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

Azmil H. Abdul-Rahim, MBChB, MRCP; Ana-Cristina Perez, MD; Rachael L. Fulton, PhD; Pardeep S. Jhund, MBChB, PhD; Roberto Latini, MD; Gianni Tognoni, MD; John Wikstrand, MD, PhD; John Kjekshus, MD, PhD; Gregory Y.H. Lip, MD; Aldo P. Maggioni, MD; Luigi Tavazzi, MD, PhD; Kennedy R. Lees, MD; John J.V. McMurray, MD; on behalf of the Investigators of the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) and GISSI-Heart Failure (GISSI-HF) Committees and Investigators*

Background—Our aim was to describe the incidence and predictors of stroke in patients who have heart failure without atrial fibrillation (AF).

Methods and Results—We pooled 2 contemporary heart failure trials, the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca-Heart Failure trial (GISSI-HF). Of the 9585 total patients, 6054 did not have AF. Stroke occurred in 165 patients (4.7%) with AF and in 206 patients (3.4%) without AF (rates 16.8/1000 patient-years and 11.1/1000 patient-years, respectively). Using Cox proportional-hazards models, we identified the following independent predictors of stroke in patients without AF (ranked by χ^2 value): age (hazard ratio, 1.34; 95% confidence interval, 1.18–1.63 per 10 years), New York Heart Association class (1.60, 1.21–2.12 class III/IV versus II), diabetes mellitus treated with insulin (1.87, 1.22–2.88), body mass index (0.74, 0.60–0.91 per 5 kg/m^2 up to 30), and previous stroke (1.81, 1.19–2.74). N-terminal pro B-type natriuretic peptide (available in 2632 patients) was also an independent predictor of stroke (hazard ratio, 1.31; 1.11–1.57 per log unit) when added to this model. With the use of a risk score formulated from these predictors, we found that patients in the upper third of risk had a rate of stroke that approximated the risk in patients with AF.

Conclusions—A small number of demographic and clinical variables identified a subset of patients who have heart failure without AF at a high risk of stroke. **(*Circulation*. 2015;131:1486-1494. DOI: 10.1161/CIRCULATIONAHA.114.013760.)**

Key words: atrial fibrillation ■ heart failure ■ risk factors ■ sinus rhythm ■ stroke ■ ventricular ejection fraction

Heart failure (HF) is thought to be a leading cause of cardioembolic stroke.[1] A meta-analysis of historical HF trials (from the 1980s to the late 1990s) found that the annual stroke rate was between 1.3% and 2.4%.[1,2] However, whether heart failure per se, rather than atrial fibrillation (AF) associated with HF, accounts for this high risk is uncertain because most analyses of stroke in HF did not disaggregate patients with and without AF. Furthermore, the total number of strokes in any individual study was usually small, in part, because of the relatively modest size and short duration of many trials in HF. As a consequence, the risk of stroke in patients with HF but without AF is poorly defined, particularly in a contemporary population.

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From Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom (A.H.A.-R., A.-C.P., R.L.F., P.S.J., K.R.L., J.J.V.M.); IRCCS-RL: Istituto Mario Negri, Milan, Italy (R.L.); Consorzio Mario Negri Sud, S Maria Imbaro, Italy (G.T.); Sahlgrenska Academy, Gothenburg University, Sweden (J.W.); Rikshospitalet University Hospital, Oslo, Norway (J.K.); University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom (G.Y.H.L.); Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark (G.Y.H.L.); ANMCO Research Center, Florence, Italy (A.P.M.); and Maria Cecilia Hospital, GVM Care&Research – E.S. Health Science Foundation, Cotignola, Italy (L.T.).

*A complete list of the Investigators of the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) and GISSI-Heart Failure (GISSI-HF) Committees and Investigators is provided in the online-only Data Supplement.

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Correspondence to John J.V. McMurray, MD, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, United Kingdom. E-mail john.mcmurray@glasgow.ac.uk

HF, particularly HF with reduced ejection fraction (HF-REF), without AF may predispose to stroke through fulfillment of the Virchow triad for thrombogenesis.[2,3] First, patients with HF may have stasis of blood flow (blood flow abnormalities) related to left ventricular systolic dysfunction and dyskinesis.[4,5] Second, patients with HF also have endocardial and endothelial dysfunction (vessel wall abnormalities).[4,5] Both of these problems may also lead to cerebral hypoperfusion and cerebral blood flow dysregulation, further increasing the risk of stroke. Third, patients with HF have a hypercoagulable state (abnormal blood constituents).[4,5] Importantly, with the availability of highly effective oral anticoagulant treatment, strokes potentially related to these factors may be preventable. In the Warfarin/Aspirin Study in Heart Failure (WASH), there was no significant difference among the groups of patients receiving warfarin, aspirin, and placebo, in the composite end point of death, stroke, or myocardial infarction, although this was a small trial.[6] The larger Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial (WATCH), which was terminated prematurely owing to slow recruitment, suggested that there was a reduction in the rate of ischemic stroke with warfarin in comparison with aspirin.[7] The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction trial (WARCEF), which was the most recent and by far the largest study, showed the potential thromboprophylaxis benefit of warfarin in WARCEF, although this was offset by an increased risk of major hemorrhage.[8] This finding highlights the need to better understand the risk and predictors of stroke in a contemporary HF population. Identification of those at highest risk of stroke coupled with the availability of newer oral anticoagulants that cause less bleeding might allow individualized and safer stroke treatment strategies in patients with HF without AF. In other words, it may be possible, with effective risk stratification and safer anticoagulants, to identify a subset of HF patients without AF in whom the potential reduction in stroke outweighs the risk of major bleeding.

We therefore combined and analyzed patient-level data from 2 large and contemporary HF trials, the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA, ClinicalTrials.gov NCT00336336)[9] and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiac-Heart Failure trial (GISSI-HF, ClinicalTrials.gov NCT00206310),[10] to provide a comprehensive description of the current incidence of and risk factors for stroke in patients with HF. We compared the rate of stroke in patients without AF, according to different risk categories, with the rate in those with AF.

Methods

Study Populations

To have a sufficiently large number of patients with HF and without AF, we pooled GISSI-HF and CORONA because both were recently conducted and neither showed an effect of study drug on the risk of the primary outcome or on stroke. Each was a randomized, double-blind, placebo-controlled, multicenter trial that enrolled 4574 and 5011 patients, respectively, with chronic HF.[9,10] Together, these trials included a broad spectrum of patients with HF. CORONA enrolled patients aged ≥60 years with New York Heart Association (NYHA) functional class II to IV and HF-REF of ischemic etiology. Patients with NYHA class III to IV symptoms were eligible if their left ventricular ejection fraction (LVEF) was ≤40% (and class II patients if their LVEF was ≤35%). The primary outcome was the composite of cardiovascular death, myocardial infarction, or stroke. GISSI-HF enrolled patients with stable chronic HF (NYHA II–IV), irrespective of age, etiology, and LVEF, that is, both patients with HF-REF and HF with preserved ejection fraction (HF-PEF) were included. Patients with HF-PEF (LVEF >40%) had to have experienced a HF hospitalization in the year before enrolment. The coprimary outcomes were death from any cause and the composite of death from any cause or cardiovascular hospitalization. In GISSI-HF patients were randomly assigned to placebo or n-3 polyunsaturated fatty acids; 4574 were also randomly assigned to placebo or rosuvastatin 10 mg daily in a factorial design. In CORONA, patients were randomly assigned to 10 mg of rosuvastatin or matching placebo, once daily. The first patient was randomly assigned on August 6, 2002 in GISSI-HF and September 15, 2003 in CORONA. The median follow-up in GISSI-HF was 3·9 years, and in CORONA the median follow-up was 2.7 years. Both trials were approved by the local ethics committees and conformed to the principles outlined in the Declaration of Helsinki. In GISSI-HF, n-3 polyunsaturated fatty acid treatment led to a small but statistically significant reduction in both coprimary end points, but it had no effect on the risk of stroke. Rosuvastatin did not reduce the primary outcome (or the risk of stroke) in either trial. The number of deaths from any cause in GISSI-HF and CORONA was 1301 and 1487, respectively.

Stroke End Point

Incident strokes were centrally adjudicated by an independent end point committee in each trial, and stroke was part of the primary or secondary composite cardiovascular outcomes in both trials.[9,10]

Incident AF

AF was prospectively collected in GISSI-HF. AF occurrence during the trial was defined as: the presence of AF on any of the ECGs performed at each follow-up visit, AF as a cause of worsening HF or hospital admission, and AF as an event occurring during a hospital admission. The occurrence of AF was not recorded prospectively in CORONA. However, we retrospectively analyzed adverse event reports for the occurrence of AF.

N-Terminal pro B-Type Natriuretic Peptide

In both studies, N-terminal pro B-type natriuretic peptide (NT-proBNP) was measured in a subset of patients at a central laboratory with the use of a commercially available assay (Roche Diagnostics, Basel, Switzerland).

Statistical Methods

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 2 subgroups, using means (standard deviation) or medians (interquartile range [IQR]) for continuous variables and count (percentage) for categorical variables.

The incidence rates of stroke (per 1000 patient-years) were calculated during the trial follow-up period and were compared between the aforementioned patient subgroups. Cumulative incidence functions of stroke occurrences were estimated accounting for competing risk of death.[11,12] To satisfy the assumption of the independence of stroke events, recurrent stroke events in a patient after randomization were not included in the analysis. Uni- and multivariable predictors of risk for stroke were assessed by using the Cox proportional hazards regression analysis. Continuous variables (eg, body mass index and ejection fraction) were evaluated by visual inspection of restricted cubic splines to identify potential nonlinear effects. For the multivariable analysis, we used previously established predictors of ischemic stroke[13–18] and added variables from our unadjusted univariable analyses that were significant at $P<0.05$. The multivariable analysis was performed in 2 steps, only including patients without AF.

