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# Prevalence and determinants of atrial fibrillation progression in paroxysmal atrial fibrillation

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## ABSTRACT

**Objective** Atrial fibrillation (AF) often progresses from paroxysmal AF (PAF) to more permanent forms. To improve personalised medicine, we aim to develop a new AF progression risk prediction model in patients with PAF.
**Methods** In this interim-analysis of the Reappraisal of AF: Interaction Between HyperCoagulability, Electrical Remodelling, and Vascular Destabilisation in the Progression of AF study, patients with PAF undergoing extensive phenotyping at baseline and continuous rhythm monitoring during follow-up of ≥1 year were analysed. AF progression was defined as (1) progression to persistent or permanent AF or (2) progression of PAF with >3% burden increase. Multivariable analysis was done to identify predictors of AF progression.
**Results** Mean age was 65 (58–71) years, 179 (43%) were female. Follow-up was 2.2 (1.6–2.8) years, 51 of 417 patients (5.5%/year) showed AF progression. Multivariable analysis identified, PR interval, impaired left atrial function, mitral valve regurgitation and waist circumference to be associated with AF progression. Adding blood biomarkers improved the model (C-statistic from 0.709 to 0.830) and showed male sex, lower levels of factor XIIa:C1-esterase inhibitor and tissue factor pathway inhibitor, and higher levels of N-terminal pro-brain natriuretic peptide, proprotein convertase subtilisin/kexin type 9 and peptidoglycan recognition protein 1 were associated with AF progression.
**Conclusion** In patients with PAF, AF progression occurred in 5.5%/year. Predictors for progression included markers for atrial remodelling, sex, mitral valve regurgitation, waist circumference and biomarkers associated with coagulation, inflammation, cardiomyocyte stretch and atherosclerosis. These prediction models may help to determine risk of AF progression and treatment targets, but validation is needed.
**Trial registration number** NCT02726698.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Atrial fibrillation progression is associated with adverse cardiovascular outcome.
⇒ The rate of atrial fibrillation progression varies and depends among others on type of rhythm monitoring.
⇒ Predictors of atrial fibrillation progression have not been well established with long-term continuous rhythm monitoring.

### WHAT THIS STUDY ADDS

⇒ This study develops an atrial fibrillation progression risk prediction model and elucidates underlying pathophysiological mechanisms in comprehensively phenotyped patients with paroxysmal atrial fibrillation using long-term continuous rhythm monitoring.
⇒ Our clinical multivariate model had a C-statistic of 0.709.
⇒ The addition of the blood biomarkers improved the initial model to a C-statistic of 0.830.
⇒ We found that predictors for progression were multifactorial including atrial remodelling, sex, mitral valve regurgitation, waist circumference and blood biomarkers associated with coagulation, cardiac stretch, cholesterol metabolism, inflammation and the immune system.
⇒ Validation is needed before implementation into clinical practice.

## INTRODUCTION

Atrial fibrillation (AF) is a progressive disease, usually starting with self-terminating short-lasting paroxysmal episodes that often progresses to more frequent episodes, eventually leading to long-lasting non-self-terminating persistent and permanent AF.[1] Progression of AF has been associated with an increased risk of cardiovascular morbidity and mortality and reduces the efficacy of pharmacological and interventional rhythm control strategies.[2 3] AF progression rates vary between studies because of differences in duration of follow-up, in comprehensive phenotyping of patients and strategies of rhythm monitoring.[3–5]

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**
⇒ This model could be clinically useful, and serves to enhance knowledge on underlying mechanisms causing progression of atrial fibrillation.
⇒ In combination with extensive phenotyping, our prediction model gives a more in-depth view into predicting risk factors for atrial fibrillation progression.
⇒ Continuous rhythm monitoring provides a more detailed and accurate view into atrial fibrillation progression.

Appropriate treatment of risk factors can improve sinus rhythm maintenance, cardiovascular outcome and reverse AF progression.[6 7] The most established risk factors for AF progression are age, hypertension, obesity, heart failure and diabetes.[5 8] Interestingly, hypercoagulability may be involved in increasing the risk of stroke and in AF progression.[9] A detailed and multimodal phenotyping at baseline and continuous rhythm monitoring has potential to increase our knowledge of AF progression and in turn contribute to personalised medicine.[2 10]

Therefore, the aim of the Reappraisal of AF: Interaction Between HyperCoagulability, Electrical Remodelling, and Vascular Destabilisation in the Progression of AF (RACE V) study is to develop a clinical AF progression risk prediction model using extensive phenotyping and continuous rhythm monitoring in patients with paroxysmal AF (PAF). In addition, to improve the clinical model and elucidate underlying pathophysiological mechanisms of AF progression, we included blood biomarkers in the progression risk prediction model.

## METHODS
### Study design
The RACE V study has previously been described.[11] In brief, the RACE V study is a prospective, investigator-initiated, Dutch multicentre observational study (Clinicaltrials.gov identifier NCT02726698).

A detailed overview of inclusion and exclusion criteria is provided in online supplemental table S1. Briefly, the aim is to include 750 patients with a history of PAF <10 years. Eligible patients had ≥2 documented episodes of PAF or one documented episode combined with ≥2 symptomatic episodes suspected of being AF, were willing to undergo implantation of a Medtronic (Minneapolis, USA) Reveal LINQ® implantable loop recorder, and did not have a history of persistent AF (intention to undergo), pulmonary vein isolation (PVI) or current amiodarone treatment. Patients with Medtronic pacemakers were also eligible if atrial high rate episodes >190 beats per min lasting >6 min, qualified as AF episodes, were detected. For the current analysis, we included patients that had ≥1 year of continuous rhythm monitoring as of 1 May 2020.

### Patient and public involvement
Patients and the public were not involved in the design or implementation of the study.

### Clinical assessment
At baseline, clinical history, symptomatology, current medication, physical examination and a 12-lead ECG were assessed. Additionally, echocardiography, vascular assessment and cardiac CT was done, processed and analysed in a central core lab (online supplemental figure S1, online supplemental data). In brief, in addition to the standard echocardiography measurements, strain measurements were performed in sinus rhythm using a point-and-click method to trace endocardial borders with a vendor-independent software (TOMTEC-ARENA, Imaging Systems, Germany). The cardiac CT was performed as a non-contrast ECG-gated scan to assess coronary calcium scores, epicardial and pericardial fat. Vascular assessment of the carotid arteries included measurements of intima-media thickness, pulse wave velocity and plaques.

### Blood biomarkers
At baseline, peripheral blood samples were collected (only during sinus rhythm with interrupted anticoagulation). With multiplex immunoassays, 92 cardiovascular biomarkers from the Olink Cardiovascular III panel were assessed by Olink Bioscience (Uppsala, Sweden) in EDTA plasma baseline samples (online supplemental table S2). Complexes of activated coagulation enzymes (FXIIa, FXIa, FIXa, FXa and thrombin) with their corresponding natural inhibitors (antithrombin, alpha1-antitrypsine or C1-esterase inhibitor) ELISA assays were performed to assess the degree coagulation activity in EDTA plasma and citrated plasma samples at baseline.[12]

### Follow-up
All patients were treated according to the European Society of Cardiology AF guidelines.[13] Follow-up visits were performed at 1 and 2.5 years (online supplemental figure S1). Patients could consent for 2.5 years continuous rhythm monitoring, until end of battery of Reveal LINQ, or for 4 years in case patients had a pacemaker.

In order to collect continuous data on arrhythmias, all patients received a home monitoring device (Medtronic Carelink). Both Reveal LINQ and pacemaker were set to AT/AF detection settings (online supplemental data).

### Definition and outcome
The primary outcome was AF progression. Before assessing AF progression, all collected episodes were independently adjudicated and corrected by five physicians. Two methods were used to assess AF progression and compared. For the first method, all AF episodes were put into a custom-made software using Microsoft Visual Basic to visualise in a graphical overview all AF episodes per patient (figure 1), which was done by six physicians. Four groups were discerned: (1) no AF recurrences during follow-up; (2) recurrences of PAF without apparent increase in number and/or duration of AF episodes based on visual inspection; (3) recurrence of PAF with increase in number and/or duration of AF based on visual inspection, but without persistent or permanent AF; (4) development of persistent or permanent AF (figure 1).

For the second method, a mathematical formula (online supplemental data) was created using a weighed AF burden with AF episodes early during follow-up weighing less than AF episodes at the end of follow-up. AF burden was defined as the cumulative duration of all AF episodes from baseline onwards, divided by total duration of monitoring. For patients without successful PVI, a 90-day blanking period after PVI was applied.

