New-onset atrial fibrillation in patients with worsening heart failure and coronary artery disease: an analysis from the COMMANDER-HF trial

João Pedro Ferreira, MD, PhD[1]; John G. Cleland, MD[2]; Carolyn S. P. Lam, MD, PhD[3,4]; Stefan D. Anker, MD, PhD[5,6]; Mandeep R. Mehra, MD, PhD[7]; Dirk J. van Veldhuisen, MD, PhD[8]; William M. Byra, MD[9]; David A. La Police, BS[9]; Barry Greenberg, MD[10]; Faiez Zannad, MD, PhD[1]

Affiliations:

[1] Université de Lorraine, Centre d'Investigations Cliniques Plurithématique Inserm 1433, Nancy, France, CHRU de Nancy, Inserm U1116, Nancy, France, FCRIN INI-CRCT, Nancy, France.

[2] Robertson Centre for Biostatistics and Clinical Trials, University of Glasgow, Glasgow, Scotland.

[3] National Heart Centre Singapore, Duke-National University of Singapore, Singapore.

[4] Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

[5] Berlin–Brandenburg Center for Regenerative Therapies, Berlin, Germany.

[6] Department of Cardiology, German Center for Cardiovascular Research partner site Berlin, Charite Universitatsmedizin Berlin, Berlin, Germany.

[7] Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

[8] Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

[9] Janssen Research and Development, Raritan, New Jersey.

[10] Cardiology Division, Department of Medicine, University of California, San Diego, La Jolla.

Correspondence to:

Professor Faiez Zannad and Dr João Pedro Ferreira

Centre d'Investigation Clinique 1433 module Plurithématique, CHRU Nancy - Hopitaux de Brabois

Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu

4 rue du Morvan, 54500 Vandoeuvre les Nancy

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

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

Mail: f.zannad@chru-nancy.fr and j.ferreira@chru-nancy.fr

Abstract

Background: Atrial fibrillation (AF) in the presence of heart failure (HF) is associated with poor outcomes including a high-risk of stroke and other thromboembolic events. Identifying patients without AF who are at high-risk of developing this arrhythmia has important clinical implications.

Aims: To develop a risk score to identify HF patients at high risk of developing AF.

Methods: The COMMANDER-HF trial enrolled 5,022 patients with HF and a LVEF ≤40%, history of coronary artery disease, and absence of AF at baseline (confirmed with an electrocardiogram). Patients were randomized to either rivaroxaban (2.5 mg bid) or placebo. New-onset AF was confirmed by the investigator at study visits.

Results: 241 (4.8%) patients developed AF during the follow-up (median 21 months). Older age (≥65 years), LVEF <35%, history of PCI or CABG, White race, SBP <110 mmHg, and higher BMI (≥25 Kg/m^2) were independently associated with risk of new-onset AF, whereas the use of DAPT was associated with a lower risk of new-onset AF. We then built a risk score from these variables (with good accuracy C-index =0.71) and calibration across observed and predicted tertiles of risk. New-onset AF events rates increased steeply by increasing tertiles of the risk-score. Compared to tertile 1, the risk of new-onset AF was 2.5-fold higher in tertile 2, and 6.3-fold higher in tertile 3. Rivaroxaban had no effect in reducing new-onset AF. In time-updated models, new-onset AF was associated with a higher risk of subsequent all-cause death: HR (95%CI) 1.38 (1.11-1.73).

Conclusions: A well-calibrated risk-score identified patients at risk of new-onset AF in the COMMANDER-HF trial. Patients who developed AF had a higher risk of subsequent death.

Introduction

Atrial fibrillation (AF) in the presence of other risk factors such as heart failure (HF) is associated with poor outcomes including a high-risk of stroke and other thromboembolic events warranting the use of anticoagulants and a strategy for the control of heart rate or rhythm[1, 2]. Thus, identifying patients (without AF) who have a high-risk of developing AF has important clinical implications and is an area of active research[3-5].

The COMMANDER-HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) trial randomised patients with heart failure and a reduced ejection fraction (HFrEF), a recent episode of worsening HF, underlying coronary artery disease (CAD), and no AF, to receive either low-dose rivaroxaban (2.5 mg bid) or placebo[6]. The clinical detection and reporting of new-onset AF was confirmed by electrocardiogram at study visits or from patient`s clinical records, as patients with new-onset AF had to exit the double-blind treatment and initiate full-dose anticoagulation targeted for stroke prevention[7]. Therefore, the COMMANDER-HF population provides an opportunity to study the incidence and predictors of new-onset AF in high-risk CAD-HF patients.

The aims of the present study are to 1) compare the characteristics of the patients who developed new-onset AF during the trial follow-up versus those who did not, 2) identify the predictors of new-onset AF, 3) build a ready-to-use risk-model with good accuracy for the prediction of new-onset AF, 4) assess whether rivaroxaban could

reduce the incidence of new-onset AF in this population; and 5) study the time-updated prognostic impact of new-onset atrial fibrillation on subsequent mortality.

Methods

Study population

The study design of the COMMANDER-HF trial has been previously described[6, 7]. Key inclusion criteria included history of chronic HF for three or more months, treatment for decompensated HF in the previous 30 days, left ventricular ejection fraction (LVEF) of 40% or less, history of CAD, and absence of AF at baseline (confirmed with an electrocardiogram) or other indication for chronic anticoagulation (subjects with isolated transient AF may be allowed at the discretion of the treating physician investigator). Decompensated HF was defined by symptoms of worsening dyspnea or fatigue, objective signs of congestion, and/or adjustment of HF medications requiring hospital admission. Rivaroxaban or placebo was given in addition to background single or dual anti-platelet therapy (DAPT).

The Ethics Committee of each participating site in each country approved the protocol and all patients gave written informed consent to participate in the study.

Study outcomes

The outcome of interest in the present study was new-onset AF (confirmed with an electrocardiogram and ascertained by the treating physician investigator). Once new-onset AF was detected during the study follow-up, patients were instructed to be started on AF target-dose oral anticoagulants and the remainder treatment decisions were performed at the discretion of the treating physician. The median follow-up was 21.1 months (percentile$_{25-75}$, 12.9-32.8).

In COMMANDER-HF, rivaroxaban did not reduce the incidence of the primary efficacy outcome of myocardial infarction, stroke or all-cause mortality nor the rate of HF re-hospitalization; however, the incidence of ischemic stroke and composite thrombo-embolic events was reduced[8, 9].