In step 1, a best clinical model was created from the pooled data set of patients without AF by using standard modeling techniques.[15] Eight variables that were found to be statistically significant from the

Table 1. Baseline Characteristics of Patients Without AF According to Stroke Outcome

	Patients Without AF (N=6054)	Nonstroke (n=5848)	Stroke (n=206)
Demographics, n (%)			
Age, y	69±10	69±10	72±9
<60	777 (13)	760 (13)	17 (8)
60–<65	906 (15)	880 (15)	26 (13)
65–<75	2539 (42)	2466 (42)	73 (35)
≥75	1832 (30)	1742 (30)	90 (44)
Female sex	1431 (24)	1388 (24)	43 (21)
NYHA class			
II	3236 (53)	3148 (54)	88 (43)
III	2724 (45)	2612 (45)	112 (54)
IV	94 (2)	88 (2)	6 (3)
Duration of heart failure, y			
<2	2697 (45)	2611 (45)	86 (42)
2–5	2058 (34)	1987 (34)	71 (34)
>5	1295 (21)	1246 (21)	49 (24)
LV ejection fraction, n %	32±7	32±7	31±8
>40%	216 (4)	207 (4)	9 (5)
≤40 and >30%	3138 (52)	3040 (52)	98 (48)
≤30%	2700 (45)	2601 (44)	99 (48)
Baseline vital signs			
BMI, kg/m^2	27±4	27±4	26±4
BP, mm Hg			
Systolic	128±17	128±17	129±17
Diastolic	77±9	77±10	77±9
Pulse pressure	52±13	52±13	51±14
Heart rate, beats/min	71±12	71±12	72±11
Laboratory measurements			
Total cholesterol, mmol/L	5.3±1.1	5.3±1.1	5.2±1.0
Serum creatinine, μmol/L	107±30	107±30	111±30
eGFR, mL/min per 1.73 m^2	65±20	65±20	62±19
eGFR <60, n (%)	2581 (43)	2476 (42)	105 (51)
NT-proBNP, pmol/L, median (IQR)	121 (9–233)	119 (8–230)	169 (42–297)
Medical history, n (%)			
Myocardial infarction	3003 (50)	2892 (50)	111(54)
Angina pectoris	2521 (42)	2421 (41)	100 (49)
CABG or PCI	1472 (24)	1427 (24)	45 (22)
Hypertension	3450 (57)	3326 (57)	124 (60)
Diabetes mellitus	1714 (28)	1648 (28)	66 (32)
Stroke	424 (7)	398 (7)	26 (13)
Pacemaker	595 (10)	573 (10)	22 (11)
ICD or CRT	297 (5)	289 (5)	8 (4)
Peripheral artery disease	578 (10)	550 (9)	28 (14)
Current smoker	864 (14)	833 (14)	31 (15)
Medication, n (%)			
Diuretic (not aldosterone antagonist)	5242 (87)	5061 (87)	181 (88)
ACE inhibitor or ARB	5646 (93)	5458 (93)	188 (91)
Aldosterone antagonist	2245 (37)	2165 (27)	80 (39)
β-Blocker	4285 (71)	4142 (71)	143 (69)
Digitalis glycoside	1595 (26)	1536 (26)	59 (28)
Long-acting nitrate	2058 (34)	1971 (34)	87 (42)
Antiarrhythmic drug	736 (12)	720 (12)	16 (8)
Antiplatelet therapy	4094 (68)	3947 (67)	147 (71)
Anticoagulant therapy	963 (16)	930 (16)	33 (16)
Antiplatelet or anticoagulant therapy	4953 (82)	4776 (82)	177 (86)
Antidiabetic drugs			
Insulin	467 (8)	443 (8)	24 (12)
Oral hypoglycemic	997 (16)	970 (17)	27 (13)

All continuous values are given in mean±standard deviation unless stated otherwise. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LV, left ventricular; n (%), number of observations (percentage of observations within the group); NT-ProBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; and PCI, percutaneous coronary intervention.

unadjusted univariable analyses were included age, body mass index, NYHA class, and history of coronary heart disease, peripheral artery disease, stroke, diabetes mellitus treated with insulin, and creatinine.

In step 2, ($\log_e$) NT-proBNP was added to the independent variables identified in the step 1 model, although this test was only available in a subset of patients.

There were no data missing for the baseline variables used in the multivariable models. We calculated the hazard ratio and corresponding 95% confidence intervals (95% CIs) to express the hazard rate of stroke. The statistical contribution of each variable to the predicted stroke was assessed by using the χ^2 statistic. The coefficients from statistically significant variables in the multivariable model were used to calculate an individual patient's risk score for stroke. Cumulative incidence function for stroke was estimated by using the competing risk technique[11,12] according to tertiles of risk score. Where appropriate, the corresponding Kaplan–Meier curves for stroke occurrences were also plotted.

Model calibration and the ability to separate populations of patients into risk groups were assessed by observing predicted versus observed outcomes in tertiles, and by using the Hosmer-Lemeshow goodness-of-fit test. The models' discrimination abilities were evaluated by the C statistics. All analyses were undertaken by using SAS version 9.2 (SAS Institute, Inc, Cary, NC). The authors had full access to the data sets and vouch for data integrity. All authors have read and agreed to the manuscript as written.

Results

A total of 9585 patients were included in this analysis, of which 3531 had AF on their baseline ECG, or a history of AF, and 6054 patients had no AF.

NT-proBNP measurements were available in 4381 patients (45.7%) overall (1749 patients [49.5%] with AF and 2632 patients [43.5%] without AF).

Baseline Characteristics

The baseline characteristics of patients with and without AF are shown in Table I in the online-only Data Supplement. The

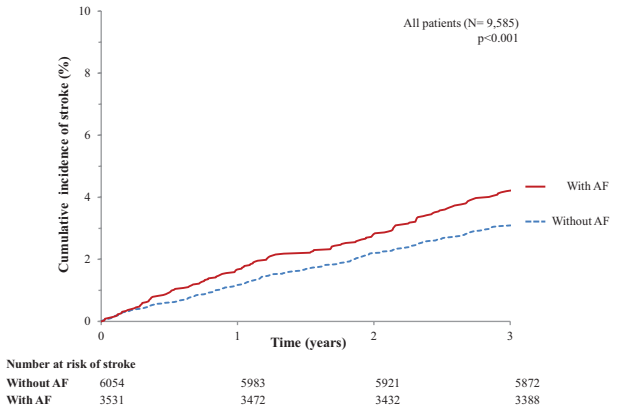

Figure 1. Cumulative incidence function of stroke by AF status at baseline (with death as competing risk). AF indicates atrial fibrillation.

characteristics of patients without AF, according to subsequent stroke, are shown in Table 1.

Patients With and Without AF

Patients without AF were slightly younger, had a slightly lower LVEF, and had better NYHA functional class. Patients without AF also had a higher mean estimated glomerular filtration rate and lower median NT-proBNP level than patients with AF. There were also several differences in medical history/comorbidity, notably in history of myocardial infarction and hypertension with the former more common and the latter less frequent in patients without AF (in comparison with those with AF). There were also notable differences in medical therapy, particularly in the use of antiplatelet therapy (68% of patients without AF versus 36% in those with AF) and anticoagulant treatment (16% versus 62%, respectively).

Patients Without AF With and Without Stroke During Follow-Up

Patients without AF who experienced stroke were older than those who did not, had worse NYHA class, and higher creatinine levels. Patients with stroke were more likely to have a history of prior stroke, myocardial infarction, peripheral arterial disease, hypertension, and diabetes mellitus.

The baseline characteristics of the 4381 patients with a NT-proBNP measurement at baseline are shown in Tables II and III in the online-only Data Supplement. These did not differ significantly from the overall population.

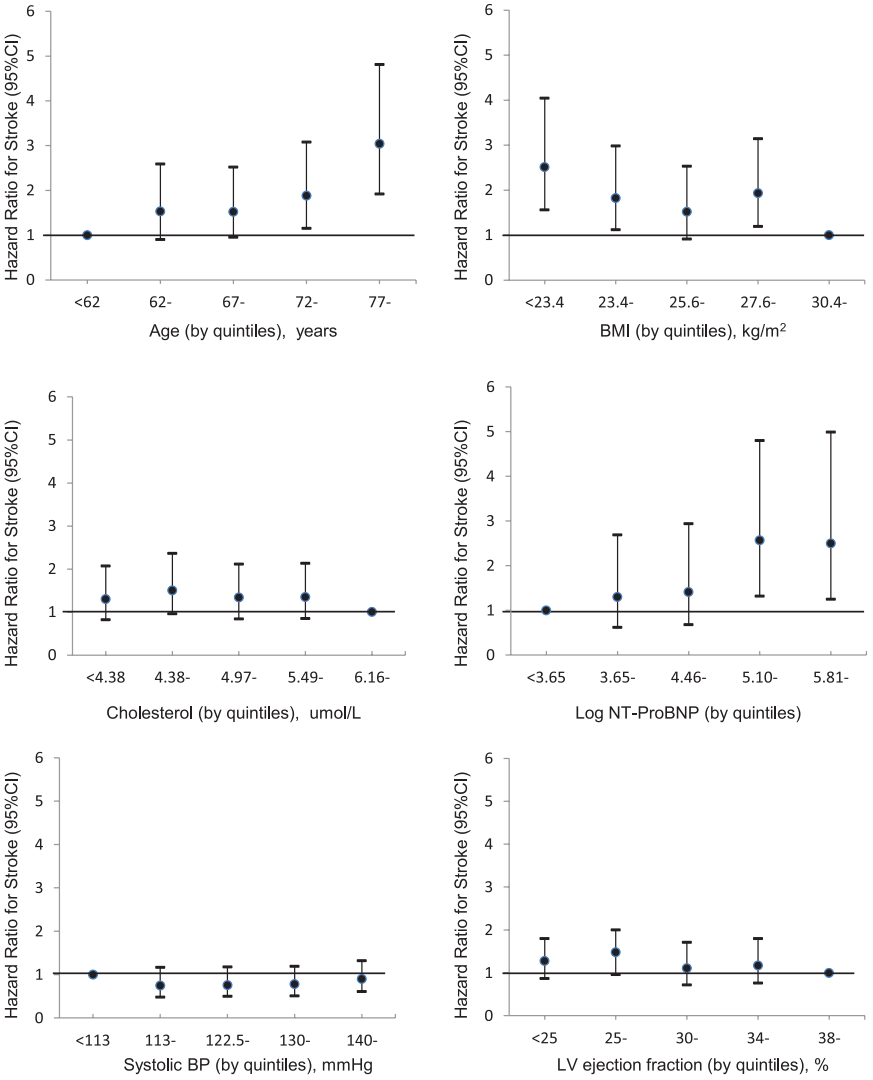

Figure 2. The relationship between baseline variables and risk of stroke in patients without atrial fibrillation. Variables are described in quintiles. AF indicates atrial fibrillation; BMI, body mass index; BP, blood pressure; LV, left ventricle; and NT-proBNP, N-terminal pro B-type natriuretic peptide.

Table 2. Best Clinical Model for Stroke Based on Forward Stepwise Cox Proportional Hazard Regression

Variables	Hazard Ratio	Lower 95% CI	Upper 95% CI	χ^2 Value	Coefficients	Standard Error	*P* Value
Age (per 10 y increase)	1.34	1.18	1.63	16.2	0.331	0.082	<0.001
NYHA class (NYHA III and IV)	1.60	1.21	2.12	10.8	0.472	0.143	0.001
Diabetes mellitus treated with insulin	1.87	1.22	2.88	8.1	0.626	0.220	0.004
BMI (per 5 kg/m^2 increase up to 30)	0.74	0.60	0.91	7.9	–0.301	0.107	0.005
Previous stroke	1.81	1.19	2.74	7.8	0.591	0.212	0.005

There were no missing data for the variables included in the model above. Variables arranged by descending χ^2 value. See the online-only Data Supplement for an explanation of how to use coefficients of the variables to calculate individual patient's risk score of stroke. BMI indicates body mass index; CI, confidence interval; and NYHA, New York Heart Association.

Rates of Stroke

Patients With AF

The median follow-up time in patients with AF was 2.97 (IQR, 2.22–3.49) years and 165 of these 3531 patients experienced a stroke (16.8/1000 patient-years). The 1-, 2-, and 3-year cumulative incidence function (CIF) rates of stroke were 1.7% (95% CI, 1.3–2.1), 2.8% (95% CI, 2.3–3.4), and 4.2% (95% CI, 3.6–4.9), respectively (Figure 1). The rate in patients treated with an anticoagulant was 14.0 per 1000 patient-years, and, in those not treated, it was 21.7 per 1000 patient-years. In patients treated with an anticoagulant, the 1-, 2-, and 3-year CIF rates of stroke were 1.3% (95% CI, 0.9–1.8), 2.3% (95% CI, 1.7–3.0), and 3.6% (95% CI, 2.9–4.5), respectively (Figure I in the online-only Data Supplement); the corresponding CIF rates for patients not treated with an anticoagulant were 2.3% (95% CI, 1.6–3.2), 3.7% (95% CI, 2.7–4.8), and 5.2% (95% CI, 4.1–6.4), respectively (Figure I in the online-only Data Supplement).

