in these patients might be reduced by treatment with an oral anticoagulant but this hypothesis needs to be tested in a clinical trial. The rate of stroke in the highest risk tertile was not quite as high as in patients with AF not treated with an anticoagulant so it is uncertain what the benefit/risk ratio of such treatment might be.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Authors’ contributions**

A.H.A.R., A.C.P., R.L.M., and B.L.C. performed the statistical analysis; J.J.V.M. and K.R.L. handled funding and supervision; J.J.V.M. and A.H.A.R. conceived and designed the research, and drafted the manuscript; all co-authors made critical revision of the manuscript for key intellectual content.

**Funding**

A.H.A.R. received departmental funding to perform the analysis. A.C.P. was supported by the Medical Research Council award MC_UU_12017/10.

**Conflict of interest:** K.R.L. chairs the Data and Safety Monitoring Board for the RESPECT-ESUS Trial, sponsored by Boehringer Ingelheim. G.Y.H.L. is a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo, and he is a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. The other co-authors declared no conflict of interest.

**References**

1. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004;43:317–327.

2. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. Prog Cardiovasc Dis 2006;48:320–332.

3. Owan TE, Hodge DO, Hersgs RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–259.

4. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Peine MC, McMurray J. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-Preserved, and I-PRESERVE? J Am Coll Cardiol 2012;60:2349–2356.

5. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray J, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–781.

6. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iversen E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456–2467.

7. Abdul-Rahim AH, Perez AC, Fulton RL, Jhund PS, Latini R, Tognoni G, Wikstrand J, Kjekshus J, Lip GY, Magnani AP, Tavazzi L, Lees KR, McMurray JJ. Investigators of the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA), GISSI-Heart Failure (GISSI-HF) Committees and Investigators. 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 Sopravvenienza nell’Insufficienza Cardiaca-Heart Failure (GISSI-HF) trials. Circulation 2015;131:1486–1494.

8. Swedberg K, Pfeffer M, Granger CB, Held P, McMurray J, Olofsson B, Ostergren J, Yusuf S. Candesartan in heart failure—assessment of reduction in mortality and morbidity (CHARM): rationale and design. J Card Fail 1999;5:276–282.

9. Carson P, Massie BM, McKelvie R, McMurray JJ, Komajda M, Zile M, Ptaszynska A, Frangin G. The irbesartan in heart failure with Preserved Systolic Function (I-PRESERVE) trial: rationale and design. J Card Fail 2005;11:576–585.

10. Freudenberger RS, Hellkamp AS, Halperin JL, Poole A, Anderson J, Johnson G, Marks DB, Lee KL, Bardi GH; SCD-HeFT Investigators. Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Circulation 2007;115:2637–2641.

11. Dries DL, Rosenbray GD, Walsawig MA, Domanski MJ. Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: evidence for gender differences in the studies of left ventricular dysfunction trials. J Am Coll Cardiol 1997;29:1074–1080.

12. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JV, Swedberg KB, Ostergren J, Michelson EL, Peper KS, Granger CB. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006;27:65–75.

13. Pocock SJ, Ariti CA, McMurray JJ, Magnani A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN; Meta-Analysis Global Group in Chronic Heart Failure. Predicting survival in heart failure: a risk score based on 39,372 patients from 30 studies. Eur Heart J 2013;34:1404–1413.

14. Pullicino PM, McClure LA, Howard VJ, Wadley VG, Safford MM, Meschia JF, Anderson A, Howard G, Soliman EZ. Identifying a high stroke risk subgroup in individuals with heart failure. J Stroke Cerebrovasc Dis 2013;22:620–626.

15. Wedel H, McMurray JJ, Lindberg M, Wikstrand J, Cleland JG, Cornel JH, Dunstapian P, Hjalmarsson A, Kjekshus J, Komajda M, Kussi T, Vanheesje E, Waggwanz F, Group C.S. Predictors of fatal and non-fatal outcomes in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA): incremental value of apolipoprotein A-1, high-sensitivity C-reactive peptide and NT-pro B type natriuretic peptide. Eur Heart J 2009;30:281–291.