Investigators reported outcomes on detailed case report forms, which were verified by the sponsor's clinical operations team using blinded source data. All participants provided written informed consent. The protocol was approved by the appropriate institutional review board or ethics committee at each site.

Based on a review of patient characteristics and event rates, blind to assigned treatment for the first 1,155 patients, the steering committee amended the enrolment criteria to require a plasma NT-pro BNP level ≥800 ng/L or BNP level ≥200 ng/L by local laboratory measured at any time between the index admission for decompensated HF and randomization. Simultaneous with the amendment, enrolment in the Asia-Pacific region and several additional countries began[7, 10].

Statistical analysis

Baseline characteristics were described using means ± SD for normally distributed continuous variables, median (percentile$_{25-75}$) for skewed continuous variables, and number (proportion) for categorical variables, and between patients who developed or did not develop AF during the follow-up. Time-to-event analyses were conducted using a competing-risk model as described by Fine and Gray[11], with AF as outcome event and death as competing-risk. The analysis was also performed using Cox regression with similar results. Log-linearity was assessed by testing the functional forms of the covariable by the Kolmogorov-type supremum test and by visual inspection by plotting the beta estimates versus the mean across deciles. All the

variables with a p-value <0.1 in Table 1 were entered in the multivariable model, and the variable selection was performed using a stepwise forward regression analysis with p-value to enter the model set to 0.05. Discrimination of the model was assessed by calculating the C-statistics. Assessment of the calibration was performed by visually plotting the cumulative incidence of observed versus expected AF events across tertiles of predicted risk. A random subsample of 3,000 patients from the COMMANDER-HF trial was used for validation of the findings i.e., the original cohort was used for "derivation" and the random subsample for "validation". For validation purposes, we have also used bootstrapping methods over 1000 samples. To create a simple risk score, integer points were assigned to each prognostic factor based on the log-hazard ratio estimates[12]. The total risk score for each patient was calculated by summing the points across all chosen prognostic variables. From the overall distribution of the risk score we formed three categories of risk (risk tertiles). Kaplan–Meier plots were drawn showing the cumulative incidence curves by risk category. A 2-sided p value of <0.05 was considered significant. Stata® version 16 (StataCorp. 2019. College Station, TX: StataCorp LLC) was used for the statistical analysis.

Results

Patients` characteristics by new-onset atrial fibrillation status

Of the 5,022 patients enrolled in COMMANDER-HF, we identified 241 (4.8%) who have developed incident AF during the follow-up, corresponding to an overall incidence rate of 2.5 (2.2-2.9) events per 100 person-years (py). Patients who developed AF were older, more often White, had higher BMI, lower SBP, poorer renal function, lower LVEF, and were less often treated with DAPT. *Table 1.*

Risk score of new-onset atrial fibrillation

Older age (65 to 75 years and >75 years), LVEF <35%, history of PCI or CABG, White race, SBP <110 mmHg, and higher BMI (25-30 Kg/m^2 and >30Kg/m^2) were independently associated with a higher risk of new-onset AF, whereas the use of DAPT was associated with a lower risk of new-onset AF. The accuracy of the model was good with a C-index of 0.71. *Table 2*. From these variables we have created an integer score ranging from a minimum of -2 to a maximum of 11 points.

Event-rates and rivaroxaban effect by tertiles of the risk score

The new-onset AF risk score was divided in tertiles with a balanced number of patients within each risk category: tertile 1 from -2 to 4 points, tertile 2 from 5 to 6 points, and tertile 3 from 7 to 11 points. The events rates (per 100py) increased steeply from tertile 1 to 3: 0.8 (0.6-1.2), 2.1 (1.7-2.7), and 5.3 (4.5-6.3), respectively. Compared to tertile 1, the risk of new-onset AF was 2.5-fold higher in tertile 2, and 6.3-fold higher in tertile 3.

Rivaroxaban had no effect in reducing new-onset AF: overall population HR (95%CI) 1.06 (0.83-1.37), p =0.63. The results across tertiles of the AF risk-score are presented in *Table 3*.

The risk score was well calibrated with a good agreement between predicted and observed events. *Figure 1*. The new-onset AF events by tertiles of the risk score is represented in *Figure 2 & Graphical Abstract*.

This model was applied to a random subsample of 3,000 patients with overlapping results. *Supplemental Table 1*. Bootstrapping over 1,000 samples provided similar results.

The effect of rivaroxaban on the study outcomes was not modified by the new-onset AF risk score. *Supplemental Table 2*.

The risk score performed poorly for predicting stroke (C-index =0.60) and with different variable associations (positive association of D-dimer levels and negative associated of White race). *Supplemental Table 3*.

A total of 2928 patients had available NT-pro BNP levels (41.7% missing). In a sensitivity analysis including only the post protocol amendment patients, NT-pro BNP (log transformed) was not associated with new-onset AF (p =0.45).

Risk of all-cause death and cardiovascular death or heart failure hospitalization after new-onset atrial fibrillation

In a time-updated model, new-onset AF was associated with a higher risk of subsequent all-cause death: HR (95%CI) 1.38 (1.11-1.73), an association that was attenuated after adjustment for the new-onset AF risk score: HR (95%CI) 1.21 (0.96-1.52). New-onset AF was also associated with a higher risk of subsequent cardiovascular death or HF hospitalization: crude HR (95%CI) 2.28 (1.94-2.67), adjusted HR (95%CI) 2.06 (1.75-2.42). *Figure 3*.

Discussion

In COMMANDER-HF we have built a well-calibrated and accurate risk-score model using readily available variables for identifying HFrEF patients at increased risk of new-onset AF. Patients in the highest tertile of the risk score had a 6-fold higher rate of new-onset AF with an AF incidence rate of 5.3 per 100 person-years compared with patients in the lowest tertile of the risk score that presented an AF incidence rate

of 0.8 person-years. Rivaroxaban had no effect on AF incidence. Patients who developed AF had a higher risk of subsequent death.