The median follow-up time in the 1749 patients with AF and a NT-proBNP measurement at baseline was 2.61 (IQR, 2.17–3.04) years; 86 of these patients experienced a stroke (rate 20.3/1000 patient-years).

Patients Without AF

The median follow-up time in patients without AF was 3.18 (IQR, 2.45–3.98) years, and 206 of these 6054 patients experienced a stroke (11.1/1000 patient-years). The 1-, 2-, and 3-year CIF rates of stroke were 1.2% (95% CI, 0.9–1.5), 2.2% (95% CI, 1.9–2.6), and 3.1% (95% CI, 2.7–3.6), respectively (Figure 1). The median follow-up time in the 2632 patients without AF but with a NT-proBNP measurement at baseline was 2.78 (IQR, 2.30–3.12) years; 94 of these patients experienced a stroke (rate 13.5/1000 patient-years).

Incident AF and Risk of Stroke

In GISSI-HF, 3138 patients did not have AF at baseline. Of these, 85 patients (2.7%) experienced a stroke. Of these 85 patients, 13 (15.3%) developed new AF before the occurrence of their stroke; the number of patients with a stroke without preceding AF was 72 (84.7%). Nineteen patients (22.4%) with an incident stroke had new AF found before or after their stroke.

In CORONA, 2916 patients did not have AF at baseline. Of these, 121 patients (4.1%) experienced a stroke. Of these 121 patients, 9 (7.4%) developed new AF before the occurrence of their stroke; the number of patients with a stroke without preceding AF was 112 (92.6%). Fourteen patients (11.6%) with an incident stroke had new AF reported before or after their stroke.

Predictors of Stroke in Patients Without AF: Model Without NT-proBNP

Figure 2 and Table IV in the online-only Data Supplement (unadjusted analysis) show the relationship between baseline variables and the risk of stroke. Table 2 shows the independent predictors of stroke (without inclusion of NT-proBNP). The 5 variables that were significant in the multivariable

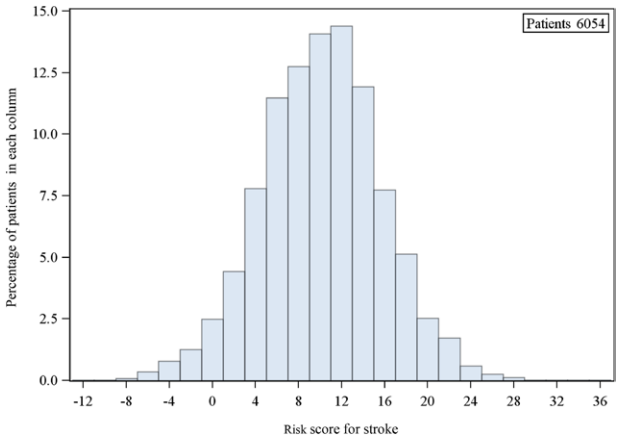

Figure 3. Distribution of the risk score for stroke–best clinical model (ie, model without NT-proBNP). NT-proBNP indicates N-terminal pro B-type natriuretic peptide.

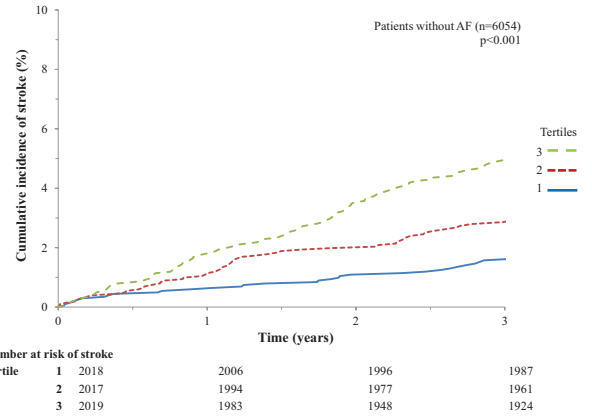

Figure 4. Cumulative incidence function plot for stroke by tertiles of their risk scores in patients without AF–best clinical model (ie, model without NT-proBNP [with death as competing risk]). AF indicates atrial fibrillation; and NT-proBNP, N-terminal pro B-type natriuretic peptide.

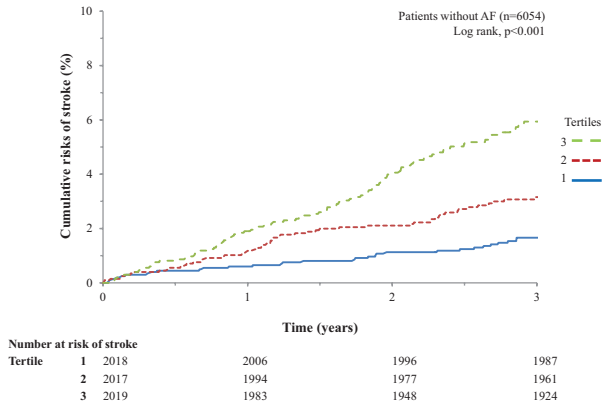

Figure 5. Kaplan–Meier plot for stroke by tertiles of their risk scores in patients without AF–best clinical model (ie, model without NT-proBNP). AF indicates atrial fibrillation.

model did not include blood pressure or ejection fraction. The model in Table 2 can be used to calculate an individual's risk of stroke as described in the online-only Data Supplement Appendix.

Figure 3 shows the distribution of the risk score for stroke. Figure 4 shows the CIF plot for stroke with patients classified into 3 equal-sized groups according to risk score. The number of strokes in tertiles 1, 2, and 3 were 36, 66, and 104, respectively. The 1-, 2-, and 3-year CIF rates of stroke in the 2 higher risk tertiles were as follows: tertile 2, 1.1% (95% CI, 0.7–1.7), 2.0% (95% CI, 1.4–2.7), and 2.9% (95% CI, 2.2–3.7), respectively; and tertile 3, 1.8% (95% CI, 1.3–2.4), 3.5% (95% CI, 2.8–4.4), and 5.0% (95% CI, 4.1–6.1), respectively. The 1-, 2-, and 3-year Kaplan–Meier rates of stroke in the 2 higher-risk tertiles were as follows: tertile 2, 1.2% (95% CI, 0.8–1.8), 2.1% (95% CI, 1.6–2.9), and 3.2% (95% CI, 2.4–4.1), respectively, and tertile 3, 1.9% (95% CI, 1.4–2.6), 4.1% (95% CI, 3.2–5.1), and 5.9% (95% CI, 4.8–7.2), respectively (Figure 5). Patients in risk tertile 3 had an overall stroke rate of 19.8 per 1000 patient-years.

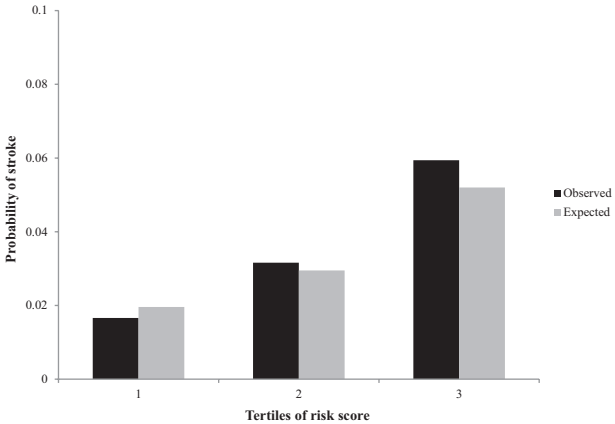

Figure 6. Comparison of observed and expected strokes rates after 3 years for patients categorized by tertiles of risk scores derived from the best clinical model (ie, without NT-proBNP). Observed indicates as read from each Kaplan–Meier tertile group at 3 years; expected, as estimated from Cox model in each tertile.

Figure 6 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 by using the Hosmer-Lemeshow test, which was P=0.122. Model discrimination was evaluated by using the C index, which was 0.75 (95% CI, 0.62–0.86).

Predictors of Stroke in Patients Without AF: Model Including NT-proBNP

When NT-proBNP was added to the 5 predictive variables described above, only 2 of the previous variables, along with log NT-proBNP, remained independent predictors: diabetes mellitus treated with insulin and history of stroke (Table 3). The model in Table 3 can be used to calculate an individual's risk of stroke as described in the online-only Data Supplement Appendix.

Figure II in the online-only Data Supplement shows the distribution of the risk score for stroke. Figure 7 shows CIF plots for stroke with patients classified into 3 equal-sized groups according to risk score. The number of strokes in tertiles 1, 2, and 3 were 16, 34, and 44, respectively. The 1-, 2-, and 3-year CIF rates of stroke in the 2 higher-risk tertiles were tertile 2, 1.4% (95% CI, 0.7–2.3), 2.5% (95% CI, 1.6–3.7), and 3.8% (95% CI, 2.6–5.4), respectively; and tertile 3, 1.9% (95% CI, 1.2–3.0), 3.3% (95% CI, 2.3–4.6), and 5.9% (95% CI, 4.2–7.9), respectively. Patients in risk tertile 3 had an overall stroke rate of 22.9 per 1000 patient-years.

Figure III in the online-only Data Supplement shows the model's goodness of fit, as described above. Calibration was good (P=0.644 for the Hosmer-Lemeshow test).

The C index for the model including NT-proBNP was 0.80 (95% CI, 0.61–0.94), which was not significantly different from the C index for the model without NT-proBNP (P=0.185).

Validation of Risk Model

We tested the predictive model in the Candesartan in Heart Failure: Reduction in Mortality and morbidity (CHARM) HF-REF trials.[19,20] These trials included 1227 patients with and 3349 patients without AF. The median follow-up was 40 months. There were 59 strokes in the patients with AF and 107 strokes in those without AF, giving stroke rates in patients with and without AF 18.3 and 11.4 per 1000 patient-years, respectively. We tested the model without NT-proBNP because natriuretic peptides were not measured in CHARM.

Using the same analytic approach (Table V in the online-only Data Supplement, Figures IV and V in the online-only Data Supplement), the 1-, 2-, and 3-year CIF rates of stroke in the 2 higher-risk tertiles were as follows: tertile 2, 1.4% (95% CI, 0.8–2.2), 1.8% (95% CI, 1.1–2.7), and 2.7% (95% CI, 1.9–3.8), respectively; and tertile 3, 1.5% (95% CI, 0.9–2.4), 3.1% (95% CI, 2.2–4.2), and 4.3% (95% CI, 3.2–5.6), respectively. Patients in risk tertile 3 of the validation model derived from CHARM HF-REF trials had an overall stroke rate of 17.9 per 1000 patient-years. The C index for the model was 0.71 (95% CI, 0.52–0.87).

The corresponding Kaplan–Meier curves for the CIFs of stroke described above are available in Figures VI through VIII in the online-only Data Supplement).

Table 3. Final Model for Stroke Based on Forward Stepwise Cox Proportional Hazard Regression, Adding NT-proBNP to Independent Predictors Identified in Table 2 (n=2632)

Variables	Hazard Ratio	Lower 95% CI	Upper 95% CI	χ^2 Value	Coefficients	Standard Error	*P* Value
Log NT-ProBNP	1.32	1.11	1.57	10.4	0.280	0.087	0.001
Diabetes mellitus treated with insulin	2.09	1.19	3.70	6.5	0.739	0.290	0.011
Previous stroke	1.92	1.10	3.35	5.3	0.653	0.283	0.021

There were no missing data for the variables included in the model above. The model as applied to subset of patients with NT-proBNP measurement at baseline only. Variables are arranged by descending χ^2 value. See the online-only Data Supplement for an explanation of how to use coefficients of the variables to calculate individual patient's risk score of stroke. CI indicates confidence interval; and NT-proBNP, N-terminal pro B-type natriuretic peptide.