16. Pencina MJ, D’Agostino RB, Overall C. As a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med 2004;23:2109–2123.

17. Liu L, Forman S, Barton B. Fitting Cox model using PROC PHREG and beyond in SAS proceedings of SAS global forum 2009. Paper 236-2009. URL: http://support.sas.com/resources/papers/proceedings09/236-2009.pdf (15 October 2014).

18. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–387.
19. Jason PF, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. JASA 1999; 94:496–509.

20. Wolbers M, Koller MT, Witterman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology 2009; 20:555–561.

21. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Arand I, Claggett B, Cluzel N, Desai AS, Diaz R, Reg JG, Gardevoir I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O’meara E, Probstfield JL, Shabaturishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2013; 367:1383–1392.

22. Wing LPH, Reid CM, Ryan P, Belin LJ, Brown MA, Jennings GLR, Johnston CI, McNeil J, MacDonald GJ, Marley JE, Morgan TO, West MJ. A comparison of outcomes with angiotensin-converting enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med 2003; 348:583–592.

23. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Beliani A, Forette F, Rajkumar C, Thöls L, Banya W, Bulpitt C. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008; 358:1887–1898.

24. The ALLHAT Offi cers, Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). JAMA 2002; 288:2981–2997.

25. Julius S, Kjeldsen SE, Weber M, Brunner HR, Elman S, Hannson L, Hua T, Laragh J, Melinos GE, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlopidine: the VALUE randomised trial. Lancet 2004; 363:2022–2031.

26. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beever G, de Faire U, Fyhquist F, Ibsen H, Kristansson K, Leiderballe-Pedersen O, Lindholm LH, Nieminen MS, Omland T, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359:995–1003.

27. Granger CB, Alexander JH, McMurtry JH, Lopes RD, Hylek EM, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:1139–1151.

28. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paulson JF, Berkowitz SD, Fox KA, Calif RM, Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365:883–891.

29. Sandhu RK, Hohnloser SH, Pfeffer MA, Yuan F, Hart RG, Yusuf S, Connolly SJ, McAlister FA, Healey JS. Relationship between degree of left ventricular dysfunction, symptom status, and risk of embolic events in patients with atrial fibrillation and heart failure. Stroke 2015; 46:667–672.

30. Faraco G, Iadecola C. Hypertension: a harbinger of stroke and dementia. Hypertension 2013; 62:810–817.

31. Guder G, Frantz S, Bauersachs J, Allolio B, Wanner C, Koller MT, Ertl G, Angermann CE, Stark S. Reverse epidemiology in systolic and nonsystolic heart failure: cumulative prognostic benefit of classical cardiovascular risk factors. Circ Heart Fail 2009; 2:563–571.

32. Kalantar-Zadeh K, Block G, Horwich T, Fornarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol 2004; 43:1439–1444.

33. Coikkinos DV, Haralabopoulos GC, Kostis JB, Toutouzas PK, HELAS Investigators. Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. Eur J Heart Fail 2006; 8:428–432.

34. Cleland JG, Findlay I, Jafari SM, Sutton G, Falk R, Bulpitt C, Prentice C, Ford I, Trainer A, Poole-Wilson PA. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J 2004; 148:157–164.

35. Massie BM, Collins JJ, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, Jafari SM, Krol WF, O’connor CM, Schultman KA, Teo K, Warren SR. WATCH trial Investigators. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and antiplatelet therapy in chronic heart failure (WATCH) trial. Circulation 2009; 119:1616–1624.

36. Homma S, Thompson JL, Pullicino PM, Levin B, Freundengerber RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GYD, Tullio MR, Sanford AR, Meja V, Gabriel AP, del Valle ML, Buchbaumer R, WARCCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med 2012; 366:1859–1869.