The primary outcome was AF progression, defined as (1) development of persistent or permanent AF during follow-up or (2) an increase of >3% AF burden over the first 6 months or total follow-up. Duration of monitoring for current analysis lasted until 1 May 2020, until last available rhythm monitoring
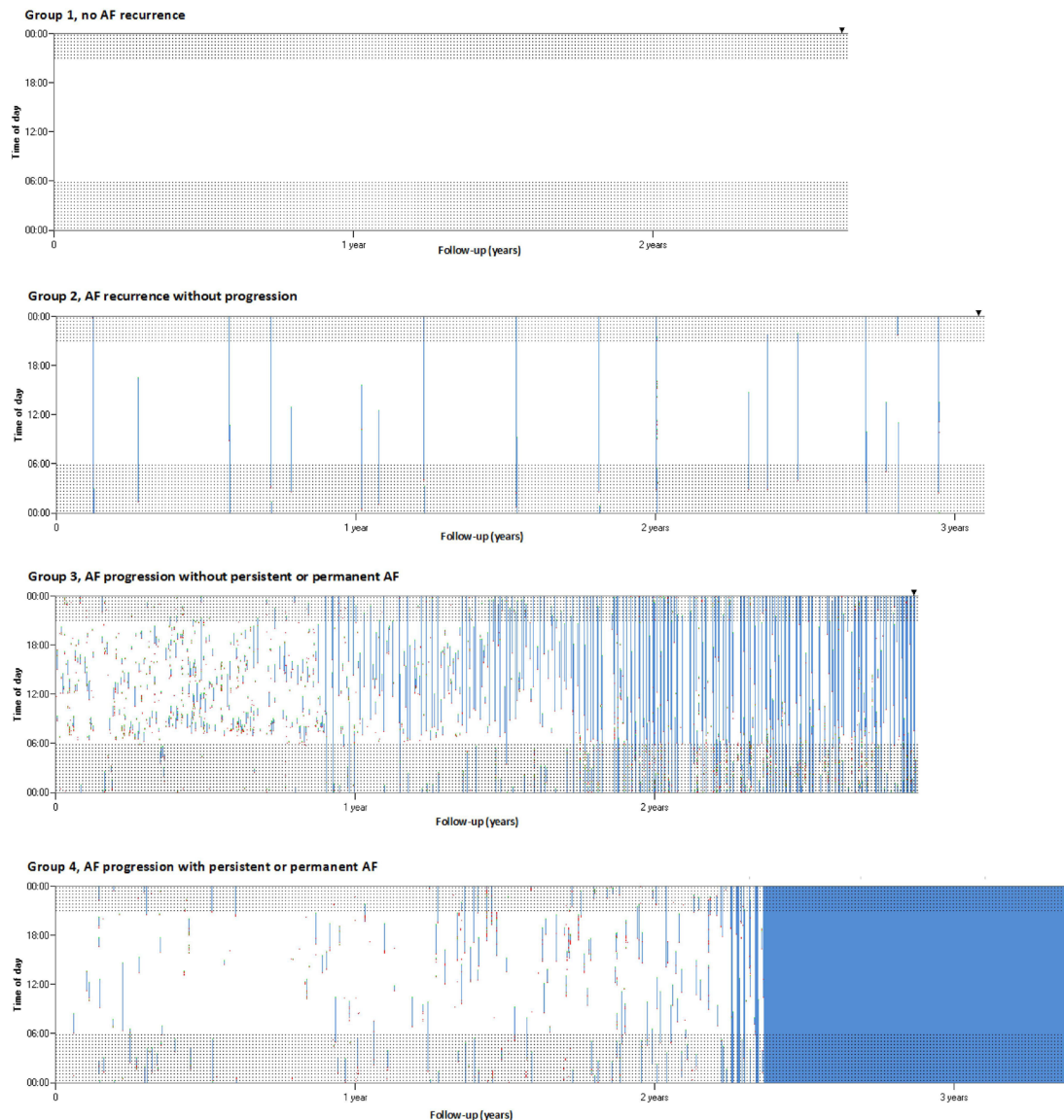
**Figure 1** Examples of continuous rhythm monitoring. Examples of individual patients without AF progression (group 1 and group 2) and with AF progression (group 3 and 4) during follow-up. The X-axis presents follow-up in years, the Y-axis is the time of the day. Shaded areas indicate nightly hours. Black triangle presents day of end of analysis. White means no AF is present, and blue represents ongoing episodes of AF. AF initiations are shown in red and AF terminations are shown in green. AF, atrial fibrillation.

for patients that died after >1 year of continuous rhythm monitoring, until date of PVI, or in case of a successful PVI.

We considered the mathematical formula as leading of both methods, because it is easier to apply in other independent cohorts. Results from both methods were compared and showed that no patients classified as 'without AF progression' by physicians were 'with AF progression' according to the mathematical formula. Fourteen (3%) patients who were classified as AF progressors (from group 3) by physicians did not have AF progression according to the mathematical formula. These patients were eventually categorised as no AF progression.

**Statistical analysis**

Baseline characteristics are presented as mean±SD for normally distributed data, and median and iIQRs for non-normally distributed continuous data. Categorical data are presented as numbers with percentages, biomarker multiplex immunoassay data as arbitrary units on a log2 scale. Fisher's exact test was used for binary variables, and T-test or Wilcoxon rank-sum test was used for continuous variables. Collected baseline variables including core lab data, with $p < 0.10$ in the age-adjusted and sex-adjusted logistic regression, with exception of European Heart Rhythm Association (EHRA) class, number of comorbidities, $CHA_2DS_2$-VASc score and medications, were included in a bidirectional stepwise variable selection leading to a final multivariable logistic regression model. Bidirectional stepping was done for model building and reduction, with a p value $\geq 0.05$ as a criterion for removing a variable from the model (online supplemental data). Imputation was implemented for missing values using the R package mice. For each logistic regression, 'massive imputation' was performed, which means that all variables in a model were at the same time also used for the imputation needed for the fit of that model. For the second model, the Olink Cardiovascular III panel biomarkers (online supplemental table S6) and coagulation markers were added to the stepwise variable selection process if they reached $p < 0.10$ in initial age-adjusted and sex-adjusted

logistic regression to assess if the model would improve. Age and sex were forced into both multivariate models. Interactions between variables was tested, no significant interactions were found. The Harrell's binary C-index was used for goodness-of-fit measure. P value <0.05 was considered statistically significant. Internal validation was done using bootstrapping. Analyses were conducted with R V.3.3.3 (www.r-project.org).

## RESULTS

For the present analysis, we included 417 patients (table 1, online supplemental table S3). Median age was 65 (58–71) years, and 179 (43%) patients were women. Median follow-up of continuous rhythm monitoring was 2.2 (1.6–2.8) years. A total of 162 215 episodes were classified as AF by the automated algorithm, 53 397 (32.9%) were adjusted after adjudication, resulting in 119 120 remaining AF episodes (reasons for adjustments are presented in online supplemental data).

During follow-up, 48 (11.5%) patients showed no AF recurrences, and 318 (76.3%) had AF recurrences without AF progression. AF progression was seen in 51 (12.2%, 5.5% per year) patients: with an increase of >3% of AF burden but without deterioration into persistent or permanent AF in 16 (3.8%) patients, and with development of persistent or permanent AF in 35 (8.4%) patients (online supplemental table S4, figure 1).

Patients with AF progression were more often men, had more often coronary artery disease, larger waist circumference, longer PR interval, larger left atrial (LA) volume and reduced atrial contractile function (table 1).

During follow-up up, one patient died of an unknown cause. Eighteen patients received a pacemaker, 1 due to AV block and 17 patients due to sick sinus syndrome. Figure 2 presents rhythm control therapy during follow-up. No differences were seen in rhythm control therapy at baseline, follow-up and end of analysis between the AF progression and no AF progression group (online supplemental figure S2).

### Blood biomarkers

The baseline levels of the 92 biomarkers are presented in online supplemental table S5). At baseline, a significant difference between the groups was observed for 14 biomarkers.

Baseline coagulation markers are presented in online supplemental table S6). At baseline, the levels of factor XIIa:C1-esterase inhibitor complex and factor XIIa:antithrombin were significantly lower in the AF progression group compared with those without AF progression.

### Prediction models

The logistical analysis adjusted for age and sex with clinical variables showed that 14 variables were associated with AF progression (online supplemental table S7). The clinical multivariable model showed that a longer PR interval, an impaired LA contractile function, moderate mitral valve regurgitation and a higher waist circumference were associated with higher risk of AF progression (table 2A), C-statistic is 0.709 (95% CI 0.614 to 0.799). The optimism caused by overfitting in the C-statistic was 3.03%.

To improve the prediction model and to assess underlying pathophysiological mechanisms, an additional analysis including blood biomarkers was performed. The logistical analysis adjusted for age and sex showed 25 variables associated with AF progression (online supplemental table S8). Table 2B and figure 3 show the multivariable predictors of AF progression including blood

biomarkers. The addition of the blood biomarkers improved the initial model (C-statistic 0.830 (95% CI 0.750 to 0.898)).

Based on the clinical multivariable model, a point risk score was developed for estimating an individual's risk of AF progression at 2 years (table 3).

## DISCUSSION

In the RACE V study, we assessed AF progression in comprehensively phenotyped patients with self-terminating PAF using long-term continuous rhythm monitoring. We showed that AF progression occurred in 5.5% of patients per year. Furthermore, using the clinical model markers of atrial remodelling, mitral valve regurgitation and waist circumference were associated with AF progression. The addition of blood biomarkers improved the C-statistic of the model and showed male sex, lower levels of coagulation markers and markers involved in cardiac stretch, cholesterol metabolism, inflammation and the immune system to be associated with AF progression.