Discussion

We confirmed that HF patients with AF are at high risk of stroke, with an average incidence rate of 1.6% per year, despite anticoagulant treatment in 62% of the patients. Patients without AF, overall, had a lower, but still substantial, risk of 1.2% per year. However, a small number of demographic and clinical variables identified a subset of these patients without AF who were at greater risk. Specifically, patients in the upper tertile of the risk score had a rate of stroke that approximated the risk of patients with AF and not treated with an anticoagulant in the 2 trials analyzed (2.0% per year versus 2.2% per year, respectively).

The risk of stroke in our patients without AF was similar to the risk of stroke in WARCEF patients treated with aspirin, which was ≈1.4% per year,[8] especially taking account of the fact that 16% of our patients were treated with an oral anticoagulant (and 82% were treated with an anticoagulant or antiplatelet agent) at baseline. A lower thromboembolism rate of 1.0% per year was reported by the SCD-HeFT investigators in patients who have systolic HF without AF (56 of the 71 events were a stroke).[13] This lower rate of events in SCD-HeFT might be explained by the higher use of antithrombotic therapy at baseline (warfarin in 28% and aspirin in 59%) in that study. In our patients with AF, the risk of stroke or systemic embolism was less than in AF patients with HF treated with warfarin in RELY-AF[21] (1.9% per year) and ROCKET-AF[22] (2.1%), and patients with left ventricular systolic dysfunction in ARISTOTLE[23] (1.8%), as well. This is likely explained by the requirement for patients in these trials to have additional risk factors for stroke. These previous reports suggest that our findings are at least generalizable to other patients with HF in clinical trials.

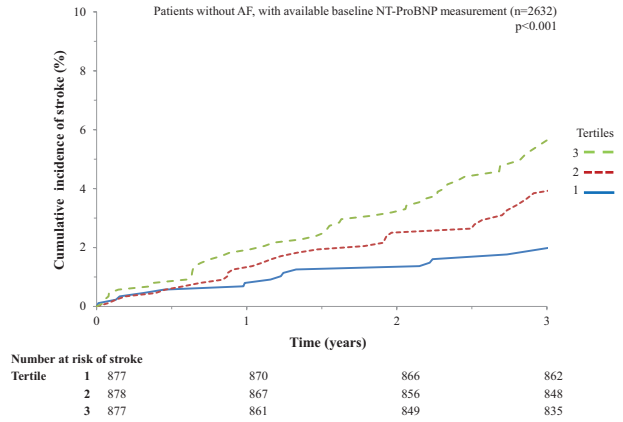

Figure 7. Cumulative incidence function plot for stroke by tertiles of their risk scores in patients without AF – model including NT-proBNP (with death as competing risk). AF indicates atrial fibrillation; and NT-proBNP, N-terminal pro B-type natriuretic peptide.

Interestingly, LVEF was not predictive of stroke in our study, despite some, but not all, previous studies suggesting otherwise.[24,25] These previous studies did not differentiate between patients with and without AF, however. Furthermore, in our study, neither systolic blood pressure nor history of hypertension were predictive of stroke. Although this is at variance with studies in other patient populations, it is consistent with the reverse epidemiology of HF and the recognized association between higher blood pressure and better outcomes in this condition.[26–28] A similar reverse epidemiological relationship was noted between both body mass index and low-density lipoprotein cholesterol and stroke.[27,28]

NT-proBNP was measured in approximately half of patients. NT-proBNP was an independent predictor of stroke when added to the variables described above. Indeed, the resultant model contained only 2 other predictive variables. However, the addition of NT-proBNP did not improve the model C statistic significantly. Although the value of NT-proBNP is a predictor of adverse outcomes in HF, to our knowledge, this is the first demonstration that NT-proBNP is a predictor of stroke in patients without AF. This finding adds to recent observations that NT-proBNP is an independent predictor of stroke risk in patients with AF.[29–31]

A particular strength of this study is the validation of our predictive model in another data set. Consequently, our findings have clear clinical implications. With a small number of routinely collected clinical variables, it is possible to identify patients with HF but without AF who are 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. It may even be that measurement of plasma NT-proBNP concentration on its own may be sufficient to risk stratify patients with respect to stroke, and this possibility should be investigated further.

Limitations

The number of strokes overall was modest but greater than in any previous study. Each of the 2 trials included had specific selection criteria and, hence, our findings may not be generalizable to all patients with HF, particularly patients with HF-PEF who were largely excluded from this analysis. Although our data suggest that only the minority of strokes are related to incident AF, detection of new-onset AF was suboptimal. New-onset AF was collected systematically in GISSI-HF but not in CORONA. However, even in GISSI-HF, paroxysms

of AF may not have been detected because ambulatory monitoring was not performed. It is well known that subclinical AF is common in HF and it is possible (or even likely) that many more strokes might be related to unrecognized/undetected AF. However, waiting for the development of clinically recognized AF before using anticoagulant therapy may not be the optimum preventive strategy. An alternative approach might be to screen for subclinical AF, but how to best do this is uncertain. Should this be done with ambulatory monitoring or an implanted device? If the former, how often would this screening have to be repeated? How much would either strategy cost? Moreover, as described above, there are other reasons why patients with HF are at risk of thromboembolic and other types of ischemic stroke. We believe that our data support the possibility of a broader preventive role for anticoagulant therapy in HF patients in sinus rhythm, especially as new agents with a lower risk of bleeding are available. Of course, this hypothesis needs to be tested prospectively in a randomized trial. NT-proBNP was only available in about half of the patients and was unavailable in our validation cohort.

In conclusion, we found that a high-risk subset of one-third of HF patients without AF have a risk of stroke that is at least as great as in HF patients with AF. This high-risk subset can be identified by using simple clinical variables. This risk of stroke in these patients might be reduced by treatment with an oral anticoagulant. This hypothesis needs to be tested in a clinical trial.

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Disclosures

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CLINICAL PERSPECTIVE

Some patients with heart failure but without atrial fibrillation may be at high risk of stroke and may potentially benefit from anticoagulation. We have combined and analyzed data from 2 large and contemporary heart failure trials, the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA, ClinicalTrials.gov NCT00336336) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiac- Heart Failure trial (GISSI-HF, ClinicalTrials.gov NCT00206310), to provide a comprehensive description of the current incidence of and risk factors for stroke in patients with heart failure but without atrial fibrillation. We built a simple clinical predictive model which shows that about one-third of these patients have a risk of stroke similar to patients with atrial fibrillation. We validated this predictive model in another large data set. The risk of stroke in these patients might be reduced by treatment with an oral anticoagulant. A clinical trial using a novel oral anticoagulant agent in these high-risk patients not in atrial fibrillation would be of considerable interest.

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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

Azmil H. Abdul-Rahim, Ana-Cristina Perez, Rachael L. Fulton, Pardeep S. Jhund, Roberto Latini, Gianni Tognoni, John Wikstrand, John Kjekshus, Gregory Y.H. Lip, Aldo P. Maggioni, Luigi Tavazzi, Kennedy R. Lees and John J.V. McMurray
on behalf of the Investigators of the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) and GISSI-Heart Failure (GISSI-HF) Committees and Investigators*

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SUPPLEMENTAL MATERIAL

Online Supplement for manuscript entitled:

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Azmil H. Abdul-Rahim, Ana-Cristina Perez, Rachael L Fulton, Pardeep S Jhund, Roberto Latini, Gianni Tognoni, John Wikstrand, John Kjekshus, Gregory Y.H Lip, Aldo P Maggioni, Luigi Tavazzi, Kennedy R Lees, and John JV McMurray.

On behalf of the Investigators of the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) and GISSI-Heart Failure (GISSI-HF) trials

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Supplemental Figures and Figure Legends: 8

Appendices: I. Examples of risk score estimation using the models presented in Tables 2 and 3.

II. List of the Investigators of the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) and GISSI-Heart Failure (GISSI-HF)

SUPPLEMENTAL TABLES

Supplementary Table 1. Baseline characteristics according to atrial fibrillation (AF) status at baseline.

	All patients (N= 9585)	**Without AF** (n= 6054)	**AF** (n= 3531)
***Demographics,* n (%)**			
Age (year)	70 ± 9	69 ± 10	73 ± 8
<60	946 (10)	777 (13)	169 (5)
60 - <65	1316 (14)	906 (15)	410 (12)
65 - <75	3936 (41)	2539 (42)	1397 (40)
≥75	3387 (35)	1832 (30)	1555 (44)
Female sex	2212 (23)	1431 (24)	781 (22)
NYHA class			
II	4717 (49)	3236 (53)	1481 (42)
III	4680 (49)	2724 (45)	1956 (55)
IV	188 (2)	94 (2)	94 (3)
Duration of heart failure, n (%)			
< 2 year	4122 (43)	2697 (45)	1425 (40)
2-5 year	3218 (34)	2058 (34)	1160 (33)
> 5 year	2241 (23)	1295 (24)	946 (27)
LV Ejection Fraction, n (%)	32 ± 8	32 ± 7	33 ± 8
>40%	461 (5)	216 (4)	245 (7)
≤40%	4936 (52)	3138 (52)	1798 (51)
≤30%	4188 (44)	2700 (45)	1488 (42)
Baseline vital signs			
BMI, kg/m^2	27 ± 5	27 ± 4	27 ± 5
BP, mmHg			
Systolic	128 ± 17	128 ± 17	128 ± 17
Diastolic	77 ± 9	77 ± 9	77 ± 9
Pulse pressure	51 ± 13	52 ± 13	51 ± 13
Heart rate, beats/min	72 ± 12	71 ± 12	75 ± 14
Laboratory measurements			
Total cholesterol, mmol/L	5.2 ± 1.1	5.3 ± 1.1	5.0 ± 1.1
Serum creatinine, µmol/L	109 ± 30	107± 30	113 ± 30
eGFR, ml/min/1.73m^2	63 ± 19	65 ± 20	60 ± 18
eGFR <60, n(%)	4451 (46)	2581 (43)	1870 (53)
NT-proBNP, pmol/L [median (IQR)]	158 (21-295)	121 (9-233)	226 (63-289)
***Medical history,* n (%)**			
Myocardial infarction	4505 (47)	3003 (50)	1502 (43)
Angina pectoris	4177 (44)	2521 (42)	1656 (47)
CABG or PCI	2191 (23)	1472 (24)	719 (20)
Hypertension	5659 (59)	3450 (57)	2209 (63)

	All patients (N= 9585)	**Without AF** (n= 6054)	**AF** (n= 3531)
Diabetes mellitus	2673 (28)	1714 (28)	959 (27)
Stroke	832 (9)	424 (7)	408 (12)
Pacemaker	1124 (12)	595 (10)	529 (15)
ICD or CRT	437 (5)	297 (5)	140 (4)
Peripheral artery disease	981 (10)	578 (10)	403 (11)
Current smoker	1172 (12)	864 (14)	308 (9)
***Medication*, n (%)**			
Diuretic (not aldosterone antagonist)	8534 (89)	5242 (87)	3292 (93)
ACE inhibitor or ARB	8875 (93)	5646 (93)	3229 (92)
Aldosterone antagonist	3800 (40)	2245 (37)	1555 (44)
Beta-blocker	6619 (69)	4285 (71)	2334 (66)
Digitalis glycoside	3478 (36)	1595 (26)	1883 (53)
Long-acting nitrate	3128 (33)	2058 (34)	1070 (30)
Anti-arrhythmic drug	1537 (16)	736 (12)	801 (23)
Antiplatelet therapy	5352 (56)	4094 (68)	1258 (36)
Anticoagulant therapy	3146 (33)	963 (16)	2183 (62)
Antiplatelet or anti-coagulant therapy	8230 (86)	4953 (82)	3277 (93)
Antidiabetic drugs			
insulin	688 (7)	467 (8)	221 (6)
oral hypoglycaemic	1553 (16)	997 (17)	556 (16)

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; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator;CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

Supplementary Table 2. Baseline characteristics according to AF status at baseline for patients with available NT-ProBNP measurement only.

