Risk markers of incident atrial fibrillation in patients with coronary heart disease

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Background In patients with coronary heart disease (CHD), atrial fibrillation (AF) is associated with increased morbidity and mortality. We investigated the associations between clinical risk factors and biomarkers with incident AF in patients with CHD.

Methods and results Around 13,153 patients with optimally treated CHD included in the STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY (STABILITY) trial with plasma samples obtained at randomization. Mean follow-up time was 3.5 years. The association between clinical risk factors and biomarkers with incident AF was estimated with Cox-regression models. Validation was performed in 1,894 patients with non-ST-elevation acute coronary syndrome included in the FRISC-II trial.

The median (min-max) age was 64 years (range 26-92) and 2,514 (19.1%) were women. A total of 541 patients, annual incidence rate of 1.2%, developed AF during follow-up. In multivariable models, older age, higher levels of NT-proBNP, higher body mass index (BMI), male sex, geographic regions, low physical activity, and heart failure were independently associated with increased risk of incident AF with hazard ratios ranging from 1.04 to 1.79 ($P \leq .05$). NT-proBNP improved the C-index from 0.70 to 0.71. In the validation cohort, age, BMI, and NT-proBNP were associated with increased risk of incident AF with similar hazard ratios.

Conclusions In patients with optimally treated CHD, the incidence of new AF was 1.2% per year. Age, NT-proBNP as a marker of impaired cardiac function, and BMI were the strongest factors, independently and consistently associated with incident AF. Male sex and low physical activity may also contribute to the risk of AF in patients with CHD. (Am Heart J 2021;233:92–101.)

In patients with coronary heart disease (CHD), atrial fibrillation (AF) is associated with increased morbidity and mortality.[1,2] Identifying the key risk factors and risk indicators might improve the identification of patients at risk of developing AF and provide opportunities to initiate preventive measures. The issue is further challenging as the antithrombotic treatments for these 2 entities differ. Patients with CHD are usually treated with platelet inhibitors and patients with AF with oral anticoagulation if the stroke risk is elevated, which is the case with concomitant vascular disease.[3,4]

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So far, studies on incidence of AF in patients with CHD are limited and investigations on the factors associated with the predisposition of new AF in patients with CHD are lacking. Data are available on the prognostic value of biomarkers for incident AF in apparently healthy community-dwelling adults.[5,6] In patients with CHD, the prognostic value of different biomarkers has been studied for different cardiovascular outcomes[7-9] but not systematically concerning incident AF.

We therefore investigated the incidence of AF in patients with CHD, assessed the prognostic value of clinical factors and biomarkers, and evaluated the discriminatory value for incident AF by adding biomarkers to a model consisting of clinical risk factors only, and validated the results in an external cohort.

Methods

Study population and design

The study population and design of the STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY (STABILITY) trial has been published in detail elsewhere.[10,11] Briefly, the STABILITY trial was a double-blind, randomized study. It included 15,828 patients with CHD between December 2008 through April 2010, all were randomized to receive either darapladib, a selective oral inhibitor of lipoprotein-associated phospholipase A_2, or placebo.[10,11] All patients had CHD, documented by at least one of the following: Previous myocardial infarction, previous percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG) or multivessel coronary artery disease confirmed by coronary angiography. Also, at least one of the following cardiovascular risk factors was required: age 60 years or older, diabetes requiring pharmacotherapy, a high-density lipoprotein (HDL)-cholesterol level less than 40 mg per deciliter (1.03 mmol per liter), smoking more than 4 cigarettes per day at study entry or within 3 months before screening, moderate renal dysfunction (<60 mL/min) or polyvascular arterial disease.[11] Those who had a planned PCI or CABG or another major surgical procedure, current liver disease, severe renal impairment (<30 mL/min), a history of nephrectomy or kidney transplantation, current New York Heart Association (NYHA) class III or IV heart failure, or severe asthma that was poorly controlled with standard medical therapy, were excluded from the STABILITY trial. Further details of the inclusion and exclusion criteria and definitions of primary and secondary endpoints have been published previously.[10,11] In the present sub-study, the primary outcome was incident AF during follow-up. Those with previous diagnosis of AF according to the CRF (all types of AF), with AF at baseline, or with previous stroke were excluded (Figure S1). The analyses were thus based on a total of 13,153 patients with biomarker data available.