Determining AF progression importantly depends on the type and amount of rhythm monitoring. Previous studies used limited rhythm monitoring and typically focused on progression from PAF to persistent or permanent AF.[3 4] Yet, more studies suggest that increase of AF burden in PAF is also of importance.[14] Therefore, we included increase of AF burden in our AF progression definition to avoid excluding patients with low burden that progressed to a significantly higher PAF burden. Although the majority of patients who showed AF progression deteriorated into persistent or permanent AF, 30% in the AF progression group were classified as progressors because of a likely clinically relevant increase of PAF burden.

In line with previous studies, we found multiple factors involved in AF progression associated with different underlying pathophysiological mechanisms.[3 8] A longer PR interval and an impaired LA contractile function were associated with AF progression. Both can be seen as signs of more severe atrial structural remodelling (atrial cardiomyopathy) promoting AF progression.[15] Previous studies showed that the PR interval was associated with incident AF but not with AF progression.[16] Mitral valve regurgitation, well known to induce volume overload and LA enlargement and thus atrial remodelling, was also associated with AF progression.[17] Atrial enlargement has been associated with incident and recurrent AF.[18] Atrial contractility dysfunction has been related to duration of AF and may increase compliance of the atria, causing atrial cardiomyopathy, which is in turn associated with AF progression.[19] A higher waist circumference was also associated with AF progression. A high body mass index (BMI) and obesity are well known risk factors for incident AF and AF progression.[5] However, BMI does not take visceral fat distribution into account, which has been shown to be an independent marker for cardiovascular morbidities associated with AF and AF progression.[5] Excess of visceral fat induces inflammation, which can promote atrial remodelling.[20] Waist circumference could therefore be seen as a marker of visceral adipose tissue and thus being associated with AF progression.

In addition to a clinical prediction model, we sought to explore the underlying pathophysiological mechanisms for AF progression adding 101 blood biomarkers including coagulation markers to our analysis. The latter improved the prediction model significantly. Furthermore, it revealed that N-terminal pro-brain natriuretic peptide (NTproBNP) was a marker for risk of AF progression. NTproBNP is secreted by myocytes in response to multiple factors, including wall stress and is increased during AF, even without overt heart failure. Our results are comparable

**Table 1** Baseline characteristics

| Characteristic | AF progression (n=51) | No AF progression (n=366) | Total population (n=417) | P value |
|---|---|---|---|---|
| Age (years) | 64 (60–73) | 65 (58–71) | 65 (58–71) | 0.278 |
| Female sex | 15 (29%) | 164 (45%) | 179 (43%) | 0.049 |
| Total history AF (years) | 2.8 (0.9–4.9) | 2.6 (0.7–5.2) | 2.6 (0.7–5.1) | 0.803 |
| Heart failure | 20 (39%) | 104 (28%) | 124 (29%) | 0.274 |
| HFrEF | 4 (8%) | 6 (2%) | 10 (2%) | 0.025 |
| HFpEF | 16 (31%) | 98 (27%) | 114 (27%) | 1 |
| Hypertension | 46 (90%) | 292 (80%) | 338 (81%) | 0.086 |
| Diabetes mellitus | 5 (10%) | 29 (8%) | 34 (8%) | 0.59 |
| Coronary artery disease | 11 (22%) | 37 (10%) | 48 (12%) | 0.031 |
| Atherosclerosis* | 26 (51%) | 178 (49%) | 204 (49%) | 0.767 |
| Peripheral artery disease | 2 (4%) | 1 (0%) | 3 (1%) | 0.041 |
| Ischaemic stroke | 1 (2%) | 18 (5%) | 19 (5%) | 0.491 |
| Pacemaker | 9 (18%) | 16 (4%) | 25 (6%) | 0.001 |
| Number of comorbidities† | 3 (2–4) | 2 (2–3) | 2 (2–3) | 0.05 |
| CHA$_2$DS$_2$-VASc score‡ | | | | 0.016 |
| <2 | 6 (12%) | 101 (28%) | 107 (26%) | |
| ≥2 | 45 (88%) | 265 (72%) | 310 (74%) | |
| **Physical examination** | | | | |
| Height (cm) | 178 (170–185) | 177 (169–184) | 178 (169–184) | 0.492 |
| Weight (kg) | 88 (73–102) | 84 (74–96) | 85 (74–97) | 0.268 |
| Body mass index (kg/m$^2$) | 27 (25–32) | 27 (24–30) | 27 (24–30) | 0.708 |
| Waist circumference (cm) | 105 (99–113) | 100 (92–108) | 100 (93–108) | 0.004 |
| **Laboratory results** | | | | |
| eGFR (mL/min/1.73 m$^2$) | 74 (67–86) | 81 (70–90) | 81 (69–90) | 0.016 |
| **ECG** | | | | |
| PR interval | 178 (160–199) | 164 (149–184) | 166 (150–186) | 0.003 |
| QRS interval | 96 (90–106) | 94 (86–103) | 94 (88–104) | 0.191 |
| **Medications** | | | | |
| β-Blocker | 32 (63%) | 181 (49%) | 213 (51%) | 0.099 |
| Verapamil/Diltiazem | 7 (14%) | 66 (18%) | 73 (18%) | 0.557 |
| Digoxin | 2 (4%) | 4 (1%) | 6 (1%) | 0.16 |
| Class I antiarrhythmic drugs | 5 (10%) | 89 (24%) | 94 (23%) | 0.02 |
| Class III antiarrhythmic drugs | 3 (6%) | 15 (4%) | 18 (4%) | 0.473 |
| ACE inhibitor | 11 (22%) | 71 (19%) | 82 (20%) | 0.709 |
| Angiotensin receptor blocker | 14 (27%) | 66 (18%) | 80 (19%) | 0.129 |
| Statin | 26 (51%) | 119 (33%) | 145 (35%) | 0.012 |
| Anticoagulant | 45 (88%) | 244 (67%) | 289 (69%) | 0.002 |
| Vitamin K antagonist | 10 (20%) | 45 (12%) | 55 (13%) | 0.182 |
| NOAC | 35 (69%) | 199 (54%) | 234 (56%) | 0.07 |
| **Echocardiographic variables** | | | | |
| Left atrial volume index (mL/m$^2$) | 34 (25–39) | 29 (23–36) | 29 (23–36) | 0.038 |
| Left atrial reservoir function (%) | 31 (26–39) | 37 (30–43) | 36 (29–43) | 0.045 |
| Left atrial contractile function (%) | 13 (11–17) | 17 (13–22) | 16 (13–21) | 0.003 |
| Left atrial conduction function (%) | 18 (14–25) | 19 (14–24) | 19 (14–24) | 0.965 |
| Left ventricular ejection fraction (%) | 50±8 | 51±8 | 51±8 | 0.893 |
| Left ventricle strain | −14.2±2.5 | −14.0±2.3 | −14.0±2.4 | 0.76 |
| Moderate aortic valve stenosis | 0 (%) | 3 (1%) | 3 (1%) | 1 |
| Moderate aortic valve regurgitation | 0 (%) | 0 (%) | 1 (0%) | 1 |
| Moderate mitral valve regurgitation | 3 (6%) | 4 (1%) | 7 (2%) | 0.045 |
| **CT** | | | | |
| Calcium score (Agatston) | 131(5–492) | 25 (0–228) | 29 (0–275) | 0.004 |
| Pericardial fat | 186 (148–235) | 166 (121–231) | 168 (124–233) | 0.205 |
| Epicardial fat | 105 (77–130) | 98 (71–128) | 98 (72–128) | 0.349 |
| **Vascular assessment** | | | | |
| IMT max-CCA >1 mm | 19 (46%) | 109 (34%) | 128 (35%) | 0.122 |
| IMT max-all segments >1 mm | 20 (49%) | 154 (48%) | 174 (48%) | 1 |
| Plaques | 15 (29%) | 125 (34%) | 140 (34%) | 0.407 |

Data are presented as mean±SD, number of patients (%) or median (IQR).

*Atherosclerosis is presence of history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, ischaemic cerebral infarction, peripheral vascular disease, Agatston score >400 or plaque.

†The number of comorbidities was calculated by awarding points for hypertension, heart failure, age >65 years, diabetes mellitus; coronary artery disease, BMI ≥25 kg/m$^2$, moderate or severe mitral valve regurgitation and kidney dysfunction (eGFR <60).

‡The CHA$_2$DS$_2$-VASc score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A$_2$=age ≥75 years; D=diabetes mellitus; S$_2$=stroke/transient ischaemic attack/systemic embolism; V=vascular disease; A=age 65–74 years; Sc=sex category (female sex).