Many patients with HFrEF have a high risk of stroke despite not presenting overt AF, with the risk of stroke being particularly elevated among severely symptomatic patients[13]. Potential explanations for the increased risk of stroke include the activation of thrombin-related pathways, inflammation and endothelial dysfunction or the development of AF during the follow-up[13-16]. Prior studies with warfarin in patients with HFrEF and sinus rhythm did not show convincing evidence of an improvement of cardiovascular outcomes but did demonstrate an increased risk of bleeding[17-20]. Rivaroxaban at a dose of 2.5 mg twice daily also did not reduce the rate of death and cardiovascular events in patients with recent worsening of chronic HFrEF, CAD, and no AF in the COMMANDER-HF trial[7]. However, rivaroxaban reduced the rate of thromboembolic events including ischemic stroke, particularly in patients with elevated d-dimer levels[8, 21]. Among patients who developed AF in COMMANDER-HF only 8 (3%) had a stroke[21]. This is likely because whenever AF was identified, the double-blinded treatment would be stopped and patients would receive full-dose anticoagulation for the prevention of stroke (at the discretion of the treating physician), with the follow-up continued until death or end of the follow-up period. However, patients who developed AF might have had a higher risk of subsequent mortality. These findings highlight the need for a better identification of patients who have a high-risk of developing AF, these can be monitored closely and, whenever AF is detected, adequate treatment can be promptly initiated. Interestingly, our model that accurately predicted AF performed poorly in predicting stroke, this might be due to the fact that patients who developed AF initiated full anticoagulation, thus preventing stroke; but is might also indicate that many patients with CAD and

worsening HFrEF might have a hypercoagulable state that increases the risk of stroke independently of AF[21]. New-onset AF should be regarded as a clinically important and predictable event, thus AF prevention or, at least, early detection is possible if targeted to selected high-risk patients.

Continuous traditional heart monitors or implantable devices increase the detection of atrial fibrillation in high-risk populations but only for limited monitoring periods and paroxysmal AF might remain undetected[22]. Screening all-comers for AF using an internet-connected device (e.g., Apple Watch) may identify people with AF; however, in the general population the proportion of people with AF is very low (0.5%) and of uncertain clinical significance under many circumstances (e.g., young patients without comorbidities), which may increase participants' anxiety and unnecessary medical appointments and treatments[4]. Therefore, targeting screening strategies to high-risk patients could be a more effective strategy; for example, screening patients in the highest tertile of our risk score.

In addition to better screening strategies, better AF prevention strategies are also required. In COMMANDER-HF, patients treated with DAPT were less likely to develop AF, this might be related to a more effective prevention of ischemic events, including microvascular events, MI and stent thrombosis, all of which may induce AF [23-25]. However, rivaroxaban had no effect on AF incidence, but also did not reduce MI rates in COMMANDER-HF[7]. Older age, lower LVEF, prior coronary intervention, lower blood pressure, white race, and higher BMI were positively associated with new-onset AF in COMMANDER-HF. Most of these factors have been previously identified to be associated with incident AF[26, 27]. A lower LVEF and coronary interventions suggest that impaired "pump" function (often due to ischemia) increases AF risk. In addition, a lower blood pressure in patients with HFrEF and

CAD is associated with poor prognosis, often indicating a more advanced disease[28]. Ageing is associated with increased fibrosis of the atria which might cause conduction disturbances leading to AF[29]. White race was also associated with a higher risk of new-onset AF, a finding that is concordant with other reports[30, 31]. White patients in COMMANDER-HF were largely represented in Eastern Europe, and these patients had lower mortality rate which could increase the opportunity for them to develop AF, compared to patients of other race/ethnicities[32]. Obesity is a well-documented AF risk-factor[26], explaining the association of higher BMI with AF found herein. For example, in at-risk obese individuals without AF, bariatric surgery, with nearly 20% weight loss, has been shown to reduce the long-term risk of incident AF[33]. This is of particular interest, as in HFrEF (and other chronic conditions) an "obesity paradox" has been described, whereby patients with higher BMI may have a better prognosis[34-36]. Our findings suggest that obesity may not be desirable in HFrEF as it may increase AF risk.

Of note, thrombin activation and hypercoagulability promote the development of AF in transgenic mice and goats; effects that could be attenuated by dabigatran and nadroparin[37]. However, in the COMMANDER-HF trial, treatment with rivaroxaban (vs. placebo) did not reduce the incidence of AF, but we cannot ascertain if this neutral effect was due to the lack of power or lack of effect for preventing AF in humans.

Overall, our findings show that in patients with recent worsening HFrEF, CAD, and no AF at baseline, new-onset AF can be predicted with good accuracy using a readily available risk score. We suggest that our AF risk score may be used for directing diagnostic (e.g., Holter detection) and treatment (e.g., rapid cardioversion and anti-coagulation) strategies.

Limitations

This is a post-hoc analysis of a randomized controlled trial, therefore causality cannot be inferred. While attention was paid to the clinical detection and reporting of new onset AF throughout the trial, there was no ambulatory electrocardiogram surveillance by protocol, nor was electrocardiogram data (beyond reporting of Q waves) available in COMMANDER-HF dataset. Other monitoring techniques, such as Holter-ECG, loop recorder, or "smart watch apps" could have increased the rate of AF detection and treatment. Furthermore, patients may have developed undetected ("clinically occult") AF[8]. Biomarkers may be useful to predict AF; however, NT-pro BNP had more than 40% missing values and high-sensitivity troponin was not available in COMMANDER-HF. Our analysis may be limited by "survival time bias" where patients living longer may develop AF more often. Our findings represent associations that can be used to inform about the risk of AF in patients with the characteristics of those enrolled in COMMANDER-HF. In this regard, external validation was not available due to the uniqueness of the COMMANDER-HF population; nonetheless, we have applied the risk score to a random sample of 3,000 patients within COMMANDER-HF and bootstrapping over 1,000 samples keeping the model`s good accuracy.

Conclusions

A well-calibrated and accurate risk-score model using readily available variables identified patients at risk of new-onset AF in the COMMANDER-HF trial. Rivaroxaban had no effect on AF incidence. Patients who developed AF had a higher risk of subsequent death.

Disclosures

The authors report no conflicts of interest regarding the content of this manuscript.

Bibliography

1.   Ferreira, J. P.; Girerd, N.; Alshalash, S.; Konstam, M. A.; Zannad, F., Antithrombotic therapy in heart failure patients with and without atrial fibrillation: update and future challenges. *Eur Heart J* **2016**.

2.   Marrouche, N. F.; Brachmann, J.; Andresen, D.; Siebels, J.; Boersma, L.; Jordaens, L.; Merkely, B.; Pokushalov, E.; Sanders, P.; Proff, J.; Schunkert, H.; Christ, H.; Vogt, J.; Bänsch, D., Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* **2018**, *378* (5), 417-427.

3.   Dörr, M.; Nohturfft, V.; Brasier, N.; Bosshard, E.; Djurdjevic, A.; Gross, S.; Raichle, C. J.; Rhinisperger, M.; Stöckli, R.; Eckstein, J., The WATCH AF Trial: SmartWATCHes for Detection of Atrial Fibrillation. *JACC Clin Electrophysiol* **2019**, *5* (2), 199-208.