For validation of the results from the STABILITY cohort, analyses were also performed in patients included in the Fast Revascularization during InStability in Coronary artery disease (FRISC) II trial. The FRISC-II trial was a prospective, randomized, multicenter trial. Between June 1996 and August 1998, 3,489 patients with non-ST-elevation acute coronary syndrome were randomized to an early invasive treatment strategy, aiming for revascularization within 7 days or a noninvasive treatment strategy with invasive procedures at severe exercise-induced ischemia or recurrent symptoms. For long-term outcomes, data were linked with national health-care registers.[12,13] A total of 1,894 patients without AF at baseline and with N-terminal pro B-type natriuretic peptide (NT-proBNP) and complete data on relevant characteristics measured at baseline were included in the analyses. Also, 1,092 patients had NT-proBNP measured at 6 weeks after inclusion and were analyzed in further sensitivity analysis (Figure S2). Physical activity was not routinely collected within the FRISC-II trial.

Both trials were approved by the relevant institutional review boards and all patients provided written informed consent. Drs. Tomasdottir, Hijazi, and Wallentin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Biochemical methods in STABILITY

Venous blood samples were obtained at baseline before start of study treatment. Samples were centrifuged at 2000 g for 10 minutes within 30 minutes after collection, plasma separated, and then stored frozen in aliquots until analysis was performed.

Concentrations of high-sensitivity (hs) troponin T, NT-proBNP, cystatin C and growth differentiation factor 15 (GDF-15) were determined in EDTA plasma centrally at the Uppsala Clinical Research Center Laboratory at Uppsala University Hospital (Uppsala, Sweden) by electrochemiluminescence immunoassays, using a Cobas Analytics e601 (ROCHE Diagnostics). EDTA plasma concentrations of hs C-reactive protein (CRP) were determined using a particle-enhanced immunonephelometry assay, *CardioPhase* hsCRP (Abbott Diagnostics) and plasma concentrations of interleukin 6 (IL-6) by using an ELISA technique[14]. The properties for these assays have been described previously.[14-16]

Outcome

The outcome in this study was incident AF. In STABILITY, screening for AF was performed by 12-lead ECG during clinic visits at 1, 3, 6, and 12 months after study inclusion, every 12 months during study participation, and during clinic visit at the end of study treatment. In addition, ECGs were also collected as needed during unscheduled visits. Ascertainment of AF was also made through reporting of adverse events or hospitalizations.

Previous medical history was collected at randomization containing detailed cardiovascular medical history.

In FRISC-II, screening for AF was performed by 12-lead ECG at inclusion and during visits at 6 weeks, 3 and 6 months after study inclusion, and also captured by data collected in the official Swedish registries held by the Centre for Epidemiology, National Board of Health and Welfare in Sweden, where all hospitalizations in Sweden are registered with ICD codes and dates. The endpoint was the first event of AF during a maximum of 5 years follow-up.

Statistical analysis

Descriptive statistics are presented as median value and 1st and 3rd quartiles (Q1, Q3) for continuous variables and numbers and percentages for binary variables. For continuous variables, a Wilcoxon-Mann-Whitney test was used to investigate the statistical significance of differences between subjects with and without incident AF during follow-up. Associations between clinical factors and biomarkers with incident AF were assessed using Cox proportional hazard models adjusting for randomized treatment group, age, gender, geographic region, systolic blood pressure, and body mass index (BMI) at baseline, previous diagnosis of hypertension, myocardial infarction, diabetes, polyvascular disease, heart failure, chronic obstructive pulmonary disease/asthma, previous PCI or CABG, smoking status (previous/current smoker compared to never smoked), alcohol consumption, and level of physical activity measured in metabolic equivalent hours/week (MET h/week) at baseline. In a second model, the biomarker NT-proBNP was added. In a third model, other standard biomarkers, cardiovascular and inflammatory biomarkers were added: hemoglobin, white blood cell count, low-density lipoprotein (LDL)-cholesterol, HDL-cholesterol, triglycerides, hsTroponin T, cystatin C, GDF-15, hsCRP, and IL-6. Hazard ratios with 95% confidence interval (CI) were estimated. The underlying proportional hazards assumptions of the Cox proportional hazards models were verified by Schoenfeld residual tests.