AF, atrial fibrillation; BMI, body mass index; CCA, common carotid artery; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IMT, intima-media thickness; LV, left ventricular; NOAC, novel oral anticoagulation.

to previous studies showing that elevated NTproBNP levels are associated with incident AF and AF progression.[5 10 21] Proprotein convertase subtilisin/kexin type 9 (PCSK9), also associated with AF progression in our model, is an enzyme involved in the homeostasis of cholesterol. Higher levels of PCSK9 are associated with cardiovascular events in patients with AF, possibly

**Figure 2** Flow chart of all patients. Four-hundred seventeen patients were included in current analysis. One patient died during follow-up and was included in the analysis until last rhythm monitoring date. AAD, anti-arrhythmic drugs; AF, atrial fibrillation; ECV, electrical cardioversion; PVI, pulmonary vein isolation.

through atherosclerosis and inflammation.[22] Peptidoglycan recognition protein 1 (PGLYRP1), a protein important in the innate immune response, was also associated with AF progression. PGLYRP1 is also involved in inflammation and associated with atherosclerosis. Elevated levels of PGLYRP1 have been associated with aortic wall thickness, aortic plaques and elevated Agatston scores.[23] The fact that PCSK9 and PGLYRP1 were markers for AF progression suggests that vascular processes are of importance in AF progression.[24 25]

Lastly, lower levels of TFPI were associated with progression. This indicates that there is less inhibition of the extrinsic coagulation cascade in patients with AF progression due to reduced TFPI, resulting in increased activity of tissue factor and factor VIIa, and thus increased activation of the extrinsic coagulation pathway. Also, lower levels of factor XIIa:C1-esterase inhibitor, an enzyme inhibitor complex of the intrinsic coagulation cascade, were associated with AF progression. The origin of both and the role in AF progression remains unknown, but the postulated enhanced potential of tissue factor stimulated coagulation, due to lower TFPI activity, by itself would be in accordance with

a role of hypercoagulability in driving AF as previously shown in preclinical studies.[9] Recently, it was shown that duration of PAF was associated with higher levels of von Willebrand factor and factor VIII.[26] Clearly, more research is warranted on the role of hypercoagulability in AF progression.

The model with additional biomarkers also revealed, unexpectedly, male sex as a clinical marker associated with AF progression. None of the previous studies showed sex differences involved in AF progression but data are still scare.[3 5 10] In our study, the percentage of females was 43%, higher than in most studies. Interestingly, women with AF are usually older, having more comorbidities.[27 28]

In summary, our models, including the point risk score, may help to identify patients at risk for AF progression. It again emphasises that AF progression is a multifactorial disease and also suggests differences between sexes. The RACE V clinical risk score may contribute to determine individuals' risks of AF progression and treatment targets. However, before introduction into clinical practice it first warrants validation. As a result, such a model may increase the complexity and burden for the

**Table 2** (A) Multivariable clinical predictors for AF progression

| | OR | 95% CI | P value |
|---|---|---|---|
| Male sex | 1.8 | 0.87 to 3.51 | 0.116 |
| PR interval (per SD) | 1.5 | 1.14 to 2.06 | 0.004 |
| Impaired left atrial contractile function (per SD) | 1.8 | 1.16 to 2.69 | 0.008 |
| Moderate mitral valve regurgitation | 5.9 | 1.02 to 33.97 | 0.048 |
| Waist circumference (per SD) | 1.5 | 1.06 to 2.03 | 0.023 |
| **(B) Multivariable predictors of AF progression including blood biomarkers** | | | |
| | OR | 95% CI | P value |
| Male sex | 3.5 | 1.65 to 7.41 | 0.001 |
| PR interval (per SD) | 1.6 | 1.21 to 2.21 | 0.002 |
| Impaired left atrial contractile function (per SD) | 1.7 | 1.05 to 2.70 | 0.031 |
| Factor XIIa:C1-esterase inhibitor (below median) | 2.7 | 1.26 to 5.56 | 0.01 |
| TFPI decrease (per SD) | 1.8 | 1.23 to 2.53 | 0.002 |
| NTproBNP (per SD) | 1.9 | 1.28 to 2.81 | 0.002 |
| PCSK9 (per SD) | 1.6 | 1.09 to 2.21 | 0.015 |
| PGLYRP1 (per SD) | 1.5 | 1.11 to 2.11 | 0.009 |

AF, atrial fibrillation; NTproBNP, N-terminal pro-brain natriuretic peptide; PCSK9, proprotein convertase subtilisin/kexin type 9; PGLYRP1, peptidoglycan recognition protein 1; TFPI, tissue factor pathway inhibitor.

physician. The Horizon 2020 EHRA-PATHs project aims to develop a software tool that may contribute to improve the feasibility of such a personalised therapeutic strategy.[29]

## LIMITATIONS

Our study has several limitations. First, in the RACE V study treatment was at the discretion of the treating physician, which may have influenced AF progression. However, although low numbers, we did not find significant differences in rhythm control therapy during follow-up between the groups. The clinical risk model obviously depends on the population included in the trial. Second, the existence of missing values in the data, which might have impacted the model, although we used multiple imputation to use the non-missing part of the data as much as possible as opposed to the removal of information from the analysis when doing regression analyses only with patients with complete information only. Third, follow-up was a median of 2.2 years, and did not met the calculated sample size of 750 patients and expected 187 AF progression events, due to a slow inclusion rate as result of the COVID-19 pandemic. To further assess AF progression, more patients and longer follow-up is needed. Fourth, for validation of the models and risk score an impact study is needed before use in clinical practice. However, according to our knowledge such a cohort with continuous rhythm monitoring and thorough phenotyping is not yet available. Fifth, not all factors contributing to AF progression may have been systematically, and repeatedly, assessed in RACE V. Finally, we did not implement temporal dynamic risk profiling into our study.[30]

## CONCLUSION

The RACE V study shows that AF progression in patients with PAF occurs in 5.5% per year as assessed with continuous rhythm recording. Clinical predictors for AF progression included markers of an atrial cardiomyopathy, higher waist circumference and male sex. The addition of cardiovascular biomarkers improved the risk prediction model and showed that increased levels of markers for atrial remodelling,
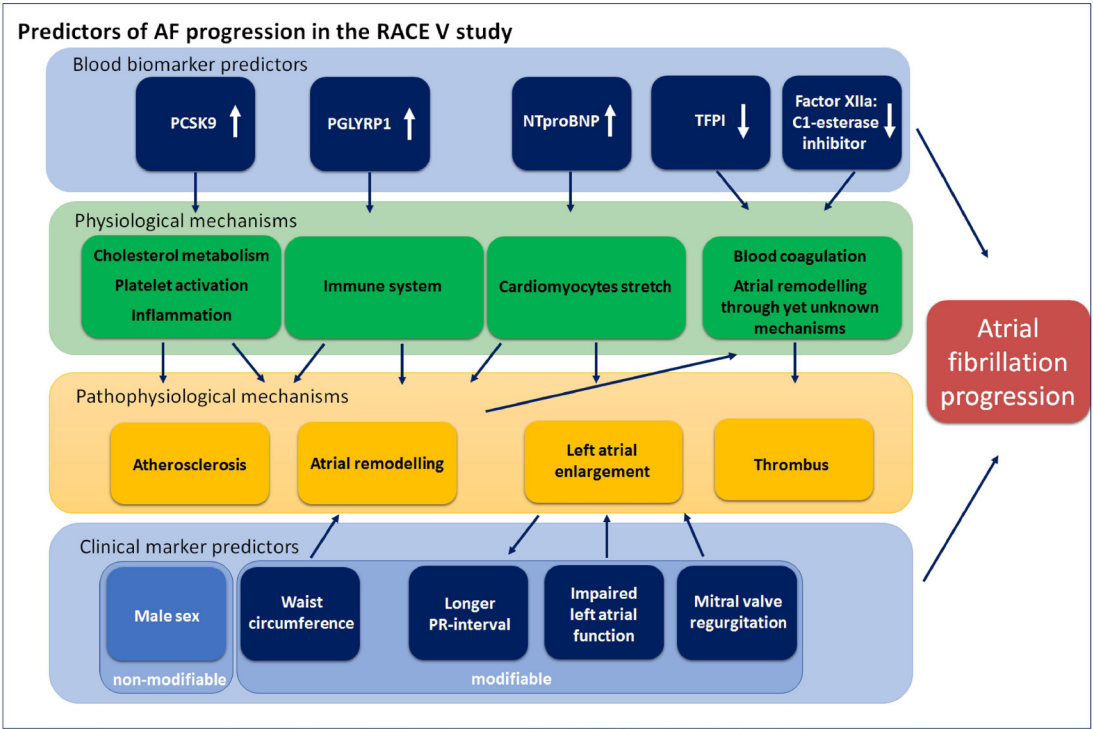


**Figure 3** Predictors of atrial fibrillation (AF) progression in the Reappraisal of AF: Interaction Between HyperCoagulability, Electrical Remodelling, and Vascular Destabilisation in the Progression of AF study. Clinical markers and blood biomarkers as predictors for atrial fibrillation progression and their physiological and pathophysiological mechanisms. The blue boxes represent the multivariable predictors of atrial fibrillation progression. The green boxes represent the physiological mechanisms, the yellow boxes represent the pathophysiological mechanisms. NTproBNP, N-terminal pro-brain natriuretic peptide; PCSK9, proprotein convertase subtilisin/kexin type 9; PGLYRP1, peptidoglycan recognition protein 1; TFPI, tissue factor pathway inhibitor.