4.   Perez, M. V.; Mahaffey, K. W.; Hedlin, H.; Rumsfeld, J. S.; Garcia, A.; Ferris, T.; Balasubramanian, V.; Russo, A. M.; Rajmane, A.; Cheung, L.; Hung, G.; Lee, J.; Kowey, P.; Talati, N.; Nag, D.; Gummidipundi, S. E.; Beatty, A.; Hills, M. T.; Desai, S.; Granger, C. B.; Desai, M.; Turakhia, M. P., Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *N Engl J Med* **2019**, *381* (20), 1909-1917.

5.   Attia, Z. I.; Noseworthy, P. A.; Lopez-Jimenez, F.; Asirvatham, S. J.; Deshmukh, A. J.; Gersh, B. J.; Carter, R. E.; Yao, X.; Rabinstein, A. A.; Erickson, B. J.; Kapa, S.; Friedman, P. A., An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet* **2019**, *394* (10201), 861-867.

6.   Zannad, F.; Greenberg, B.; Cleland, J. G.; Gheorghiade, M.; van Veldhuisen, D. J.; Mehra, M. R.; Anker, S. D.; Byra, W. M.; Fu, M.; Mills, R. M., Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial. *Eur J Heart Fail* **2015**, *17* (7), 735-42.

7.   Zannad, F.; Anker, S. D.; Byra, W. M.; Cleland, J. G. F.; Fu, M.; Gheorghiade, M.; Lam, C. S. P.; Mehra, M. R.; Neaton, J. D.; Nessel, C. C.; Spiro, T. E.; van Veldhuisen, D. J.; Greenberg, B., Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. *N Engl J Med* **2018**.

8.   Mehra, M. R.; Vaduganathan, M.; Fu, M.; Ferreira, J. P.; Anker, S. D.; Cleland, J. G. F.; Lam, C. S. P.; van Veldhuisen, D. J.; Byra, W. M.; Spiro, T. E.; Deng, H.; Zannad, F.; Greenberg, B., A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMANDER HF trial. *Eur Heart J* **2019**, *40* (44), 3593-3602.

9.   Greenberg, B.; Neaton, J. D.; Anker, S. D.; Byra, W. M.; Cleland, J. G. F.; Deng, H.; Fu, M.; La Police, D. A.; Lam, C. S. P.; Mehra, M. R.; Nessel, C. C.; Spiro, T. E.; van Veldhuisen, D. J.; Vanden Boom, C. M.; Zannad, F., Association of Rivaroxaban With Thromboembolic Events in Patients With Heart Failure, Coronary Disease, and Sinus Rhythm: A Post Hoc Analysis of the COMMANDER HF Trial. *JAMA Cardiol* **2019**, *4* (6), 515-523.

10.   Cunningham, J. W.; Ferreira, J. P.; Deng, H.; Anker, S. D.; Byra, W. M.; Cleland, J. G. F.; Gheorghiade, M.; Lam, C. S. P.; La Police, D.; Mehra, M. R.; Neaton, J. D.; Spiro, T. E.; van Veldhuisen, D. J.; Greenberg, B.; Zannad, F., Natriuretic Peptide-Based Inclusion Criteria in a Heart Failure Clinical Trial: Insights From COMMANDER HF. *JACC Heart Fail* **2020**.

11.   JP, F.; RJ, G., A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* **1999**, *94* :496–509.   .

12.   Collier, T. J.; Pocock, S. J.; McMurray, J. J.; Zannad, F.; Krum, H.; van Veldhuisen, D. J.; Swedberg, K.; Shi, H.; Vincent, J.; Pitt, B., The impact of eplerenone at different levels of risk in patients with systolic heart failure and mild symptoms: insight from a novel risk score for prognosis derived from the EMPHASIS-HF trial. *Eur Heart J* **2013**, *34* (36), 2823-9.

13.   Abdul-Rahim, A. H.; Perez, A. C.; Fulton, R. L.; Jhund, P. S.; Latini, R.; Tognoni, G.; Wikstrand, J.; Kjekshus, J.; Lip, G. Y.; Maggioni, A. P.; Tavazzi, L.; Lees, K. R.; McMurray, J. J., Risk of Stroke in Chronic Heart Failure Patients Without Atrial Fibrillation: Analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials. *Circulation* **2015,** *131* (17), 1486-94; discussion 1494.

14.   Borissoff, J. I.; Spronk, H. M.; Heeneman, S.; ten Cate, H., Is thrombin a key player in the 'coagulation-atherogenesis' maze? *Cardiovasc Res* **2009,** *82* (3), 392-403.

15.   Abdul-Rahim, A. H.; Perez, A. C.; MacIsaac, R. L.; Jhund, P. S.; Claggett, B. L.; Carson, P. E.; Komajda, M.; McKelvie, R. S.; Zile, M. R.; Swedberg, K.; Yusuf, S.; Pfeffer, M. A.; Solomon, S. D.; Lip, G. Y. H.; Lees, K. R.; McMurray, J. J. V., Risk of stroke in chronic heart failure patients with preserved ejection fraction, but without atrial fibrillation: analysis of the CHARM-Preserved and I-Preserve trials. *Eur Heart J* **2017,** *38* (10), 742-750.

16.   Ferreira, J. P.; Girerd, N.; Gregson, J.; Latar, I.; Sharma, A.; Pfeffer, M. A.; McMurray, J. J. V.; Abdul-Rahim, A. H.; Pitt, B.; Dickstein, K.; Rossignol, P.; Zannad, F., Stroke Risk in Patients With Reduced Ejection Fraction After Myocardial Infarction Without Atrial Fibrillation. *J Am Coll Cardiol* **2018,** *71* (7), 727-735.

17.   Cleland, J. G.; Findlay, I.; Jafri, S.; Sutton, G.; Falk, R.; Bulpitt, C.; Prentice, C.; Ford, I.; Trainer, A.; Poole-Wilson, P. A., The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* **2004,** *148* (1), 157-64.

18.   Cokkinos, D. V.; Haralabopoulos, G. C.; Kostis, J. B.; Toutouzas, P. K., Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. *Eur J Heart Fail* **2006,** *8* (4), 428-32.

19.   Massie, B. M.; Collins, J. F.; Ammon, S. E.; Armstrong, P. W.; Cleland, J. G.; Ezekowitz, M.; Jafri, S. M.; Krol, W. F.; O'Connor, C. M.; Schulman, K. A.; Teo, K.; Warren, S. R., 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* (12), 1616-24.