To evaluate the relative strength of association of different covariates with AF, the partial χ^2 minus the predictor degrees of freedom was plotted. This statistic allows comparison of predictors in the same model with different number of parameters, with a higher number indicating a stronger association.[17]

Harrellś C-index[17,18] was used to evaluate the discriminatory ability of the models.

All statistical analyses were performed at Uppsala Clinical Research Center using SAS software version 9.4 (SAS Institute, Cary, North Carolina) and R version 3.6.1. All tests were 2-sided and a statement of statistical significance implies a P-value $< .05$.

In the FRISC-II cohort, associations between available clinical factors and biomarkers with incident AF were assessed using Cox proportional hazard models adjusting for the strongest risk variables identified in the identification cohort; age, sex, BMI and, NT-proBNP at baseline, and 6 weeks after inclusion as an additional sensitivity analysis.

Results

Identification cohort

Baseline characteristics and incident AF

In a total of 13,153 patients, without previous AF or stroke/TIA, the median age was 64 years, and 2,514 (19.1%) were women. A total of 541 (4.1%) of the patients had incident AF during the mean follow-up time of 3.5 years, resulting in an annual incidence rate of 1.2%. The demographic and baseline characteristics according to incident AF or not during follow-up are shown in Table 1. Those who developed AF were older, had higher body weight, BMI and systolic blood pressure, and were more likely to have a diagnosis of hypertension, heart failure or polyvascular disease (Table 1). Concerning the biomarker concentrations at baseline, those who developed AF had higher levels of NT-proBNP, hsTroponin T, hsCRP, IL-6, Cystatin C and GDF-15, and lower levels of hemoglobin (Hb) and triglycerides (Table 1).

Risk of incident AF in multivariable models

In a multivariable model containing demographic data, clinical variables, and biomarker data, older age, increasing BMI, male sex, geographic region (other than Asia/Pacific), history of heart failure and lower levels of physical activity at baseline were independently associated with higher risk of incident AF during follow-up (Table 2). Of the biomarkers included in the multivariable model, only NT-proBNP was independently associated with incident AF (Table 2). Assessment of variable importance showed that age, NT-proBNP, and BMI were the most important variables for incident AF (Figure 1).

Prediction of incident AF

A model based solely on clinical variables yielded a C-index of 0.700 (95% CI 0.677-0.723). The addition of NT-proBNP improved the discriminatory accuracy to C-index 0.712 (95% CI 0.689-0.735).

Sensitivity analyses

No U-shaped associations were detected between the variables BMI or physical activity with incident AF (Figures S3-6 show the nonlinear association with incident AF). Sensitivity analyses containing the variable alcohol consumption, did not affect the results. Similarly, waist/hip ratio levels were not associated with increased risk of incident AF in models containing clinical variables (including BMI) and biomarkers. As a final sensitivity analysis, statin therapy and treatment with ACEi/ARB were added to the model without changing the results.

Table 1. Baseline characteristics according to incident atrial fibrillation (AF) during follow-up.