**Table 3**  Clinical point risk score

| Sex | Points |
|---|---|
| Female | −2 |
| Male | 0 |
| **PR interval (ms)** | **Points** |
| ≤122 | 0 |
| 123–148 | 1 |
| 149–174 | 2 |
| 175–200 | 3 |
| 201–226 | 4 |
| 227–252 | 5 |
| 253–278 | 6 |
| 279–304 | 7 |
| 305–330 | 8 |
| 331–356 | 9 |
| >356 | 10 |
| **Left atrial contractile function (%)** | **Points** |
| ≤12 | 3 |
| 13–17 | 2 |
| 18–22 | 1 |
| 23–27 | 0 |
| 28–32 | -1 |
| >32 | -3 |
| **Waist circumference** | **Points** |
| ≤84 | 0 |
| 85–96 | 1 |
| 97–108 | 2 |
| 109–120 | 3 |
| 121–132 | 4 |
| >132 | 5 |
| **Mitral valve regurgitation** | **Points** |
| Yes | 5 |
| No | 0 |

| 2-year risk estimation atrial fibrillation progression based on total points | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Total points | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Risk % | 2.3 | 3.1 | 4.2 | 5.6 | 7.5 | 9.9 | 13.0 | 16.9 | 21.6 | 27.2 | 33.7 |

AF, atrial fibrillation.

inflammation, atherosclerosis and coagulation were predictive for AF progression.

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**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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# Supplementary Data

**Prevalence and determinants of AF progression in self-terminating atrial fibrillation - data from RACE V.**

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**Core lab measurement methods**

Reveal LINQ and pacemaker arrhythmia episode adjustments

All collected episodes continuous data on arrhythmias of the included patients up until 1 May 2020 saved by the Reveal LINQ and pacemaker were independently adjudicated and corrected by 5 physicians. Any episode of AF ≥2 minutes was automatically detected. Arrhythmias with ≥182 beats per minute (cycle length ≤330 ms) with a duration of ≥24 beats were automatically classified as tachycardia. Arrhythmias with ≤30 beats per minute (cycle length ≥2000 ms), lasting 12 beats were automatically classified as bradycardia. An asystole ≥4.5 seconds was classified as a pause. The most common reasons for adjustments were false positive AF episodes (premature atrial or ventricular complexes or artefacts), on-going episodes, and episodes classified as atrial tachycardia instead of AF.

Echocardiography

Echocardiography recordings were anonymized and transferred to a core-lab facility for further analysis. Strain analysis was conducted offline, during one cardiac cycle, in sinus rhythm by one experienced observer blinded to clinical data and outcomes. Analysis was performed using vendor-independent software (TOMTEC-ARENA, Imaging Systems, Germany). LV global longitudinal strain (GLS) was analysed in the apical two-, three- and four-chamber views. Left atrial, right atrial and right ventricular strain were assessed in apical four-chamber view only. The region of interest was determined by a manual point-and-click method to trace endocardial borders during LV end-systolic frame. End-systole was automatically defined by the software and was manually adjusted for accuracy when needed. The software automatically produced myocardial speckle tracking in each frame during one cardiac cycle (RR-interval). Atrial contractile function measurements were performed by setting the base or zero strain reference at left ventricular end-diastole. Therefore, left atrial (LA) reservoir strain was measured as difference of the strain value at mitral valve opening minus the zero strain reference. LA contractile function was measured as the difference of the peak strain value at the onset of atrial contraction minus the zero strain reference.

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LA conduit was measured as the difference of the strain value at mitral valve opening (LA reservoir) minus the peak strain value at the onset of atrial contraction.

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Vascular assessment

Vascular assessment of the carotid arteries included measurements of intima media thickness (IMT), pulse wave velocity (PWV) and plaques. PWV was assessed by Complior (Alam Medical, France) or SphygmoCor (Atcor Medical Blood Pressure Analysis System, Australia) at the carotid and femoral arteries. The aortic PWV was determined by using $\geq 20$ consecutive pressure waveforms at the carotid and femoral artery. The wave transit time was calculated by the system software using the R-wave from the simultaneous ECG recording. of the simultaneously recorded ECG. Distance between both measure points was determined and corrected by multiplying the distance by 0.8. The PWV was calculated by dividing the distance between the femoral and carotid artery by the wave transit time. IMT and presence of plaques was assessed by ultrasound (Siemens Acuson S2000) with the Syncho US Workplace 3.5, Arterial Health Package for automated IMT measurement. Assessment of the IMT was done bilaterally in the common carotid artery, the carotid bifurcation, and internal carotid artery.

Cardiac computed tomography (CT)

Epicardial fat was measured on ECG-triggered, native CT heart scans according to the methodology introduced by Fox et al.(1). Tube voltage of scan protocols varied between 80–120kV. The region of interest (ROI) was defined as described by Versteylen(2): The cranial slice limit was set at the level of the

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carina of the pulmonary artery, and the caudal slice limit was the last slice containing any portion of the heart. The anterior border of the ROI was defined by the sternum, the posterior border by the ribs and vertebral column. Images were reconstructed using a soft-tissue algorithm. The pericardium was traced by a blinded reader placing 5-7 control points per slice using axial views as described earlier. Afterwards Catmull-Rom cubic spline functions are then automatically generated to obtain a smooth closed pericardial contour. Ultimately fat was automatically summed with a dedicated volumetric software (syngo.via Frontier, Cardiac risk assessment package, Siemens Healthineers, Forchheim, Germany). Epicardial and pericardial fat were defined as previously described by Iacobellis: Epicardial fat is located between the outer wall of the pericardium and the visceral layer of the pericardium. Pericardial fat is localized between visceral and pericardial myocardium(3).

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3. Iacobellis G. Epicardial and pericardial fat: close, but very different. Obesity (Silver Spring). 2009;17(4):625; author reply 6-7.

Blood biomarkers

At baseline peripheral blood samples were collected. Patients needed to be in sinus rhythm during blood sampling and oral anticoagulation was temporarily interrupted. All blood samples were processed and stored at -80°C.

## Clinical definitions used in this study

Heart Failure definition

At baseline presence of:

1) history of heart failure admission;

2) left ventricular ejection fraction ≤45%;

3) left ventricular ejection fraction >45%,

    with either signs of:

- structural heart disease (left ventricular hypertrophy [left ventricular mass index >95 $g/m^2$ in women and >115 $g/m^2$ in men] OR posterior wall thickness ≥11 mm OR septal wall thickness ≥11 mm)
- and/or signs of diastolic dysfunction (mean E' velocity <8 cm/s & deceleration time >220ms & E/e' >8).

Heart Failure with Preserved Ejection Fraction (HFpEF) definition

- combination of LVEF >45% + structural heart disease

and/or

- combination of LVEF >45% + diastolic dysfunction

Hypertension definition

At baseline presence of:

- History of hypertension
- Use of a beta blocker, with exception of not daily used.
- Use of any calcium channel blocker
- Use of any ACE-inhibitor
- Use of any angiotensin receptor blocker
- Use of any diuretic, including mineralocorticoid receptor antagonist, excluding furosemide amiloride and bumetanide use.
- Use of an alpha blocker
- Baseline blood pressure >140/90mmHg.

Atherosclerosis definition

At baseline presence of:

- history of myocardial infarction
- history of percutaneous coronary intervention
- history of coronary artery bypass graft
- history of ischemic cerebral infarction
- history of peripheral vascular disease
- coronary Agatston score of >400
- plaque on vascular measurement

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**Extensive statistical description**

Fisher's exact was used for binary variables and the T-test and Wilcoxon test were used depending on normality for continuous variables. For non-binary categorical variables, the Chi-squared test with simulation

Multivariable logistic regression model
Collected baseline variables including core lab data, with $p<0.10$ in the age and sex adjusted logistic regression, with exception of EHRA class, number of comorbidities, $CHA_2DS_2$-VASc score and medications, were included in a bidirectional step-wise variable selection, starting with age and sex in the model. Variables were then added to the model in order of (increasing) p-value of age and sex-adjusted analyses, starting with the variable that has the lowest p-value in the age and sex-adjusted logistic regressions.
Before a new variable is added, variables in the model with $p>=0.05$ were identified and removed, starting with the one with the biggest p-value. Before each potential next removal, the model was refit and thus the recalculated p-value was used to determine if there was a next variable with $p>=0.05$. If no variables were to be removed the next variable was added.
The bi-directional stepping consists of a single forward stepping of all the variables, interspersed with backwards stepping of the variables in the model before each next step in the forward-stepping.
The statistical criterion for removing a variable from the model (during each backwards stepping) was $p>=0.05$.
The step-wise variable selection will ensure that no variables with $p>=0.05$ will end up in the final multivariable model. However, due to possible negative confounding even a variable with $p>=0.05$ in an age and sex-adjusted model, may have $p<0.05$ in a model with additional covariates. The aim was also not to keep a too big set of variables to be included in the step-wise process. Therefore, a $p<0.10$ was selected as a trade-off between the most stringent selection (based on $p<0.05$) and the least-stringent selection (that is without taking into account the p-value of age and sex-adjusted regressions).
In the final multivariate model (obtained at the end of the bidirectional stepping), testing for each possible second-order interaction was done (i.e. an interaction between two variables or an interaction with itself (quadratic term), what happened if this interaction is added to the model). Specifically, the p-value of the interaction was checked. Of all possible interactions, none reached Bonferroni significance (taking into account multiple testing).