20.   Homma, S.; Thompson, J. L.; Pullicino, P. M.; Levin, B.; Freudenberger, R. S.; Teerlink, J. R.; Ammon, S. E.; Graham, S.; Sacco, R. L.; Mann, D. L.; Mohr, J. P.; Massie, B. M.; Labovitz, A. J.; Anker, S. D.; Lok, D. J.; Ponikowski, P.; Estol, C. J.; Lip, G. Y.; Di Tullio, M. R.; Sanford, A. R.; Mejia, V.; Gabriel, A. P.; del Valle, M. L.; Buchsbaum, R., Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* **2012,** *366* (20), 1859-69.

21.   Ferreira, J. P.; Lam, C. S. P.; Anker, S. D.; Mehra, M. R.; van Veldhuisen, D. J.; Byra, W. M.; La Police, D. A.; Cleland, J. G. F.; Greenberg, B.; Zannad, F., Plasma D-dimer concentrations predicting stroke risk and rivaroxaban benefit in patients with heart failure and sinus rhythm: an analysis from the COMMANDER-HF trial. *Eur J Heart Fail* **2020**.

22.   Belkin, M. N.; Soria, C. E.; Waldo, A. L.; Borleffs, C. J. W.; Hayes, D. L.; Tung, R.; Singh, J. P.; Upadhyay, G. A., Incidence and Clinical Significance of New-Onset Device-Detected Atrial Tachyarrhythmia: A Meta-Analysis. *Circ Arrhythm Electrophysiol* **2018,** *11* (3), e005393.

23.   Degrauwe, S.; Pilgrim, T.; Aminian, A.; Noble, S.; Meier, P.; Iglesias, J. F., Dual antiplatelet therapy for secondary prevention of coronary artery disease. *Open Heart* **2017,** *4* (2), e000651.

24.   Mauri, L.; Kereiakes, D. J.; Yeh, R. W.; Driscoll-Shempp, P.; Cutlip, D. E.; Steg, P. G.; Normand, S. L.; Braunwald, E.; Wiviott, S. D.; Cohen, D. J.; Holmes, D. R., Jr.; Krucoff, M. W.; Hermiller, J.; Dauerman, H. L.; Simon, D. I.; Kandzari, D. E.; Garratt, K. N.; Lee, D. P.; Pow, T. K.; Ver Lee, P.; Rinaldi, M. J.; Massaro, J. M., Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* **2014,** *371* (23), 2155-66.

25.   Bhatia, G. S.; Lip, G. Y., Atrial fibrillation post-myocardial infarction: frequency, consequences, and management. *Curr Heart Fail Rep* **2004,** *1* (4), 149-55.

26.   Lau, D. H.; Nattel, S.; Kalman, J. M.; Sanders, P., Modifiable Risk Factors and Atrial Fibrillation. *Circulation* **2017,** *136* (6), 583-596.

27.   Alonso, A.; Krijthe, B. P.; Aspelund, T.; Stepas, K. A.; Pencina, M. J.; Moser, C. B.; Sinner, M. F.; Sotoodehnia, N.; Fontes, J. D.; Janssens, A. C.; Kronmal, R. A.; Magnani, J. W.; Witteman, J. C.; Chamberlain, A. M.; Lubitz, S. A.; Schnabel, R. B.; Agarwal, S. K.; McManus, D. D.; Ellinor, P. T.; Larson, M. G.; Burke, G. L.; Launer, L. J.; Hofman, A.; Levy, D.; Gottdiener, J. S.; Kääb, S.; Couper, D.; Harris, T. B.; Soliman, E. Z.; Stricker, B. H.; Gudnason, V.; Heckbert, S. R.; Benjamin, E. J., Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* **2013,** *2* (2), e000102.

28.   Ferreira, J. P.; Duarte, K.; Pfeffer, M. A.; McMurray, J. J. V.; Pitt, B.; Dickstein, K.; Zannad, F.; Rossignol, P., Association between mean systolic and diastolic blood pressure throughout the follow-up and cardiovascular events in acute myocardial infarction patients with systolic dysfunction and/or heart failure: an analysis from the High-Risk Myocardial Infarction Database Initiative. *Eur J Heart Fail* **2018,** *20* (2), 323-331.

29.   Schmitt, J.; Duray, G.; Gersh, B. J.; Hohnloser, S. H., Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. *Eur Heart J* **2009,** *30* (9), 1038-45.

30.   Lau, C. P.; Gbadebo, T. D.; Connolly, S. J.; Van Gelder, I. C.; Capucci, A.; Gold, M. R.; Israel, C. W.; Morillo, C. A.; Siu, C. W.; Abe, H.; Carlson, M.; Tse, H. F.; Hohnloser, S. H.; Healey, J. S., Ethnic differences in atrial fibrillation identified using implanted cardiac devices. *J Cardiovasc Electrophysiol* **2013,** *24* (4), 381-7.

31.   Alonso, A.; Agarwal, S. K.; Soliman, E. Z.; Ambrose, M.; Chamberlain, A. M.; Prineas, R. J.; Folsom, A. R., Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* **2009,** *158* (1), 111-7.

32.   Ferreira, J. P.; Cleland, J. G. F.; Lam, C. S. P.; van Veldhuisen, D. J.; Byra, W. M.; La Police, D. A.; Anker, S. D.; Mehra, M. R.; Leroy, C.; Eschwege, V.; Toussaint-Hacquard, M.; Rossignol, P.; Greenberg, B.; Zannad, F., Impact of Geographic Region on the COMMANDER-HF Trial. *JACC Heart Fail* **2021,** *9* (3), 201-211.

33.   Jamaly, S.; Carlsson, L.; Peltonen, M.; Jacobson, P.; Sjöström, L.; Karason, K., Bariatric Surgery and the Risk of New-Onset Atrial Fibrillation in Swedish Obese Subjects. *J Am Coll Cardiol* **2016,** *68* (23), 2497-2504.

34.   Stienen, S.; Ferreira, J. P.; Girerd, N.; Duarte, K.; Lamiral, Z.; McMurray, J. J. V.; Pitt, B.; Dickstein, K.; Zannad, F.; Rossignol, P., Mean BMI, visit-to-visit BMI variability and BMI changes during follow-up in patients with acute myocardial infarction with systolic dysfunction and/or heart failure: insights from the High-Risk Myocardial Infarction Initiative. *Clin Res Cardiol* **2019,** *108* (11), 1215-1225.