	All patients (N= 4381)	**Without AF** (n=2632)	**AF** (n=1749)
Demographics			
Age (year)	72± 8	71 ± 8	74 ± 7
<60, n(%)	165 (4)	148 (6)	17 (1)
60 - <65, n(%)	641 (15)	436 (17)	205 (12)
65 - <75, n(%)	1867 (43)	1157 (44)	710 (41)
≥75, n(%)	1708 (39)	891 (34)	817 (47)
Female, n(%)	1048 (24)	665 (25)	383 (22)
NYHA class, n (%)			
II	1849 (42)	1222 (46)	627 (36)
III	2459 (56)	1370 (52)	1089 (62)
IV	73 (2)	40 (2)	33 (2)
Duration of heart failure (year), n (%)			
< 2	1708 (39)	1064 (40)	644 (37)
2-5	1563 (36)	956 (36)	607 (35)
> 5	1110 (25)	612 (23)	498 (29)
LV Ejection Fraction, %	31 ± 7	31 ± 7	32 ± 8
>40, n(%)	97 (2)	50 (2)	47 (3)
≤40 and >30, n(%)	2347 (54)	1401 (53)	946 (54)
≤30, n(%)	1937 (44)	1181 (45)	756 (43)
Baseline vital signs			
BMI, kg/m^2	27 ± 5	27 ± 5	27 ± 5
BP, mmHg			
Systolic	129 ± 17	129 ± 17	128± 17
Diastolic	76 ± 9	76 ± 9	76 ± 9
Pulse pressure	52 ± 13	53 ± 13	52 ± 13
Heart rate, beats/min	72 ± 12	70 ± 11	74 ± 13
Laboratory measurements			
Total cholesterol, mmol/L	5.3 ± 1.1	5.4 ± 1.1	5.1 ± 1.1
Serum creatinine, µmol/L	112 ± 29	111 ± 29	115 ± 28
eGFR, ml/min/1.73m^2	60 ± 17	61 ± 17	58 ± 15
eGFR <60, n(%)	2302 (53)	1295 (49)	1007 (58)
NT-proBNP, pmol/L [median (IQR)]	158 (21-295)	121(9-233)	226 (63-390)
Medical history, **n (%)**			
Myocardial infarction	2350 (54)	1503 (574)	847 (484)
Angina pectoris	2727 (62)	1610 (61)	1117 (64)
CABG or PCI	1059 (24)	664 (25)	395 (23)
Hypertension	2759 (63)	1622 (62)	1137 (65)
Diabetes mellitus	1258 (29)	766 (29)	492 (28)
Stroke	489 (11)	251 (10)	238 (14)

	All patients (N= 4381)	**Without AF** (n=2632)	**AF** (n=1749)
Pacemaker	497 (11)	244 (9)	253 (15)
ICD or CRT	160 (4)	99 (4)	61 (4)
Peripheral arterial disease	529 (12)	307 (12)	222 (13)
Current smoker	476 (11)	335 (13)	141 (8)
***Medication,* n (%)**			
Diuretic (not aldosterone antagonist)	3900 (89)	2273 (86)	1627 (93)
ACE inhibitor or ARB	4065 (93)	2459 (93)	1606 (92)
Aldosterone antagonist	1785 (41)	994 (38)	791 (45)
Beta-blocker	3263 (75)	1981 (75)	1282 (73)
Digitalis glycoside	1449 (33)	553 (21)	896 (51)
Long-acting nitrate	1353 (31)	861 (33)	492 (28)
Anti-arrhythmic drug	569 (13)	241 (9)	328 (19)
Antiplatelet therapy	2578 (59)	1918 (73)	660 (38)
Anticoagulant therapy	1497 (348)	431 (168)	1066 (618)
Antiplatelet or anti-coagulant therapy	3895 (89)	2276 (87)	1619 (93)
Antidiabetic drugs			
insulin	337 (8)	229 (9)	108 (6)
oral hypoglycaemic	724 (17)	448 (17)	276 (16)

All 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; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator;CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

Supplementary Table 3. Baseline characteristics according to stroke outcome for patients without AF and available NT-ProBNP measurement only.

	All patients (N=2632)	**Non-Stroke** (n=2538)	**Stroke** (n=94)
Demographics			
Age (year)	71 ± 8	71 ± 8	71 ± 8
<60, n(%)	148 (6)	143 (6)	5 (5)
60 - <65, n(%)	436 (17)	421 (17)	15 (16)
65 - <75, n(%)	1157 (44)	1120 (44)	37 (39)
≥75, n(%)	891 (34)	854 (34)	37 (40)
Female, n(%)	665 (25)	648 (26)	17 (18)
NYHA class, n (%)			
II	1222 (46)	1182 (47)	40 (23)
III	1370 (52)	1319 (52)	51 (54)
IV	40 (2)	37 (2)	3 (3)
Duration of heart failure (year), n (%)			
< 2	1064 (40)	1022 (40)	42 (45)
2-5	956 (36)	928 (37)	28 (30)
> 5	612 (24)	588 (23)	24 (26)
LV Ejection Fraction, %	31 ± 7	31 ± 7	31 ± 8
>40, n(%)	50 (2)	48 (2)	2 (2)
≤40 and >30, n(%)	1401 (53)	1357 (53)	44 (47)
≤30, n(%)	1181 (45)	1133 (45)	48 (51)
Baseline vital signs			
BMI, kg/m^2	27 ± 5	27 ± 5	27 ± 5
BP, mmHg			
Systolic	129 ± 17	129 ± 17	129 ± 17
Diastolic	76 ± 9	76 ± 9	78 ± 9
Pulse pressure	53 ± 13	53 ± 13	51 ± 13
Heart rate, beats/min	70 ± 11	70 ± 11	73 ± 12
Laboratory measurements			
Total cholesterol, mmol/L	5.4 ± 1.1	5.4 ± 1.1	5.2 ± 0.9
Serum creatinine, µmol/L	111 ± 29	111 ± 29	113 ± 29
eGFR, $ml/min/1.73m^2$	61 ± 17	61 ± 17	61 ± 18
eGFR <60, n(%)	1295 (49)	1245 (49)	50 (53)
NT-proBNP, pmol/L [median (IQR)]	121 (9-233)	119 (8-230)	169 (41-297)
***Medical history,* n (%)**			
Myocardial infarction	1503 (57)	1448 (57)	55 (59)
Angina pectoris	1610 (61)	1560 (610	50 (53)
CABG or PCI	664 (25)	644 (25)	20 (21)
Hypertension	1622 (62)	1566 (62)	56 (60)
Diabetes mellitus	766 (29)	732 (29)	34 (36)
Stroke	251 (10)	236 (9)	15 (16)

	All patients (N=2632)	**Non-Stroke** (n=2538)	**Stroke** (n=94)
Pacemaker	244 (9)	233 (9)	11 (12)
ICD or CRT	99 (4)	95 (4)	4 (4)
Peripheral arterial disease	307 (12)	295 (12)	12 (13)
Current smoker	335 (13)	322 (13)	13 (14)
***Medication,* n (%)**			
Diuretic (not aldosterone antagonist)	2273 (86)	2191 (86)	82 (87)
ACE inhibitor or ARB	2459 (93)	2372 (93)	87 (93)
Aldosterone antagonist	994 (38)	955 (38)	39 (41)
Beta-blocker	1981 (75)	1913 (75)	68 (72)
Digitalis glycoside	553 (21)	534 (21)	19 (20)
Long-acting nitrate	861 (33)	823 (32)	38 (40)
Anti-arrhythmic drug	241 (9)	232 (9)	9 (10)
Antiplatelet therapy	1918 (73)	1848 (73)	70 (74)
Anticoagulant therapy	431 (16)	414 (16)	17 (18)
Antiplatelet or anticoagulant therapy	2276 (86)	2192 (86)	84 (89)
Antidiabetic drugs			
insulin	229 (9)	215 (8)	14 (15)
oral hypoglycaemic	448 (17)	437 (17)	11 (12)

All 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; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator;CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.*

Supplementary Table 4. Exploratory unadjusted univariable analysis for outcome of stroke in patients without AF.

Variables	HR (95% CI)	p-value
Age (per 10 year increase)	**1.48 (1.34-1.79)**	**<0.001**
Female sex	0.84 (0.60-1.18)	0.313
Heart rate (per 1bpm up to 70)*	1.03 (0.99-1.05)	0.056
Systolic blood pressure (per 1mmHg increase)	1.00 (0.99-1.01)	0.962
LVEF (per 5% increase up to 40%)†	0.87 (0.71-1.06)	0.172
Creatinine (per 1 umol/L increase up to 350)†	**1.01 (1.00-1.01)**	**0.001**
BMI (per 5kg/m^2 increase up to 30)†	**0.73 (0.59-0.90)**	**0.003**
NYHA class (III & IV vs. I & II)	**1.83 (1.39-2.41)**	**<0.001**
HF duration (> 5 years vs. ≤ 5 years)	1.22 (0.88-1.68)	0.228
Current smoker	1.04 (0.71-1.53)	0.828
Coronary heart disease (angina, MI, revascularisation, CABG, IHD)	**1.65 (1.21-2.24)**	**0.001**
Peripheral artery disease	**1.73 (1.16-2.59)**	**0.007**
Previous Stroke	**2.19 (1.45-3.30)**	**<0.001**
Hypertension	1.16 (0.88-1.54)	0.287
Insulin treated diabetes	**1.74 (1.14-2.66)**	**0.011**
Cholesterol	0.90 (0.79-1.02)	0.107
NT-proBNP (log)‡	**1.29 (1.13-1.46)**	**<0.001**

Significant level at conventional p<0.05 in bold. LVEF indicates left ventricular ejection fraction; BMI: body mass index; NYHA: New York Heart Association; MI: myocardial infarction; CABG: coronary arter bypas graft; IHD: ischaemic heart disease.
* Heart rate was truncated to 70bpm to avoid co-linearity with possible atrial fibrillation.
† The values were truncated to the level displayed due to individual variable's non-linearity.
‡ Univariable analysis for log NT-ProBNP was performed for patients with NT-ProBNP measurements only.