Hosmer and Lemeshow test was used for goodness of fit test with 8 degrees of freedom, Chi-squared = 6.68, p-value = 0.572
Discrimination slope of the main model = 0.082

Imputation
Imputation was implemented for missing values using the R package mice. Mice creates multiple imputations for multivariate missing data. For this article 4000 imputations for each model fit that required imputation were performed. Each incomplete variable was imputed by a separate model. The default methods of predictive mean matching for numeric data and logistic regression for binary data.
For each logistic regression "massive imputation" was performed, which means that all variables in a model were at the same time also used for the imputation needed for the fit of that model. Internally, mice performs the logistic regression fit on all 4000 imputations. It pools the results according to Rubin's rules for imputation, with a small sample refinement of the method to compute degrees of freedom according to Barnard and Rubin.

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Internal validation

Internal validation was accessed using bootstrapping.(1) Fifty bootstrap samples were used.(2). The optimism caused by overfitting in the C-statistic of our model without biomarkers to be 3.03%."

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Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker *Heart* 2012;**98:**683-690.
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Risk score

The multivariable model was used to calculate the linear predictor for all patients with complete data. This was done in the standard way, namely linear combinations of the variables with the beta coefficients as weights, specifically we obtained the following expression for the linear predictor (centering continuous variables on their respective means):

Linear prediction.= Female sex * (-0.5586208) + (PR-interval - 168.8658) * 0.01309933 + (LA contraction function - 17.30064) * (-0.08169752) + (waist circumference - 101.1294) * 0.02787357 + mitral valve regurgitation * 1.771005

Next, these linear predictors was used to calculate a factor (called F here for simplicity), such that the 95% interval of the linear predictors (from the 2.5% quantile to the 97.5% quantile), when multiplied with this factor, is of length 10. This was done, because the aim was a point-based risk score that can vary from 0 up to and including 10 with only very few occurrences outside of this interval.

F can be interpreted as a conversion factor such that the product of a variable with its beta coefficient and F represents a certain number of points. This factor F was then used to obtain a preliminary scoring scheme in the following way:

For binary variables, the no-level gets zero points and the yes-level gets beta * F points. The number of points was rounded to the nearest integer value. For continuous variables, the step size is defined as the inverse of the absolute value of its beta coefficient and F rounded up to the nearest integer value. Step size can be interpreted as the number of units of the variable per point. The number of levels the variable has in the point-based risk score is then set to the range of the variable (maximum minus minimum) divided by the step size rounded down to the nearest integer value.

The range of the variable is then divided using intervals of length equal to the step size and centered in the range of the variable. The number of points assigned to the interval is the value of the variable in its midpoint times its beta coefficient times F, rounded to the nearest integer value. Finally, the first interval is the extended to include also the smallest values of the variable and the last one to include also the largest values, so that the entire range of the variable is covered. Age was removed from the point based risk score.

Mathematical formula of AF progression

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$B = \Sigma_i T_i$

$B$ = AF burden
$\Sigma_i$ = sum of all AF episodes in the time period of which the AF burden or weighted AF burden is calculated.
$T_i$ = time of AF episode i.

$B_{weighed} = \Sigma_i w_i T_i$

$B_{weighed}$ = weighted AF burden,
$\Sigma_i$ = sum of all AF episodes in the time period of which the AF burden or weighted AF burden is calculated.
$w_i$ = weight factor for AF episode i.

$\qquad w_i = 2 \times (t_i - t_{start})/(t_{stop} - t_{start})$

$\qquad t_i$ = time when AF episode took place (time choses is in the middle of the episode)
$\qquad t_{start}$ = start time of the period of which the weighted AF burden is calculated,
$\qquad t_{stop}$ = end time of the period of which the weighted AF burden is calculated.

$T_i$ = length of time of AF episode *i*.

AF progression is calculated with the formulas of $B$ and $B_{weighed}$:
$P = B_{weighed} - B$

$P$ = AF progression.

Progression is presented as percentage

$100 \times (P/(t_{stop} - t_{start}))\%$

$t_{start}$ = start time of the period of which the weighted AF burden is calculated,
$t_{stop}$ = end time of the period of which the weighted AF burden is calculated.

An increase >3% AF burden over the first six months or total follow-up was chosen as definition for atrial fibrillation progression. This cut-off point was chosen because the results were most consistent with the assessment of the physicians.

**Supplementary Figure S1. RACE V study design overview**

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| Investigations at baseline and during follow-up | T = 0 | T = 1 year | T = 2.5 years | End of device/ End of study* |
|---|:---:|:---:|:---:|:---:|
| Clinical history | ● | ● | ● | |
| Examination | ● | ● | ● | |
| Blood | ● | | ● | |
| Electrocardiogram | ● | ● | ● | |
| Echocardiography | ● | | ● | |
| Blood biomarkers | ● | | ● | |
| Questionnaires | ● | ● | ● | |
| Genotyping | ● | | | |
| Vascular assessment | ● | | | |
| CT heart | ● | | | |
| Adverse events | ━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━ | | | |
| Rhythm monitoring | ━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━ | | | |

* End of study was variable and dependent on form of consent for study follow-up with continuous rhythm monitoring until 2,5 years, at end of battery of Reveal LINQ or at 4 years for patients with a pacemaker.

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**Supplementary Figure S2. RACE V rhythm control therapy overview**
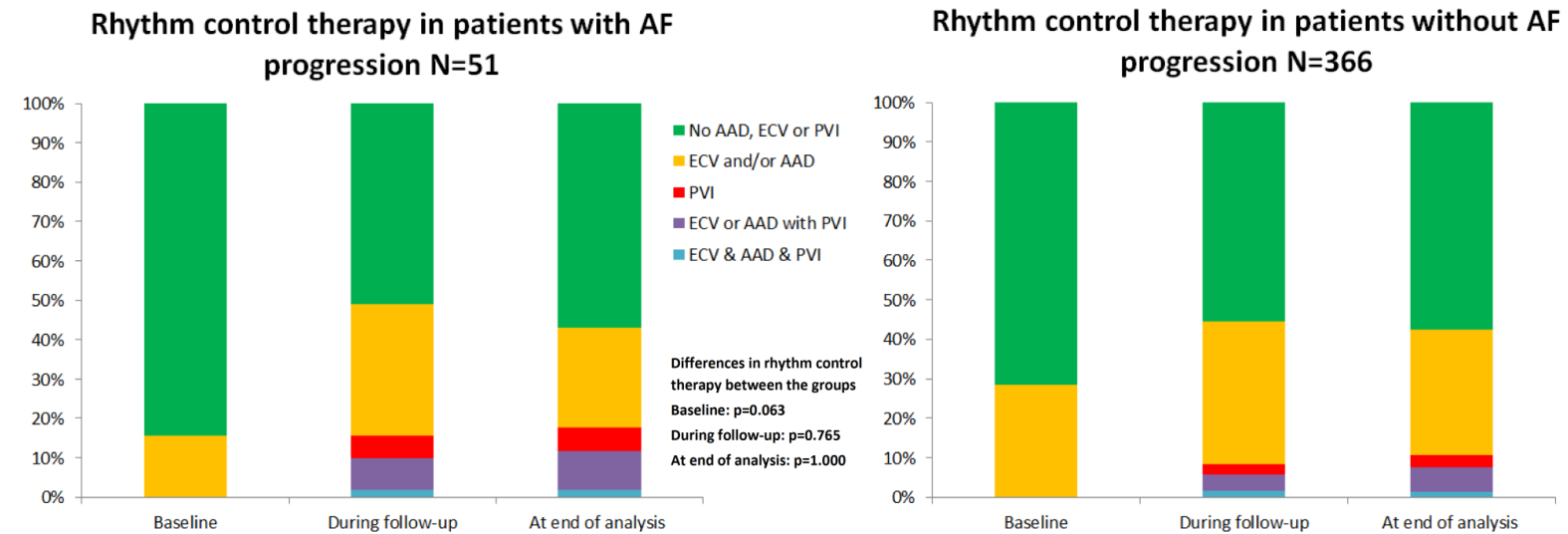


Use of rhythm control therapy.

AAD= antiarrhythmic drug; AF= atrial fibrillation; ECV = electro cardioversion; PVI = pulmonary vein isolation

2 patients with AF progression used amiodarone, both started during follow-up, 1 stopped during follow-up, 1 continued until end of analysis.

4 patients without AF progression used amiodarone, all started during follow-up, 1 stopped during follow-up, 3 continued until end of analysis.

5 of 26 patients (19%) undergoing PVI showed AF progression. 9 of 30 patients (30%) undergoing ECV showed AF progression. 3 of 14 (21%) patients undergoing both ECV and PVI showed AF progression.