35.   Padwal, R.; McAlister, F. A.; McMurray, J. J.; Cowie, M. R.; Rich, M.; Pocock, S.; Swedberg, K.; Maggioni, A.; Gamble, G.; Ariti, C.; Earle, N.; Whalley, G.; Poppe, K. K.; Doughty, R. N.; Bayes-Genis, A., The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. *Int J Obes (Lond)* **2014,** *38* (8), 1110-4.

36.   Oreopoulos, A.; Padwal, R.; Kalantar-Zadeh, K.; Fonarow, G. C.; Norris, C. M.; McAlister, F. A., Body mass index and mortality in heart failure: a meta-analysis. In *Am Heart J*, United States, 2008; Vol. 156, pp 13-22.

37.   Spronk, H. M.; De Jong, A. M.; Verheule, S.; De Boer, H. C.; Maass, A. H.; Lau, D. H.; Rienstra, M.; van Hunnik, A.; Kuiper, M.; Lumeij, S.; Zeemering, S.; Linz, D.; Kamphuisen, P. W.; Ten Cate, H.; Crijns, H. J.; Van Gelder, I. C.; van Zonneveld, A. J.; Schotten, U., Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation. *Eur Heart J* **2017,** *38* (1), 38-50.

Table 1. Patients' characteristics by new-onset atrial fibrillation status

Patients' characteristics	No AF	New-onset AF	p-value
N.	4781	241	-
Age, years	66.0 (59.0, 74.0)	70.0 (64.0, 76.0)	<0.001
Age <65 yr	2281 (47.7%)	74 (30.7%)	<0.001
Age 65-75 yr	1509 (31.6%)	104 (43.2%)	
Age >75 yr	991 (20.7%)	63 (26.1%)	
Female sex	1101 (23.0%)	49 (20.3%)	0.33
White race	3910 (81.8%)	218 (90.5%)	<0.001
Other race	871 (18.2%)	23 (9.5%)	
Geographic Region			<0.001
Eastern Europe	3054 (63.9%)	170 (70.5%)	
Western Europe And South Africa	423 (8.8%)	35 (14.5%)	
North America	143 (3.0%)	6 (2.5%)	
Asia Pacific	716 (15.0%)	17 (7.1%)	
Latin America	445 (9.3%)	13 (5.4%)	
Baseline BMI, kg/m2	27.1 (24.2, 30.6)	28.0 (25.4, 31.8)	<0.001
BMI <25 kg/m2	1548 (32.4%)	54 (22.4%)	0.004
BMI 25-30 kg/m2	1875 (39.2%)	103 (42.7%)	
BMI >30 kg/m2	1358 (28.4%)	84 (34.9%)	
SBP, mmHg	122.0 (110.0, 132.0)	120.0 (110.0, 130.0)	0.053
SBP <110 mmHg	1219 (25.5%)	83 (34.4%)	0.008
SBP 110-130 mmHg	2276 (47.6%)	101 (41.9%)	

SBP >130 mmHg	1286 (26.9%)	57 (23.7%)	
Heart rate, bpm	70.0 (64.0, 78.0)	70.0 (62.0, 78.0)	0.23
Heart rate >70 bpm	2168 (45.3%)	103 (42.7%)	0.43
Hemoglobin, g/dL	13.6 (12.3, 14.8)	13.5 (12.3, 14.7)	0.33
Anemia	1464 (30.6%)	78 (32.4%)	0.57
eGFR, mL/min/1.73m2	66.9 (52.0, 82.4)	61.8 (48.5, 76.0)	0.007
eGFR <60 mL/min/1.73m2	1830 (38.3%)	115 (47.7%)	0.003
LVEF, %	34.0 (28.0, 38.0)	31.0 (25.0, 35.0)	<0.001
LVEF <35%	2883 (60.3%)	182 (75.5%)	<0.001
Fragile	1735 (36.3%)	105 (43.6%)	0.022
NYHA II	2258 (47.2%)	110 (45.6%)	0.63
NYHA III/IV	2523 (52.8%)	131 (54.4%)	
Diabetes	1949 (40.8%)	103 (42.7%)	0.54
Hypertension	3598 (75.3%)	185 (76.8%)	0.60
Myocardial infarction	3611 (75.5%)	192 (79.7%)	0.14
Q wave on ECG	1648 (34.5%)	96 (39.8%)	0.088
PCI or CABG	2984 (62.4%)	166 (68.9%)	0.043
Stroke	433 (9.1%)	20 (8.3%)	0.69
D-dimer <255 ng/mL	1327 (33.9%)	46 (23.2%)	0.007
D-dimer 255-515 ng/mL	1291 (33.0%)	74 (37.4%)	
D-dimer 516-15775 ng/mL	1291 (33.0%)	78 (39.4%)	
ICD/CRT	82 (1.7%)	12 (5.0%)	<0.001
ACEi/ARB	4439 (92.8%)	221 (91.7%)	0.50
MRA	3654 (76.4%)	186 (77.2%)	0.79

Beta-blocker	4418 (92.4%)	224 (92.9%)	0.76
Digoxin	406 (8.5%)	27 (11.2%)	0.14
DAPT	1699 (35.5%)	47 (19.5%)	<0.001
Diuretic	4758 (99.5%)	241 (100.0%)	0.28
ARNI	40 (0.8%)	1 (0.4%)	0.48

Legend: BMI, body mass index; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICD, intra-cardiac defibrillator; CRT, cardiac resynchronization therapy; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; DAPT, dual anti-platelet therapy; ARNI, angiotensin-receptor neprilysin inhibitor.

Table 2. Risk score for new onset atrial fibrillation

Variable	HR (95%CI)	Beta coef.	P-value	Points
Age <65yr	Ref.	-	-	0
Age 65-75yr	2.39 (1.77-3.23)	0.87	<0.001	+2
Age >75yr	2.68 (1.89-3.80)	0.99	<0.001	+3
LVEF <35	2.41 (1.78-3.26)	0.88	<0.001	+2
DAPT	0.48 (0.35-0.66)	-0.73	<0.001	-2
PCI or CABG	1.52 (1.15-2.00)	0.42	0.003	+1
White race	1.71 (1.09-2.67)	0.53	0.02	+2
SBP <110mmHg	1.56 (1.19-2.05)	0.45	0.001	+1
BMI <25 Kg/m2	Ref.	-	-	0
BMI 25-30 Kg/m2	1.56 (1.11-2.18)	0.44	0.011	+1
BMI >30 Kg/m2	1.83 (1.28-2.64)	0.61	0.001	+2

C-index =0.71.