	No AF	Incident AF	*P*-value
Number of patients	12,612	541	
Age (years)*	63.5 (58.0, 70.0)	68.0 (63.0, 74.0)	<.0001
Female sex	2,420 (19.2%)	94 (17.4%)	Ns
Geographic region:			<.0001
Asia/Pacific	2,659 (21.1%)	64 (11.8%)	
East Europe	2,732 (21.7%)	135 (25.0%)	
North America	3,030 (24.0%)	161 (29.8%)	
South America	1,026 (8.1%)	47 (8.7%)	
West Europe	3,165 (25.1%)	134 (24.8%)	
Body mass index (kg/m^2)*	28.1 (25.4, 31.5)	29.5 (26.4, 33.3)	<.0001
Weight (kg)*	81.4 (71.0, 93.0)	86.0 (76.0, 99.1)	<.0001
Height (cm)*	170.0 (128, 203)	171.0 (142, 196)	.0019
Hypertension	8,824 (70.0%)	422 (78.0%)	.0001
Systolic blood pressure (mm Hg)*	130.0 (120.0, 142.0)	133.0 (122.0, 147.0)	.0005
Heart failure	2,441 (19.4%)	150 (27.7%)	<.0001
Prior myocardial infarction	7,555 (59.9%)	302 (55.8%)	Ns
Prior PCI or CABG	9,364 (74.2%)	417 (77.1%)	Ns
Diabetes mellitus	4,778 (37.9%)	222 (41.0%)	Ns
Renal dysfunction (<60 mL/min)	4,036 (29.0%)	204 (37.7%)	<.0001
Never smoked	3,885 (30.8%)	170 (31.4%)	Ns
Physical activity (MET h/week)*	40.0 (18.0, 74.0)	40.0 (16.0, 66.0)	Ns
ACE inhibitor or ARB therapy	9,647 (76.5%)	449 (83.0%)	.0005
Statin therapy	12,293 (97.5%)	527 (97.4%)	Ns
Beta blocker therapy	9,955 (78.9%)	442 (81.7%)	Ns
Aspirin therapy	11,925 (94.6%)	500 (92.4%)	.0338
NT-proBNP (ng/L)*	151.0 (75.0, 313.0)	314 (161, 588)	<.0001
Hemoglobin (g/L)*	144 (134, 152)	141 (131, 151)	<.0001
White blood count (GI/L)*	6.50 (5.50, 7.80)	6.40 (5.40, 7.65)	Ns
Triglycerides (mmol/L)*	1.53 (1.11, 2.15)	1.38 (1.06, 1.92)	.0001
Cystatin C (mg/L)*	0.98 (0.85, 1.15)	1.06 (0.91, 1.24)	<.0001
GDF-15 (ng/L)*	1,207 (888, 1749)	1,379 (1039, 1984)	<.0001
hsCRP (mg/L)*	1.30 (0.60, 3.10)	1.50 (0.70, 3.45)	.0022
hsTroponin T (ng/L)*	8.7 (5.9, 13.2)	12.6 (8.3, 18.4)	<.0001
IL-6 (ng/L)*	2.00 (0.85, 3.10)	2.40 (1.70, 3.60)	<.0001

*Median (first quartile, third quartile). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockade; CABG, coronary artery bypass graft; CRP, C-reactive protein; GDF-15, growth differentiation factor 15; hs, high sensitivity; IL-6, interleukin 6; MET h/week, metabolic equivalent hour/week; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCI, percutaneous coronary intervention.

Validation cohort

In a total of 1,894 patients, without previous AF, the median age was 65.4 years, and 577 (30.5%) were women (Table S1). A total of 128 (6.8%) of the patients had incident AF during the mean follow-up time of 5.0 years, resulting in an annual incidence rate of 1.5%. The demographic and baseline characteristics according to incident AF or not during follow-up are shown in Table S2. Using similar evaluation modeling, older age, higher BMI, and higher levels of NT-proBNP were associated with increased risk of incident AF, with almost identical hazard ratios as compared with the identification cohort (Figure 2). Sensitivity analyses using the NT-proBNP levels at 6 weeks after inclusion showed very similar results although with an attenuation of BMI, probably due to smaller sample size (Figure S7). Physical exercise was not measured in the FRISC-II study.

Discussion

In this study of 13,153 patients with optimally treated CHD, a total of 4.1% had incident AF during a mean follow-up of 3.5 years, corresponding to an annual incidence of 1.2%. The variables most strongly associated with increased risk of incident AF were older age, higher BMI, higher levels of NT-proBNP. These 3 variables were also consistently associated with incident AF in the validation cohort. Male sex, low levels of physical activity, heart failure, and geographic region, contributed to an increased risk as well.