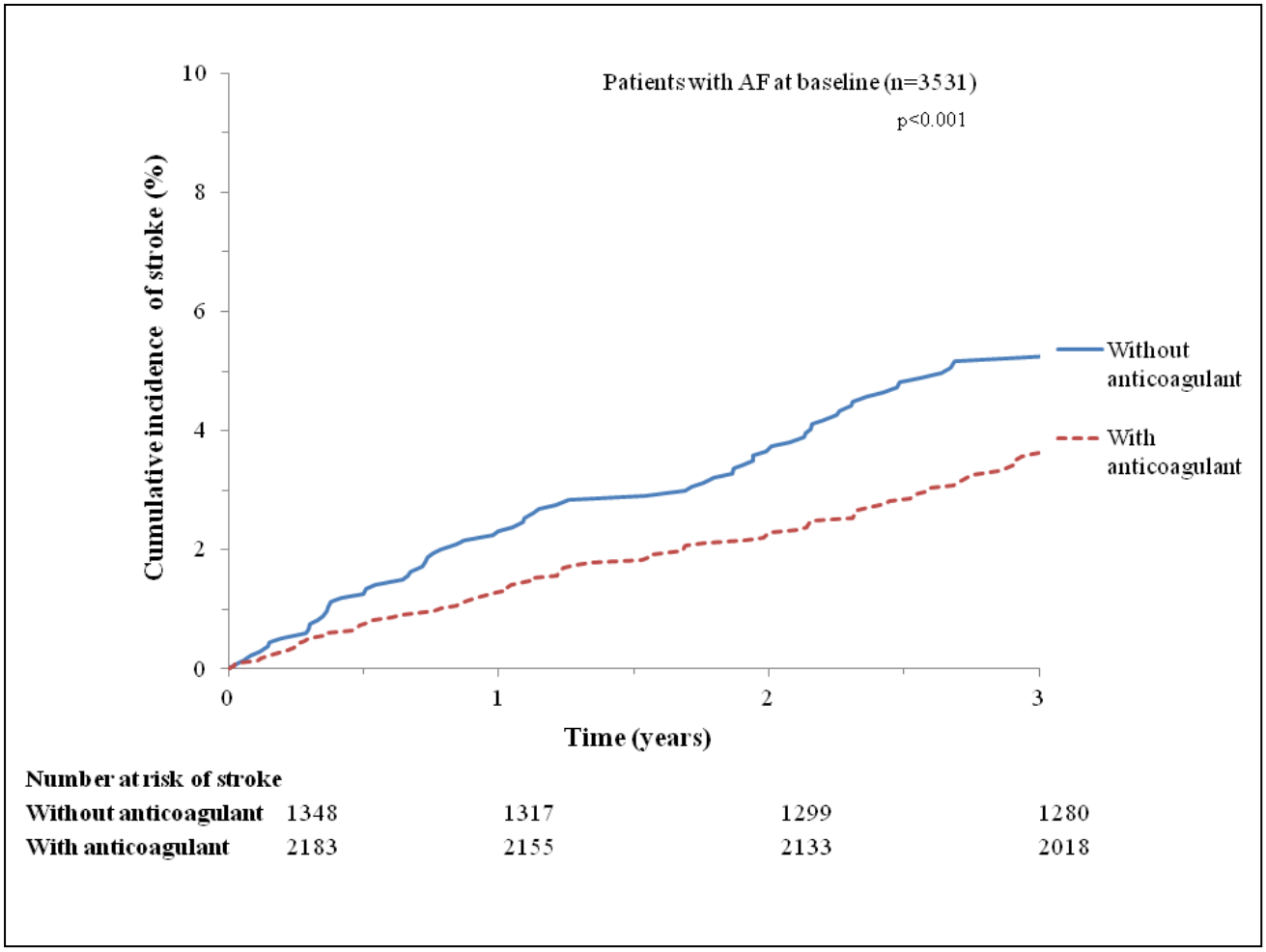
Supplementary Table 5. Validation of “best clinical model” using CHARM HF-REF for patients without AF (n=3,349)

Variables	Hazard ratio	Lower 95%CI	Upper 95%CI	X^2-value	P-value	Coefficients derived from CORONA-GISSI
Age (per 10 year increase)	1.63	1.34	1.97	24.2	<0.001	0.331
Previous Stroke	2.02	1.18	3.45	6.7	0.010	0.591
Insulin treated diabetes	1.59	0.89	2.86	2.4	0.121	0.626
BMI (per 5kg/m^2 up to 30)	0.86	0.66	1.16	1.0	0.321	-0.301
NYHA (III and IV)	1.04	0.70	1.56	<0.1	0.840	0.472

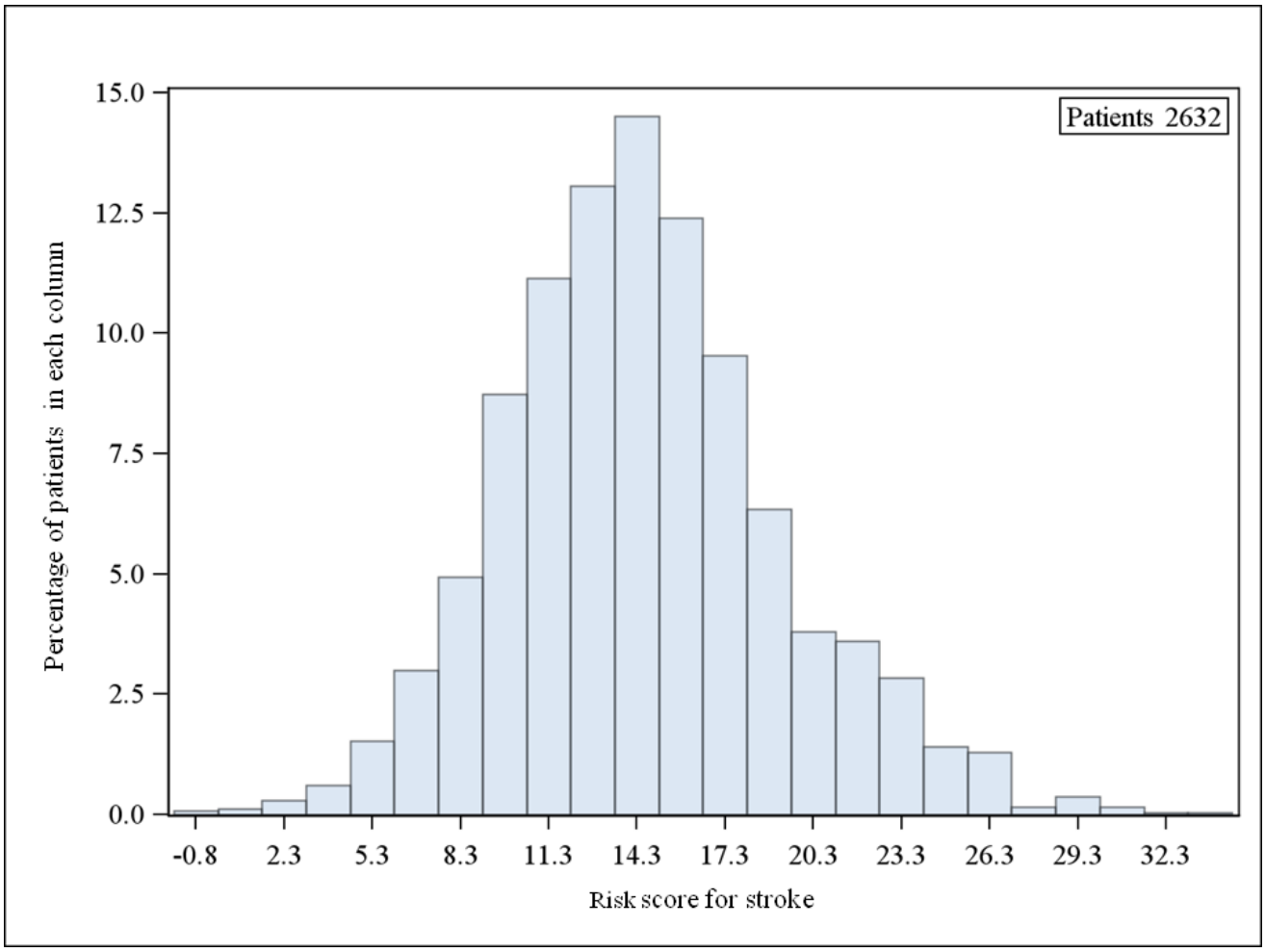
See the appendix for explanation of how to use coefficients of the significant variables (in bold) to predict individual patient’s risk of stroke. AF indicates atrial fibrillation. AF defined as medical history of AF or baseline ECG that confirmed AF; BMI: body mass index; NYHA: New York Heart Association.

SUPPLEMENTAL FIGURES AND FIGURE LEGENDS

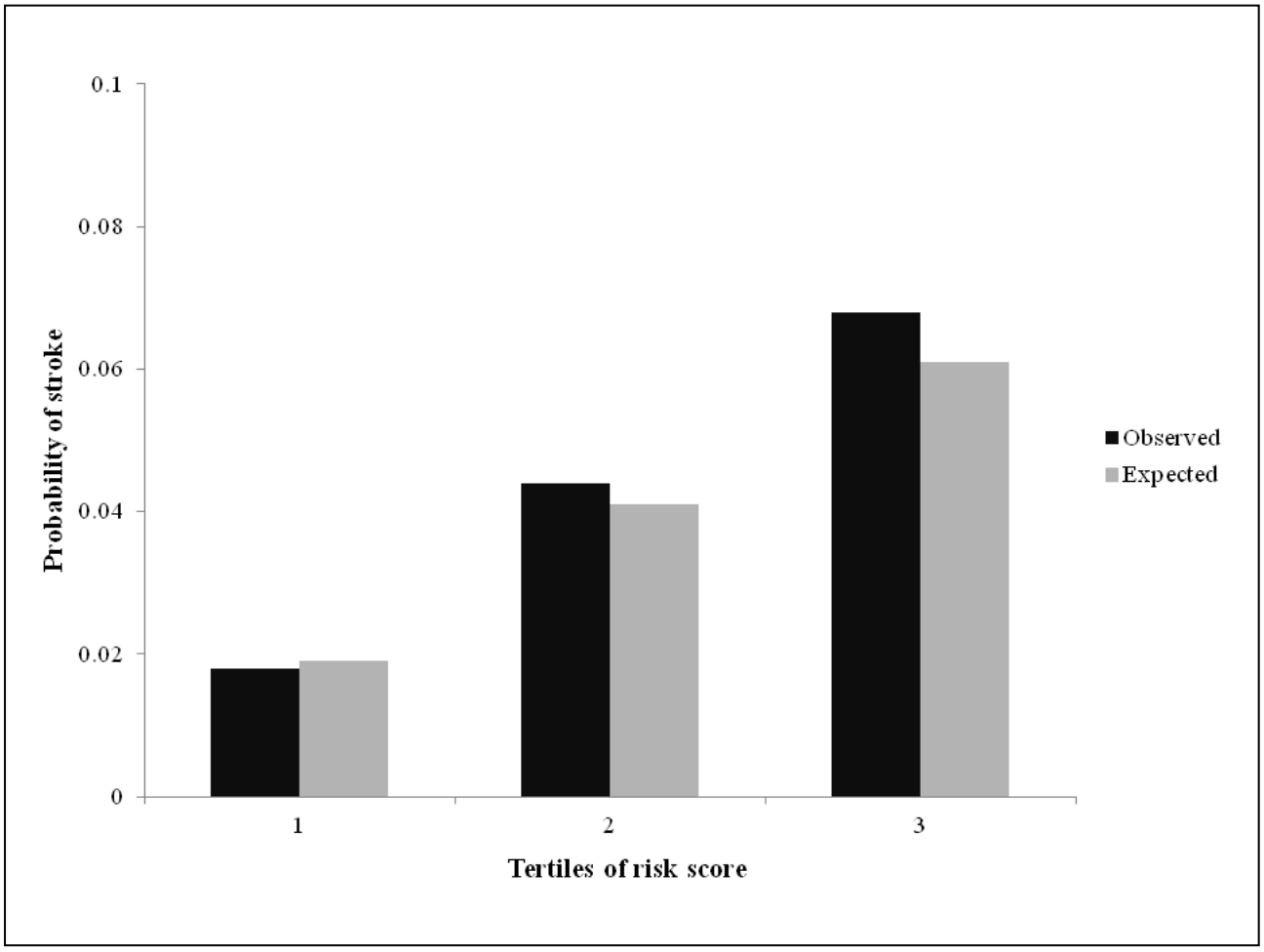
Supplementary Figure 1. Cumulative incidence function of stroke for chronic heart failure patients with atrial fibrillation, according to anticoagulant treatment at baseline (with death as competing risk). AF indicates atrial fibrillation.