Legend: LVEF, left ventricular ejection fraction; DAPT, dual anti-platelet therapy;

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting;

SBP, systolic blood pressure; BMI, body mass index; HR, hazard ratio.

Table 3. Rates of new-onset atrial fibrillation and effect of rivaroxaban on new-onset

atrial fibrillation by tertiles of risk score

Risk score	Events	Event-rate (per 100py)	HR (95%CI)	Riv. effect	InteractionP
Tertile 1: -2 to 4 points (n =1766)	30 (1.7%)	0.8 (0.6-1.2)	Ref.	1.64 (0.78-3.44)	
Tertile 2: 5 to 6 points (n =1738)	72 (4.1%)	2.1 (1.7-2.7)	2.53 (1.65-3.87)	1.17 (0.73-1.85)	0.47
Tertile 3: 7 to 11 points (n =1518)	139 (9.2%)	5.3 (4.5-6.3)	6.26 (4.22-9.30)	1.00 (0.72-1.39)	

Legend: HR, hazard ratio; Riv., rivaroxaban.

Figure 1. Predicted vs. observed risk of new-onset atrial fibrillation up to 4 years of follow-up

Legend: AF, atrial fibrillation; Tertile 1: -2 to 4 points (n =1766); Tertile 2: 5 to 6 points (n =1738); Tertile 3: 7 to 11 points (n =1518).

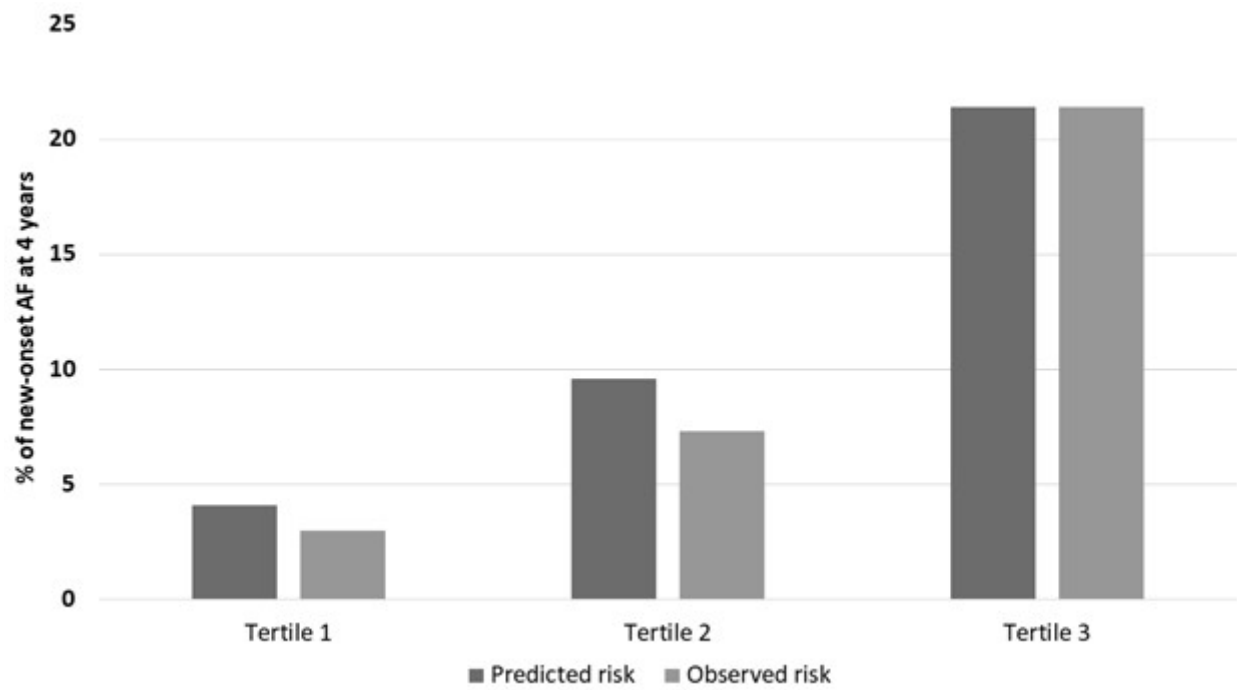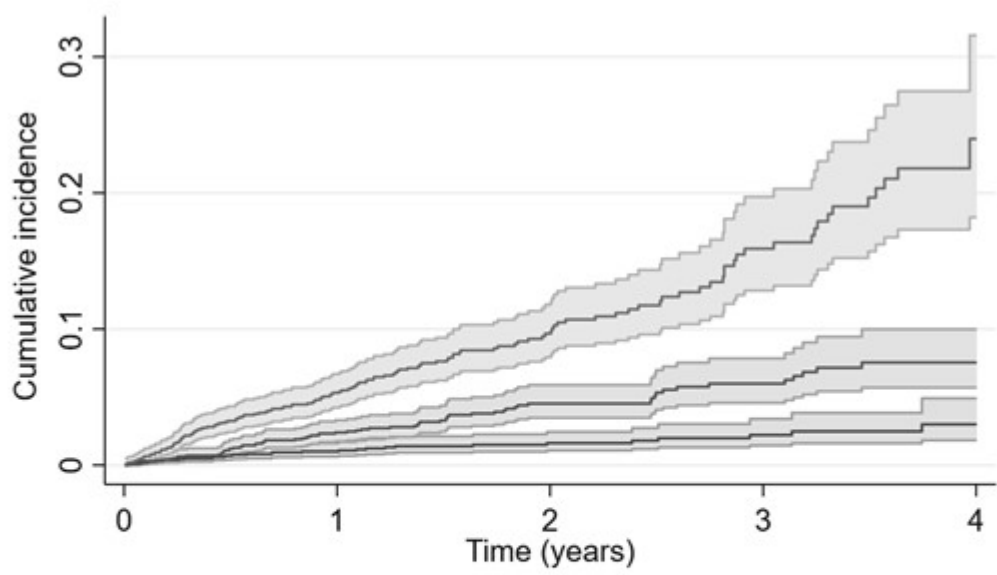Good agreement between the predicted and observed risk, the model is well calibrated.

Figure 2. Cumulative incidence of new-onset atrial fibrillation by tertiles of the risk score

Legend: Tertile 1: -2 to 4 points (n =1766); Tertile 2: 5 to 6 points (n =1738); Tertile 3: 7 to 11 points (n =1518).