The prognostic value of different biomarkers in patients with CHD has been widely studied,[7-9] but not the association with incident AF. In patients with CHD, baseline natriuretic peptides, hsCRP, cystatin C, D-dimer and hs-troponin have been shown to improve the prediction of fatal and nonfatal cardiovascular events.[8,19,20]

Table 2. Cox multivariable hazard models for incident AF adjusting for clinical variables and biomarkers.

Variable	Clinical variables		Clinical variables plus NT-proBNP		Clinical variables plus other biomarkers	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Randomized treatment group	1.00 (0.84-1.19)	.98	1.00 (0.83-1.19)	.97	1.03 (0.85-1.24)	.76
Age at randomization *	1.06 (1.05-1.07)	<.0001	1.06 (1.05-1.07)	<.0001	1.06 (1.04-1.07)	<.0001
Systolic blood pressure †	1.01 (0.96-1.07)	.60	1.01 (0.96-1.07)	.64	1.03 (0.97-1.10)	.31
Body mass index*	1.06 (1.04-1.08)	<.0001	1.06 (1.04-1.08)	<.0001	1.06 (1.04-1.09	<.0001
Male sex	1.39 (1.08-1.78)	.0099	1.38 (1.07-1.78)	.014	1.50 (1.12-2.01)	.0065
Hypertension	1.15 (0.92-1.43)	.22	1.18 (0.94-1.48)	.15	1.26 (0.99-1.61)	.058
Geographic region:		.028		.14		.048
Asia/Pacific	0.57 (0.39-0.84)		0.63 (0.42-0.94)		0.56 (0.37-0.86)	
East Europe	1.08 (0.81-1.43)		1.07 (0.80-1.43)		1.09 (0.81-1.49)	
South America	1.03 (0.74-1.43)		0.96 (0.66-1.39)		0.96 (0.65-1.42)	
West Europe	0.95 (0.75-1.21)		0.95 (0.74-1.21)		0.92 (0.71-1.19)	
Prior myocardial infarction	0.92 (0.76-1.11)	.40	0.92 (0.75-1.11)	.37	0.95 (0.78-1.17)	.63
Prior PCI or CABG	1.11 (0.89-1.38)	.35	1.14 (0.91-1.44)	.26	1.16 (0.91-1.48)	.23
Diabetes Mellitus	1.02 (0.85-1.23)	.83	1.05 (0.86-1.27)	.64	1.01 (0.82-1.25)	.91
Smoking status:		.27		.23		.12
Current smoker	1.23 (0.91-1.64)		1.24 (0.91-1.67)		1.26 (0.91-1.74)	
Former smoker	0.99 (0.81-1.21)		0.97 (0.79-1.20)		0.92 (0.74-1.15)	
Polyvascular disease	1.07 (0.82-1.39)	.63	1.08 (0.82-1.41)	.60	1.11 (0.84-1.48)	.45
Renal dysfunction	1.24 (1.03-1.50)	.024	1.16 (0.95-1.41)	.14	na§	
Alcohol consumption	1.10 (0.91-1.33)	.31	1.17 (0.96-1.43)	.11	1.18 (0.96-1.45)	.12
Heart failure	1.53 (1.23-1.89)	.0001	1.41 (1.12-1.77)	.0031	1.33 (1.04-1.69)	.021
COPD/Asthma	1.05 (0.79-1.39)	.74	1.07 (0.80-1.42)	.66	1.10 (0.82-1.48)	.52
Physical activity (MET h/week)†	0.97 (0.95-1.00)	.029	0.97 (0.95-1.00)	.028	0.96 (0.94-0.99)	.010
NT-proBNP (ng/L)‡			1.16 (1.12-1.20)	<.0001	1.14 (1.10-1.19)	<.0001
Hemoglobin (g/L)‡					0.91 (0.82-1.02)	.11
White blood cell count (1×10^9/L)‡			0.93 (0.83-1.03	.16		
LDL-cholesterol (mmol/L)‡					1.03 (0.93-1.15)	.53
HDL-cholesterol (mmol/L)‡			1.04 (0.94-1.16)	.43		
Triglycerides (mmol/L)‡					0.92 (0.79-1.06)	.26
Cystatin C (ng/L)‡					0.96 (0.86-1.07	.41
GDF-15 (ng/L)‡			1.05 (0.94-1.16)	.40		
hsCRP (mg/L)‡			1.07 (1.00-1.15)	.065		
hsTroponin T (ng/L)‡			1.04 (0.99-1.10)	.13		
IL-6 (ng/L)‡					1.04 (0.96-1.13)	.29