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**Supplementary Table S1. RACE V inclusion and exclusion criteria**

| Inclusion criteria | Age > 18 years |
|---|---|
| | Total history <10 years of paroxysmal, self-terminating AF |
| | At least one documented episode of AF and 2 symptomatic episodes or two documented episodes, documented as: <br> - AF on ECG, Holter-recording, loop recorder, event recorder or MyDiagnostick; or <br> - Subclinical AF (SCAF) detected in a Medtronic pacemaker (atrial rate > 190 bpm lasting > 6 minutes) |
| | Able and willing to sign informed consent for the registry |
| | Able and willing to undergo implantation of ILR (in patients without a CIED) |
| | CHA2DS2-VASc score ≤5 |
| | No other indication for oral anticoagulation (e.g. mechanical valve prosthesis) |
| Exclusion criteria | Non-self-terminating, persistent AF; |
| | Only AF due to a trigger (i.e. postoperative, due to infection) |
| | Congenital heart disease |
| | Refusing to temporarily stop (N)OAC for coagulation phenotyping (in patients already on (N)OAC before inclusion in this study), with the exception for patients with a history of ischemic stroke/ transient ischemic attack; |
| | Prior pulmonary vein isolation (PVI) or on waiting list for PVI or expected to be placed on waiting list within one year, since it is expected that those patients will not show much AF recurrences. |
| | Expected to start with, or currently using amiodarone, since it is expected that those patients will not show AF recurrences. |
| | Pregnancy |
| | ICD, CRT or pacemaker that is not a Medtronic pacemaker due to differences in AHRE algorithm or incompatibility with the type of home-monitoring |
| | Life expectancy of less than 2.5 years |
| | Ventricular pacing >50% in patients with a Medtronic pacemaker |

**Supplementary Table S2. List of 92 biomarkers, Olink Cardiovascular III panel (v.6113)**

| Abbreviations | Biomarkers | Uniprot ID | OlinkID |
|---|---|---|---|
| ALCAM | CD166 antigen | Q13740 | OID00572 |
| AP-N | Aminopeptidase N | P15144 | OID00611 |
| AXL | Tyrosine-protein kinase receptor UFO | P30530 | OID00612 |
| AZU1 | Azurocidin | P20160 | OID00597 |
| BLM hydrolase | Bleomycin hydrolase | Q13867 | OID00581 |
| CASP-3 | Caspase-3 | P42574 | OID00630 |
| CCL15 | C-C motif chemokine 15 | Q16663 | OID00629 |
| CCL16 | C-C motif chemokine 16 | O15467 | OID00654 |
| CCL24 | C-C motif chemokine 24 | O00175 | OID00592 |

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| CD163 | Scavenger receptor cysteine-rich type 1 protein M130 | Q86VB7 | OID00577 |
|-------|-------------------------------------------------------|--------|----------|
| CD93 | Complement component C1q receptor | Q9NPY3 | OID00639 |
| CDH5 | Cadherin-5 | P33151 | OID00587 |
| CHI3L1 | Chitinase-3-like protein 1 | P36222 | OID00633 |
| CHIT1 | Chitotriosidase-1 | Q13231 | OID00605 |
| CNTN1 | Contactin-1 | Q12860 | OID00586 |
| COL1A1 | Collagen alpha-1(I) chain | P02452 | OID00641 |
| CPA1 | Carboxypeptidase A1 | P15085 | OID00624 |
| CPB1 | Carboxypeptidase B | P15086 | OID00632 |
| CSTB | Cystatin-B | P04080 | OID00575 |
| CTSD | Cathepsin D | P07339 | OID00622 |
| CTSZ | Cathepsin Z | Q9UBR2 | OID00643 |
| CXCL16 | C-X-C motif chemokine 16 | Q9H2A7 | OID00601 |
| DLK-1 | Protein delta homolog 1 | P80370 | OID00598 |
| EGFR | Epidermal growth factor receptor | P00533 | OID00637 |
| Ep-CAM | Epithelial cell adhesion molecule | P16422 | OID00610 |
| EPHB4 | Ephrin type-B receptor 4 | P54760 | OID00569 |
| FABP4 | Fatty acid-binding protein, adipocyte | P15090 | OID00589 |
| FAS | Tumor necrosis factor receptor superfamily member 6 | P25445 | OID00615 |
| Gal-3 | Galectin-3 | P17931 | OID00578 |
| Gal-4 | Galectin-4 | P56470 | OID00626 |
| GDF-15 | Growth/differentiation factor 15 | Q99988 | OID00595 |
| GP6 | Platelet glycoprotein VI | Q9HCN6 | OID05026 |
| GRN | Granulins | P28799 | OID00579 |
| ICAM-2 | Intercellular adhesion molecule 2 | P13598 | OID00646 |
| IGFBP-1 | Insulin-like growth factor-binding protein 1 | P08833 | OID00604 |
| IGFBP-2 | Insulin-like growth factor-binding protein 2 | P18065 | OID00650 |
| IGFBP-7 | Insulin-like growth factor-binding protein 7 | Q16270 | OID00638 |
| IL-17RA | Interleukin-17 receptor A | Q96F46 | OID00566 |
| IL-18BP | Interleukin-18-binding protein | O95998 | OID00640 |
| IL-1RT1 | Interleukin-1 receptor type 1 | P14778 | OID00613 |
| IL-1RT2 | Interleukin-1 receptor type 2 | P27930 | OID00627 |
| IL-2RA | Interleukin-2 receptor subunit alpha | P01589 | OID00570 |
| IL-6RA | Interleukin-6 receptor subunit alpha | P08887 | OID00602 |
| ITGB2 | Integrin beta-2 | P05107 | OID00565 |
| JAM-A | Junctional adhesion molecule A | Q9Y624 | OID00625 |
| KLK6 | Kallikrein-6 | Q92876 | OID00647 |

| | | | |
|---|---|---|---|
| LDL receptor | Low-density lipoprotein receptor | P01130 | OID00564 |
| LTBR | Lymphotoxin-beta receptor | P36941 | OID00583 |
| MB | Myoglobin | P02144 | OID00616 |
| MCP-1 | Monocyte chemotactic protein 1 | P13500 | OID00576 |
| MEPE | Matrix extracellular phosphoglycoprotein | Q9NQ76 | OID00132 |
| MMP-2 | Matrix metalloproteinase-2 | P08253 | OID00614 |
| MMP-3 | Matrix metalloproteinase-3 | P08254 | OID00644 |
| MMP-9 | Matrix metalloproteinase-9 | P14780 | OID00568 |
| MPO | Myeloperoxidase | P05164 | OID00600 |
| Notch 3 | Neurogenic locus notch homolog protein 3 | Q9UM47 | OID00584 |
| NT-proBNP | N-terminal prohormone brain natriuretic peptide | NA | OID00131 |
| OPG | Osteoprotegerin | O00300 | OID00571 |
| OPN | Osteopontin | P10451 | OID00621 |
| PAI | Plasminogen activator inhibitor 1 | P05121 | OID00591 |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 | Q8NBP7 | OID00619 |
| PDGF subunit A | Platelet-derived growth factor subunit A | P04085 | OID00648 |
| PECAM-1 | Platelet endothelial cell adhesion molecule | P16284 | OID00652 |
| PGLYRP1 | Peptidoglycan recognition protein 1 | O75594 | OID00623 |
| PI3 | Elafin | P19957 | OID00609 |
| PLC | Perlecan | P98160 | OID00582 |
| PON3 | Paraoxonase | Q15166 | OID00642 |
| PRTN3 | Myeloblastin | P24158 | OID00618 |
| PSP-D | Pulmonary surfactant-associated protein D | P35247 | OID00608 |
| RARRES2 | Retinoic acid receptor responder protein 2 | Q99969 | OID00645 |
| RETN | Resistin | Q9HD89 | OID00603 |
| SCGB3A2 | Secretoglobin family 3A member 2 | Q96PL1 | OID00636 |
| SELE | E-selectin | P16581 | OID00596 |
| SELP | P-selectin | P16109 | OID00574 |
| SHPS-1 | Tyrosine-protein phosphatase non-receptor type substrate 1 | P78324 | OID00628 |
| SPON1 | Spondin-1 | Q9HCB6 | OID00599 |
| ST2 | ST2 protein | Q01638 | OID00634 |
| TFF3 | Trefoil factor 3 | Q07654 | OID00573 |
| TFPI | Tissue factor pathway inhibitor | P10646 | OID00590 |
| TIMP4 | Metalloproteinase inhibitor 4 | Q99727 | OID00585 |
| TLT-2 | Trem-like transcript 2 protein | Q5T2D2 | OID00588 |
| TNF-R1 | Tumor necrosis factor receptor 1 | P19438 | OID00649 |

| | | | |
|---|---|---|---|
| TNF-R2 | Tumor necrosis factor receptor 2 | P20333 | OID00567 |
| TNFRSF10C | Tumor necrosis factor receptor superfamily member 10C | O14798 | OID00594 |
| TNFRSF14 | Tumor necrosis factor receptor superfamily member 14 | Q92956 | OID00563 |
| TNFSF13B | Tumor necrosis factor ligand superfamily member 13B | Q9Y275 | OID00617 |
| t-PA | Tissue-type plasminogen activator | P00750 | OID00635 |
| TR | Transferrin receptor protein 1 | P02786 | OID00593 |
| TR-AP | Tartrate-resistant acid phosphatase type 5 | P13686 | OID00606 |
| uPA | Urokinase-type plasminogen activator | P00749 | OID00631 |
| U-PAR | Urokinase plasminogen activator surface receptor | Q03405 | OID00620 |
| vWF | Von Willebrand factor | P04275 | OID00651 |