Number at risk

Tertile 1	1766	1386	783	417	106
Tertile 2	1738	1329	713	374	93
Tertile 3	1518	1106	494	224	39

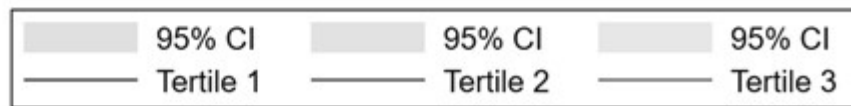| 95% CI	95% CI	95% CI
Tertile 1	Tertile 2	Tertile 3

Figure 3. Time-updated model for risk of all-cause death and cardiovascular death or heart failure hospitalization after a new-onset atrial fibrillation episode

A) All-cause death

B) CV death or HF hospitalization

Time-updated new-onset AF	No event	Event	Crude HR (95%CI)	P-value	Adj. HR (95%CI)	P-value
All-cause death	158/3920 (4.0%)	83/1019 (7.5%)	1.38 (1.11-1.73)	0.004	1.21 (0.96-1.52)	0.099
CV death or HF hosp.	71/3161 (2.3%)	170/1861 (9.1%)	2.28 (1.94-2.67)	<0.001	2.06 (1.75-2.42)	<0.001

Legend: AF, atrial fibrillation; CV, cardiovascular; HF, heart failure; Adj., model adjusted on the risk model depicted in Table 2.
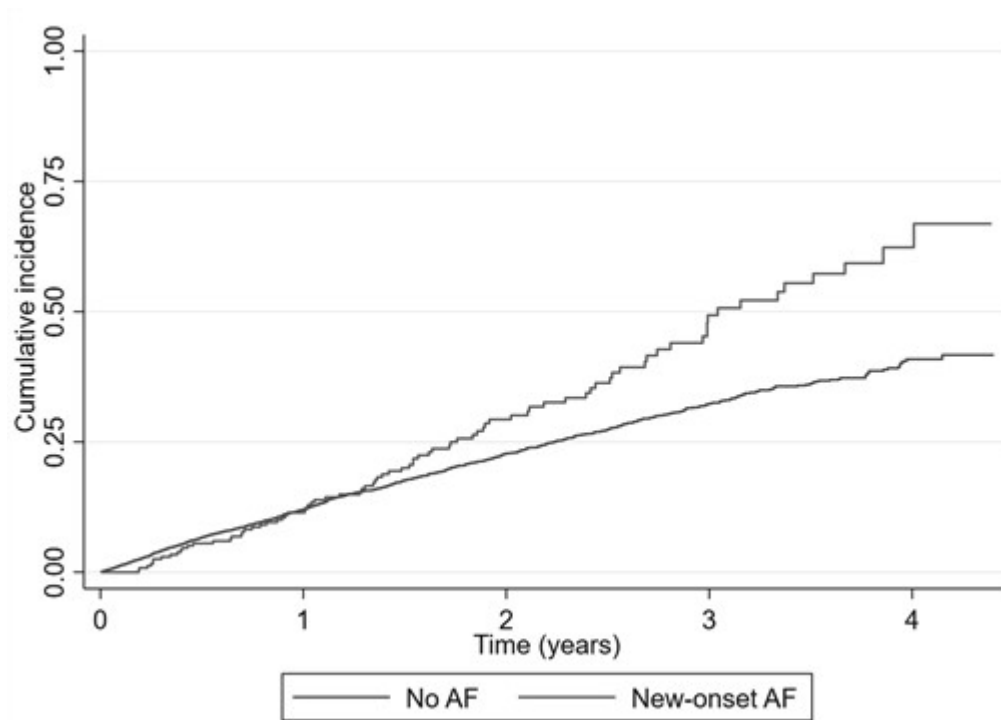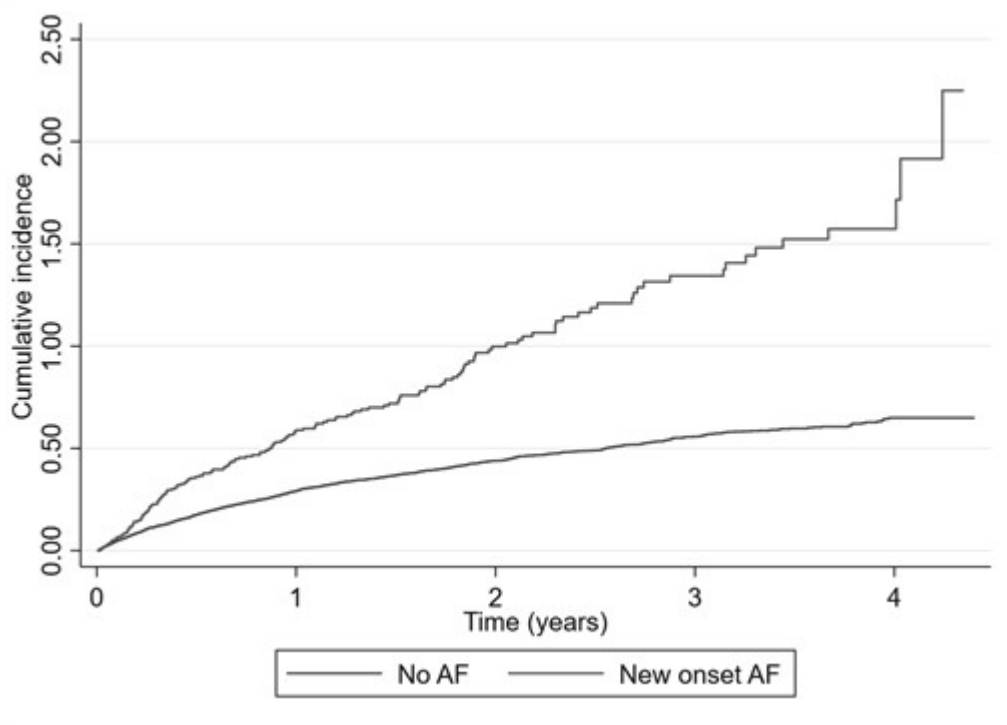
Graphical abstract. The risk of atrial fibrillation can be determined with simple and readily available variables.

Legend: LVEF, left ventricular ejection fraction; DAPT, dual anti-platelet therapy; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; SBP, systolic blood pressure; BMI, body mass index.

Age >65yr
LVEF <35%
PCI or CABG
White race
SBP <110mmHg
BMI >25Kg/m2

5.3 events per 100py