AF, atrial fibrillation; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GDF-15, growth differentiation factor 15; HDL, high density lipoprotein; hs, high sensitivity; IL-6, interleukin 6; LDL, low density lipoprotein; MET h/week, metabolic equivalent hour/week; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCI, percutaneous coronary intervention.

* Hazard ratio based on 1 unit increase.

† Hazard ratio based on 10 unit increase.

‡ Hazard ratio based on 1 SD unit increase.

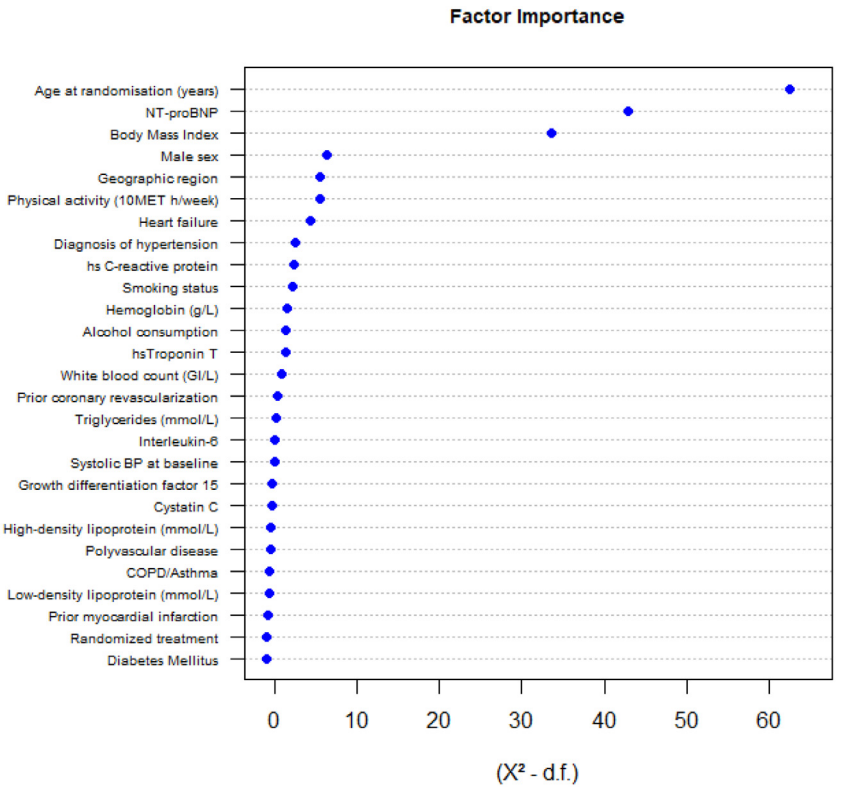
§ Renal function assessed with the biomarker cystatin C.

Both, BNP and NT-proBNP have been associated with increased risk of major adverse cardiovascular event in patients with CHD.[7,21] The present results thus expand upon these findings and show that NT-proBNP is independently associated also with incident AF in patients with CHD.

In large general population cohort studies, several independent risk factors for AF have been identified. Older age, higher weight/BMI, diabetes, hypertension, heart failure, myocardial infarction, and valvular disease are among factors that have been associated with increased risk of AF.[22,23] On the other hand, there seems to be a lower incidence of AF in Asian cohorts.[24,25] A lower risk of AF in Asia was also observed in this study and was probably the predominant reason for geographic differences.