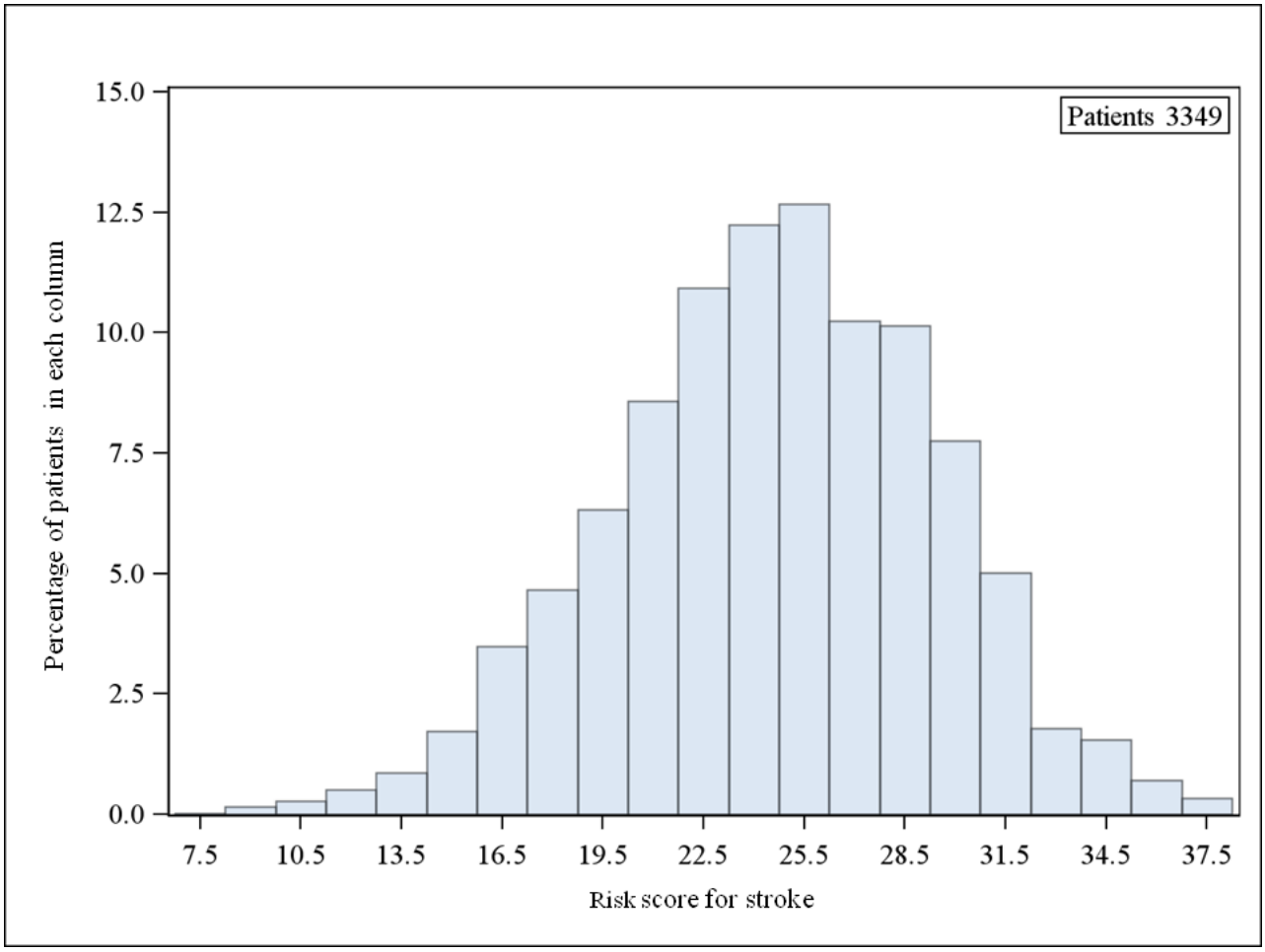
Supplementary Figure 2. Distribution of the risk score for stroke derived from model including NT-proBNP.



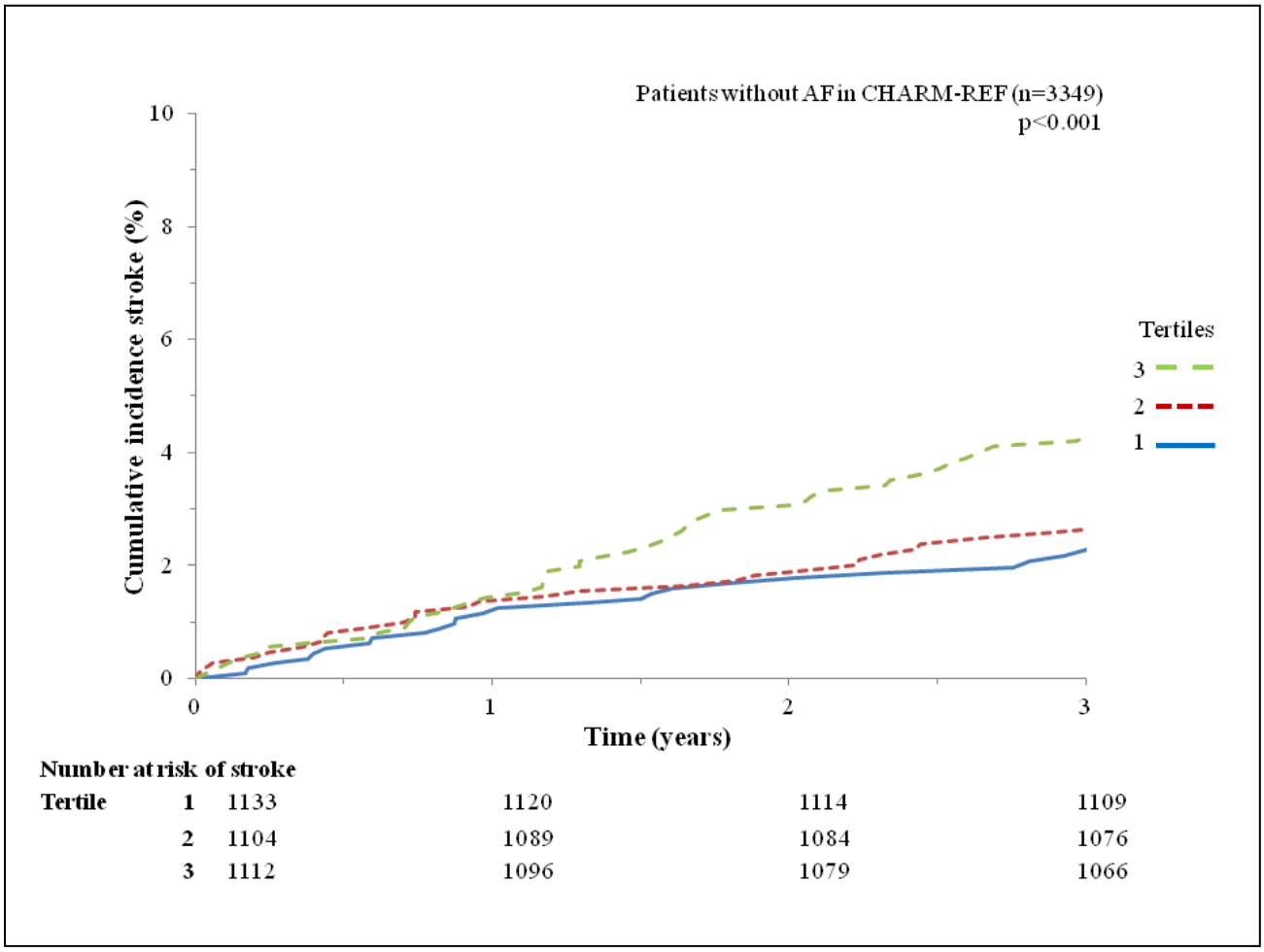
Supplementary Figure 3. Comparison of observed and expected strokes rates after 3 years for patients categorised by tertiles of risk-scores derived from model including NT-proBNP.
Observed, as read off from each Kaplan-Meier's tertiles-group at 3 years; expected, as estimated from Cox model in each tertile.



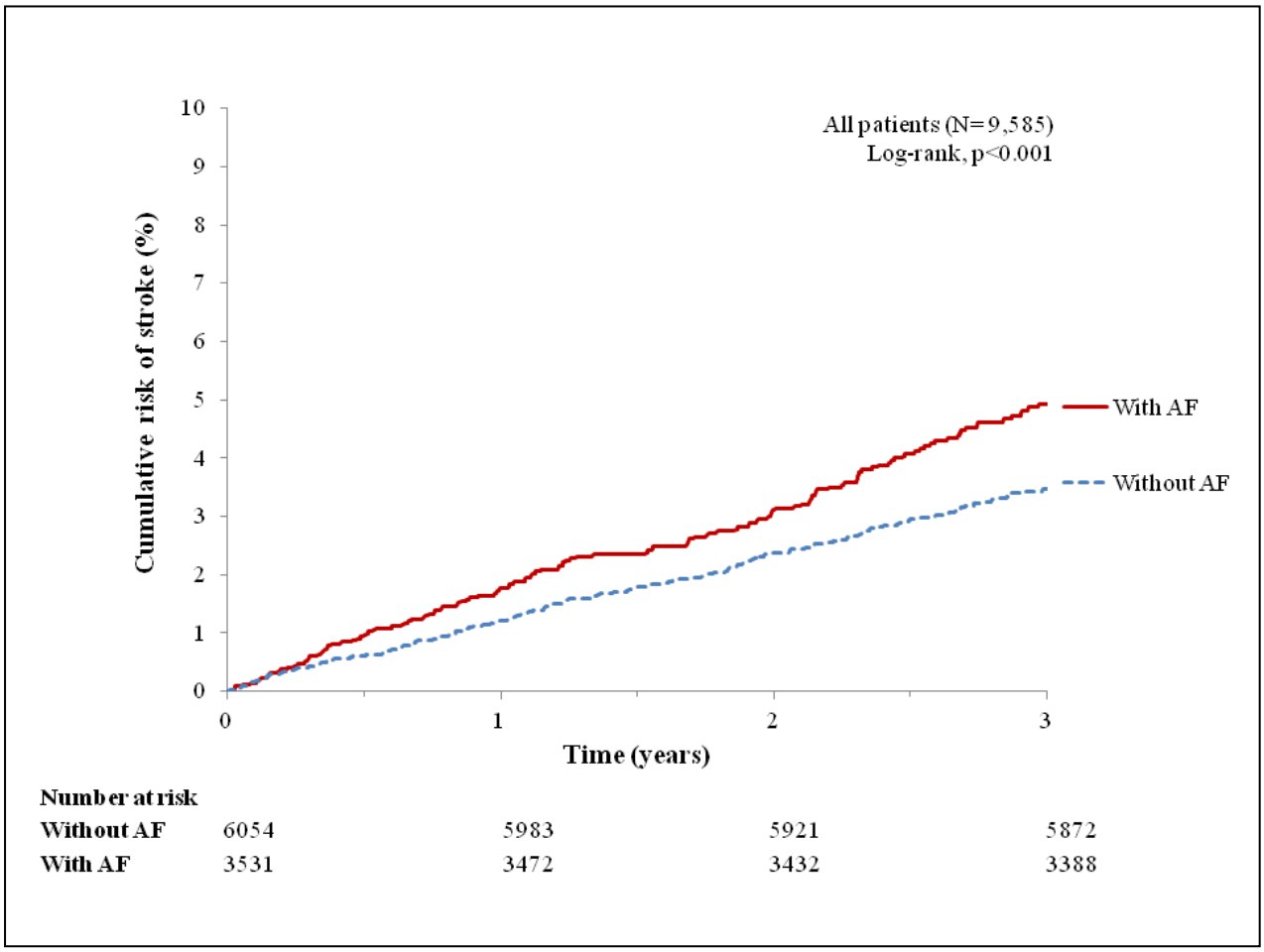
Supplementary Figure 4. Validation using CHARM HF-REF, for patients without AF: Distribution of the risk score for stroke – "best clinical model", i.e. model without NT-proBNP.