However, the studies on the incidence of AF in patients with CHD are limited. A recent Finnish report based on 1,710 patients included in the ARTEMIS (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection) study with angiographically documented CHD and sinus rhythm at baseline, showed that 8.4% developed AF during a mean follow-up time of 5.7 years.[26] However, since those with previous AF were not excluded, a direct comparison with the present results is difficult.[26] Another study, based on 7,665 patients with CHD without overt heart failure included in the ACTION (A Coronary disease Trial Investigating Outcome with

Figure 1



Relative importance of each variable in the multivariable hazard model for incident atrial fibrillation. Importance measured as chi-square statistic minus the predictor degrees of freedom (d.f.). BP, blood pressure; COPD, chronic obstructive pulmonary disease; hs, high sensitivity; MET h/week, metabolic equivalent hour/week; NT-proBNP, N-terminal pro B-type natriuretic peptide.

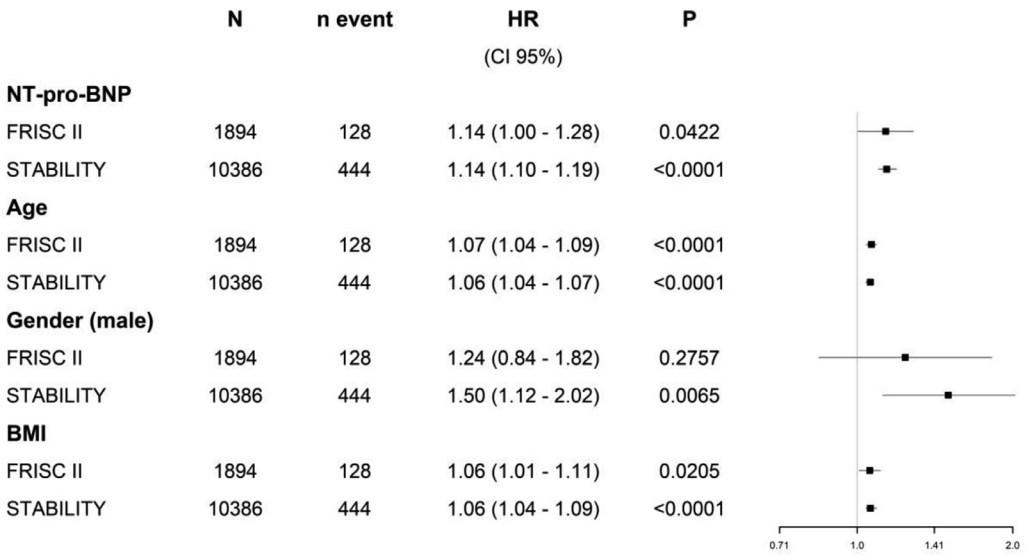
Nifedipine GITS) trial, found an incidence rate of AF of 1.64/100 patient-years for patients without previous/baseline AF over a mean follow-up of 4.9 years.[1] Differences in baseline characteristics, in particular age and NT-proBNP levels, and time of follow-up seem to influence the incidence rate. This pattern was also seen in the 2 cohorts in this study, where the FRISC-II cohort had a slightly higher incidence rate of AF as compared with the STABILITY cohort.

Systematic evaluations on factors associated with the development of AF in patients with CHD are however lacking. In the ARTEMIS study, the clinical factors of advanced age and higher weight were, similar to our results, found to be independently associated with new-onset AF during follow-up.[26] In contrast to our study, hsCRP was associated with significantly higher risk for AF[26] but not BNP. This is unexpected as several studies in community-dwelling adults which, in accordance with the present results, indicate that natriuretic peptides are strong biomarkers concerning the risk of incident AF.[6,27-29] It is possible that the observed differences are due to the previously described differences of the study populations.

In comparison with risk factors identified to be associated with incident AF in general community dwelling populations, there seem to be some differences in the risk factor profile in those with stable CHD. For instance, general vascular disease, such as hypertension, diabetes and smoking, seem to be less important predictors of incident AF in stable CHD. Also, beyond presence of heart failure, other cardiac diseases, such as previous myocardial infarction or coronary revascularization, does not seem to constitute significant risk factors. Thus, even if patients with stable CHD share some risk factors with the general population, eg, age, BMI, physical exercise, natriuretic peptides, they seem to exhibit a partly distinct risk profile concerning AF development.

Inflammation is a key process in both CHD as well as in AF.[30,31] However, biomarkers of inflammation have so far not shown a consistent association with incident AF in different populations, nor in the present CHD cohort based on CRP and IL-6 concentrations. Previous studies,

Figure 2



Comparison of hazard ratios based on multivariable Cox models in the FRISC -II and the STABILITY cohorts. Models adjusting for the strongest risk variables identified in the identification cohort: N-terminal pro B-type natriuretic peptide (NT-proBNP), age, sex, and body mass index (BMI). NT-proBNP measured at baseline in the FRISC-II cohort.

such as an analysis of patients with CHD in the Heart and Soul Study, have shown some inflammation biomarkers such as IL-6 to be higher in those with AF at baseline in comparison with those without AF at baseline.[32] However, regarding the association with incident AF the value of inflammation biomarkers becomes markedly limited in models also accounting for cardiovascular biomarkers such as NT-proBNP[7] in similarity with the present results.

Several strategies have been investigated for the improved identification of those with AF in the general population. Mass screening in an older population with intermittent ECG recordings identified a significant proportion of participants with unknown AF, and NT-proBNP was shown to be increased in individuals with newly detected AF.[6] Since BNP and NT-proBNP have been associated with AF in general population cohorts repeatedly,[6,28,33] randomized trials are now being conducted to evaluate if AF screening, using NT-proBNP levels to divide the screened patients into low- and high-risk group may improve the screening strategies.[34] In the latest 2020 European Society of Cardiology (ESC) Guidelines on the Management of AF, opportunistic screening for AF by palpating pulse or with ECG is recommended in patients >65 years, and in those >75 years of age or at high stroke risk, systematic ECG screening should be considered.[3] No special recommendations regarding screening for AF in patients with CHD have been proposed in the European or U.S. guidelines on the management of chronic coronary syndrome.[4,35] Being a high-risk group, patients with known CHD might benefit from screening for AF even more than the general population. The present results suggest that a few selected variables were among the most strongly, and consistently, associated with incident AF; age, NT-proBNP, and BMI. Thus, these parameters could be used to improve the risk prediction in these patients. Importantly, some of these risk factors, such as BMI, physical activity, and to some extent NT-proBNP, are modifiable which may provide the means to address the risk of AF. Also, age and natriuretic peptides are strong predictors of stroke in patients with AF, and a NT-proBNP guided screening strategy also targets patients who are both most likely to have AF and to have the greatest benefit from OAC.[36]

Limitations

The STABILITY trial included patients with CHD and at least one clinical risk factor for coronary heart disease and excluded patients with certain comorbidities such as severe renal impairment and those with heart failure with current NYHA class III and IV. It is possible that using a more stringent screening methodology for AF, the incidence rates of AF would be higher, in particular for asymptomatic paroxysmal AF. The availability of echocardiography might have provided additional information concerning the risk of AF. The FRISC-II trial included patients with acute coronary syndrome which might have influenced the NT-proBNP concentrations. However, the sensitivity analysis using biomarker

concentrations during a stable phase, 6 weeks later, showed identical results concerning the risk associated with NT-proBNP for incident AF. Health economics was not evaluated in this study. Although systematic opportunistic mass-screening for AF seems to be cost-effective in general populations,[34,37] such evaluations has to our knowledge not been performed in selected cohorts of stable CHD. Similarly, although enhanced AF-screening using a blood biomarker such as NT-proBNP seem promising, analyses of cost-effectiveness need to be shown.

Conclusions

In patients with optimally treated CHD, the incidence of new AF was 1.2% per year. Older age, higher BMI, and higher levels of NT-proBNP as a marker of impaired cardiac function, were the strongest factors, independently and consistently, associated with higher risk of incident AF. Male sex and low levels of physical activity may also contribute to the risk of incident AF in patients with CHD.

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Supplementary materials

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