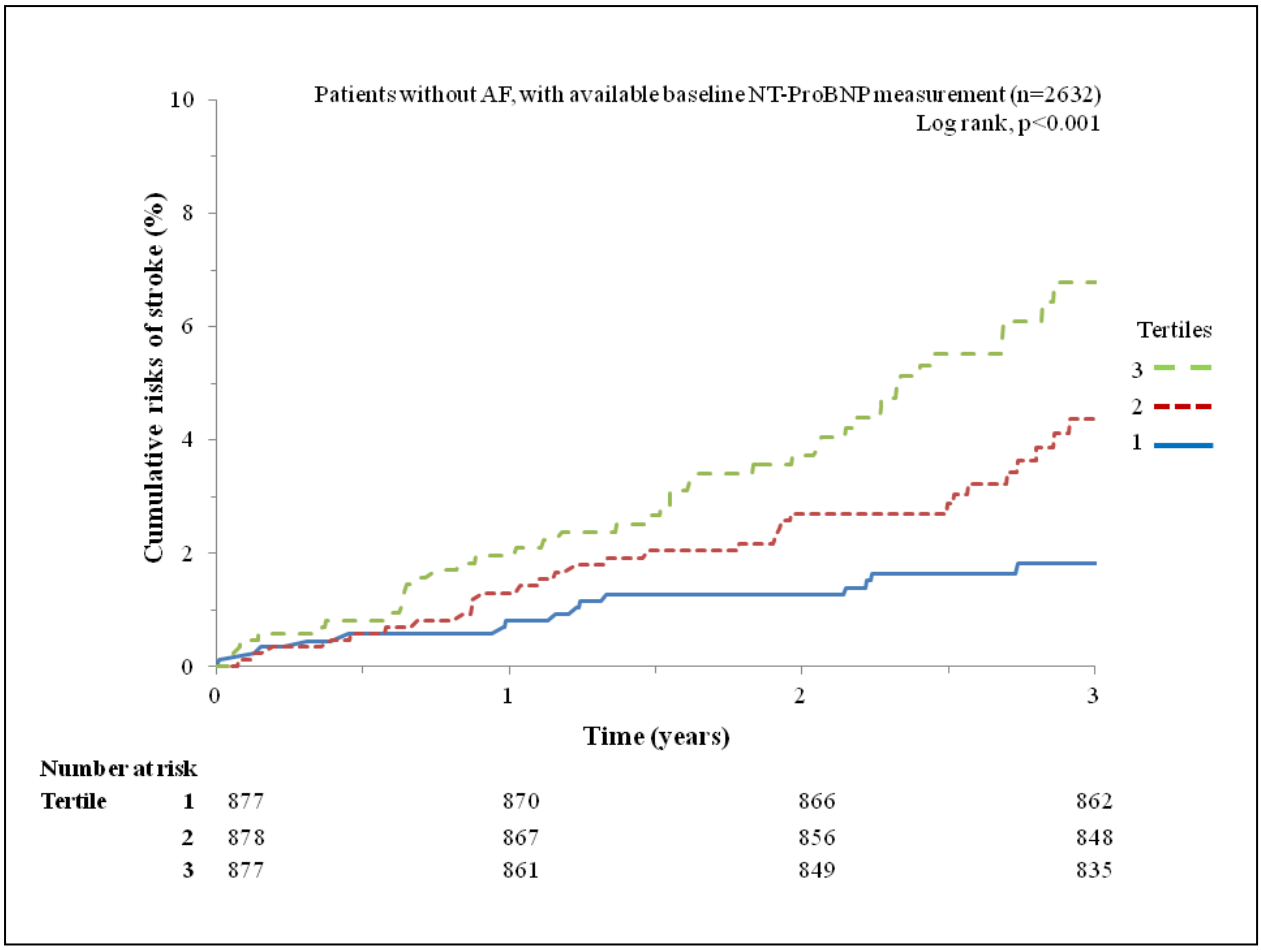
Supplementary Figure 5. Cumulative incidence function plot for stroke by tertiles of their risk scores in patients without AF – "best clinical model" (using CHARM HF-REF, for patients without AF- accounting death as competing risk).



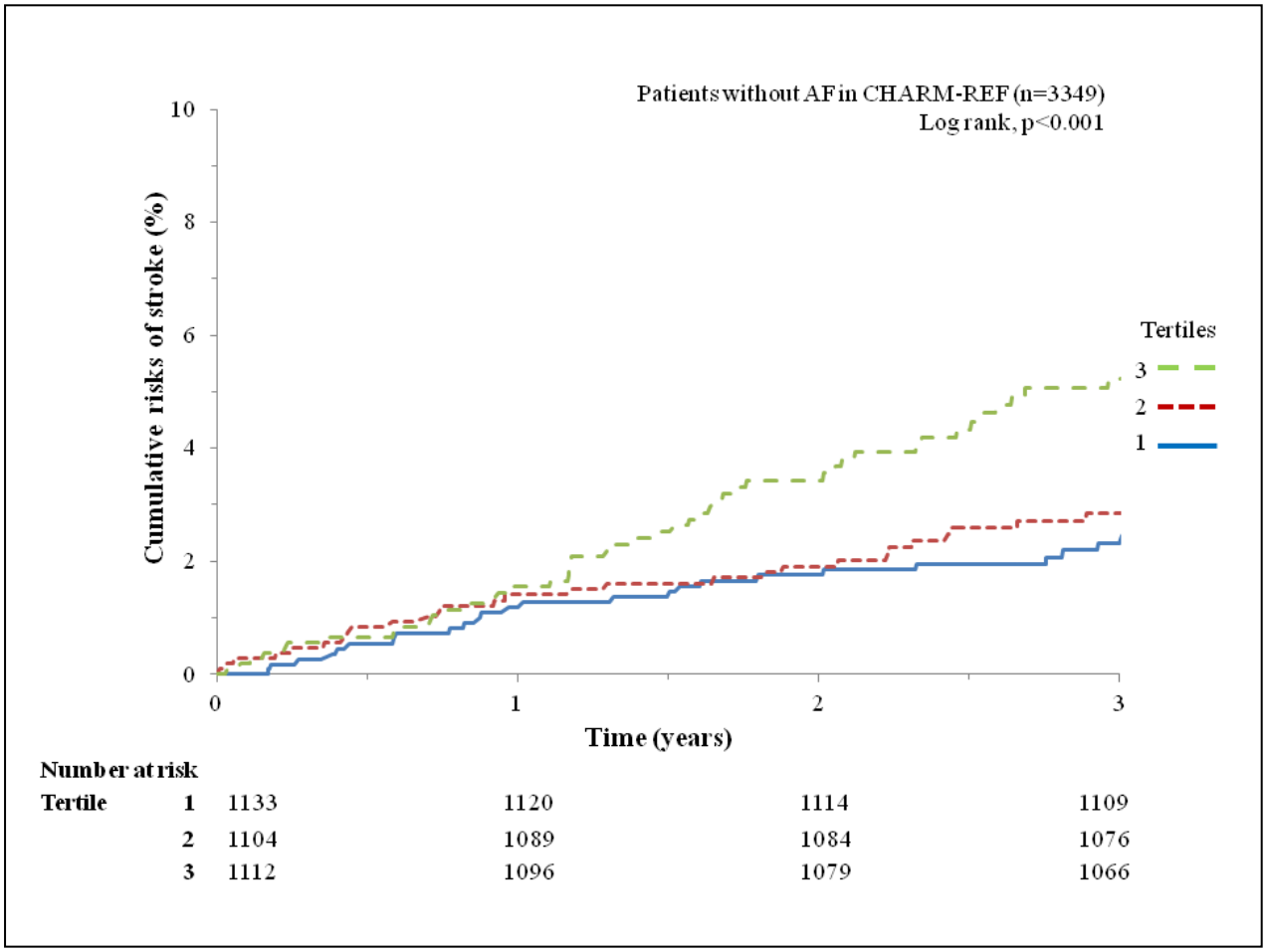
Supplementary Figure 6. Kaplan-Meier plot stroke for chronic heart failure patients according to atrial fibrillation status at baseline.



Supplementary Figure 7. Kaplan-Meier plot for stroke by tertiles of their risk scores in patients without AF – model including NT-proBNP. AF indicates atrial fibrillation.



Supplementary Figure 8. Kaplan-Meier plot for stroke by tertiles of their risk scores in patients without AF – "best clinical model" (using CHARM HF-REF, for patients without AF).



Appendices

Appendix 1. Examples of risk score calculation using the models presented in Tables 2 and 3

This example illustrates the use of Tables 2 and 3, and associated Figure 3 and Supplementary Figure II, respectively, to calculate the risk score of stroke in individual patients.

For example, consider a patient aged 70 years in NYHA functional class II with a BMI of 25 kg/m^2 and a previous stroke. Using the coefficients in Table 2, each multiplied by 10, this patient's risk score for stroke is: (7 x 3.11) + [5 x (-3.01)] + 5.91 = 12.63. Note that age in decades, hence 70 becomes 7; BMI in steps of 5, hence BMI of 25 becomes 5.

For patient with available NT pro-BNP measurement, risk score for stroke can be estimated using coefficients in Table 3 and Supplementary Figure II, using similar steps as described above.

Appendix 2. List of the Investigators of the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) and GISSI-Heart Failure (GISSI-HF)

CORONA group: John Kjekshus, Eduard Apetrei, Vivencio Barrios, Michael Böhm, John G.F. Cleland, Jan H. Cornel, Peter Dunselman, Cândida Fonseca, Assen Goudev, Peer Grande, Lars Gullestad, Åke Hjalmarson, Jaromir Hradec, András Jánosi, Gabriel Kamenský, Michel Komajda, Jerzy Korewicki, Timo Kuusi, François Mach, Vyacheslav Mareev, John J.V. McMurray, Naresh Ranjith, Maria Schaufelberger, Johan Vanhaecke, Dirk J. van Veldhuisen, Finn Waagstein, Hans Wedel, John Wikstrand.

GISSI-HF group: Luigi Tavazzi, Gianni Tognoni, Aldo P Maggioni, Roberto Marchioli, Roberto Latini, Maria Grazia Franzosi, Gian Luigi Nicolosi, Maurizio Porcu, Simona Barlera, Donata Lucci.