**Supplementary Table S3. Inclusion distribution per participating centre**

| Centre | Number of inclusion |
|---|---|
| University Medical Centre Groningen | 100 |
| Maastricht University Medical Centre | 106 |
| Ommelander Hospital Groningen | 31 |
| Martini Hospital | 111 |
| Rijnstate Hospital | 40 |
| University of Amsterdam | 22 |
| Isala Hospital | 4 |
| Laurentius Hospital | 2 |
| VU Medical Centre Amsterdam | 2 |

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Supplemental material

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*Heart*

**Supplementary Table S4. Baseline Characteristics of AF progression groups**

| Characteristic | No AF recurrence (group 1) | AF recurrence without AF progression (group 2) | AF progression without persistent AF (group 3) | AF progression with persistent AF (group 4) |
|---|---|---|---|---|
| | (N=48) | (N=318) | (N=16) | (N=35) |
| Age (years) | 63 (54-72) | 65 (58-71) | 63 (58-71) | 65 (62-74) |
| Female sex | 19 (40%) | 145 (46%) | 5 (31%) | 10 (29%) |
| Total history AF (years) | 1.6 (0.5-4.7) | 2.6 (0.8-5.3) | 2.5 (1.0-3.4) | 3.6 (0.9-5.7) |
| Heart failure | 11 (39%) | 93 (50%) | 6 (55%) | 15 (63%) |
| HFrEF | 2 (4%) | 4 (1%) | 1 (1 %) | 3 (9%) |
| HFpEF | 9 (19%) | 89 (28%) | 5 (31%) | 11 (31%) |
| Hypertension | 42 (88%) | 250 (78%) | 16 (100%) | 30 (86%) |
| Diabetes mellitus | 3 (6%) | 26 (8%) | 1 (6%) | 4 (11%) |
| Coronary artery disease | 4 (8%) | 33 (10%) | 2 (13%) | 9 (26%) |
| Atherosclerosis* | 25 (52%) | 153 (48%) | 9 (56%) | 17 (49%) |
| Peripheral artery disease | 0 (0%) | 1 (0%) | 0 (0%) | 2 (6%) |
| Ischemic stroke | 3 (6%) | 15 (5%) | 1 (6%) | 0 (0%) |

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*Heart*

| | | | | |
|---|---|---|---|---|
| Chronic obstructive pulmonary disease | 0 (0%) | 19 (6%) | 2 (13%) | 2 (6%) |
| Number of Comorbidities** | 2 (2-3) | 2 (2-3) | 3 (2-3) | 3 (2-4) |
| CHA$_2$DS$_2$-VASc score*** | | | | |
| ≤ 2 | 35 (73%) | 230 (72%) | 15 (94%) | 30 (86%) |
| >2 | 13 (27%) | 88 (28%) | 1 (6%) | 5 (14%) |
| EHRA class | | | | |
| I | 9 (19%) | 23 (7 %) | 4 (25%) | 7 (20%) |
| IIa | 16 (33%) | 98 (31%) | 4 (25%) | 17 (49%) |
| IIb | 16 (33%) | 139 (44%) | 6 (38%) | 6 (17%) |
| III | 7 (15%) | 56 (18%) | 2 (13%) | 5 (14%) |
| IV | 0 (0%) | 2 (1%) | 0 (0%) | 0 (0%) |
| Physical examination | | | | |
| Height (cm) | 178 (172-183) | 176 (168-184) | 177 (172-187) | 179 (170-183) |
| Weight (kg) | 88 (77-98) | 84 (74-96) | 91 (72-104) | 88 (75-100) |
| BMI (kg/m$^2$) | 27(25- 30) | 27 (24-30) | 26 (25-30) | 27 (24-32) |
| Obesity (BMI>30) | 13 (27%) | 79 (25%) | 4 (25%) | 11 (32%) |
| Waist circumference (cm) | 99 (93-109) | 100 (92-108) | 103 (95-111) | 106 (101-114) |
| Systolic blood pressure (mmHg) | 133 (124-140) | 134 (125-145) | 130 (122-136) | 130 (124-144) |
| Diastolic blood pressure (mmHg) | 80 (75-85) | 80 (74-85) | 75 (72-83) | 80 (72-85) |
| Laboratory results | | | | |
| Creatinine (µmol/L) | 77 (67-85) | 80 (69-91) | 89 (80-99) | 87 (80-100) |
| eGFR (mL/min*1.73m$^2$) | 85 (76-93) | 81 (69-90) | 71 (63-83) | 76 (68-86) |
| Electrocardiogram | | | | |
| PR-interval | 166 (148-173) | 164 (149-186) | 170 (160-200) | 180 (168-199) |
| QRS-interval | 94 (88-101) | 94 (86-104) | 94 (90-103) | 96 (90-110) |
| Medications | | | | |
| β-blocker | 25 (52%) | 156 (49%) | 11 (69%) | 21 (60%) |
| Verapamil/Diltiazem | 8 (17%) | 58 (18%) | 3 (19%) | 4 (11%) |
| Digoxin | 0 (0%) | 4 (1 %) | 0 (0 %) | 2 (6%) |
| Class I antiarrhythmic drugs | 13 (27 %) | 76 (24%) | 3 (19%) | 2 (6%) |
| Class III antiarrhythmic drugs | 1 (2%) | 14 (4%) | 1 (6%) | 3 (9%) |
| ACE-inhibitor | 12 (25%) | 59 (19%) | 3 (19%) | 8 (23%) |
| Angiotensin Receptor Blocker | 8 (17%) | 58 (18%) | 5 (31 %) | 9 (26%) |
| Statin | 10 (21%) | 109 (34%) | 10 (63%) | 16 (46%) |
| Diuretic | 7 (15%) | 47 (15%) | 3 (19%) | 7 (20%) |
| Anticoagulant | 29 (60%) | 215 (68%) | 13 (81%) | 32 (91%) |
| Vitamin K antagonist | 4 (8%) | 41 (13%) | 3 (19%) | 7 (20%) |
| NOAC | 25 (52%) | 174 (55%) | 10 (63%) | 25 (71%) |
| Echocardiographic variables [a] | | | | |
| Left atrial volume (mL) | 58 (46-67) | 58 (47-74) | 60 (55-76) | 68 (55-85) |
| Left atrial volume index (mL/m$^2$) | 28 (22-34) | 29 (24-36) | 32 (25-35) | 35 (26-39) |
| Left atrial reservoir function (%) | 38 (31-47) | 37 (29-43) | 35 (27- 53) | 31 (25-35) |

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| | | | | |
|---|---|---|---|---|
| **Left atrial contractile function (%)** | 18 (13-23) | 17 (13-21) | 15 (10-23) | 13 (11-15) |
| **Left atrial conduction function (%)** | 19 (15-24) | 19 (14-24) | 23 (15-34) | 18 (13-23) |
| **Right atrial volume (mL)** | 39 (34-56) | 48 (38-65) | 55 (47-79) | 55 (46-63) |
| **Right atrial volume indexed (mL/m$^2$)** | 21 (16- 29) | 24 (20 - 31) | 32 (23- 33) | 28 (24 - 33) |
| **Left ventricular ejection fraction (%)** | 51 ± 10 | 51 ± 8 | 52 ± 9 | 50 ± 8 |
| **Left ventricular mass (g)** | 150 (140-165) | 148 (126-178) | 152 (139-182) | 161 (134-188) |
| **Left ventricular mass index (g/m$^2$)** | 75 (68-83) | 76 (64-88) | 86 (69-88) | 78 (67-96) |
| **Left ventricle strain** | -14.5 ± 2.5 | -14.0 ± 2.3 | -14.2 ± 2.6 | -14.3 ± 2.6 |
| **Computed Tomography [b]** | | | | |
| **Calcium score (Agatston)** | 15 (0-75) | 22 (0-227) | 94 (15-3270) | 152 (4-917) |
| **Agatston >400** | | | | |
| **Pericardial fat** | 171 (134-223) | 166 (118- 232) | 205 (160-224) | 167 (137-235) |
| **Epicardial fat** | 102 (74-132) | 97 (70-128) | 104 (90-126) | 105 (72-137) |
| **Vascular assessment [c]** | | | | |
| **IMT max–CCA (mm)** | 0.90 (0.82-1.04) | 0.92 (0.81-1.07) | 1.03 (0.85-1.19) | 0.97 (0.83-1.13) |
| **IMT max-CCA** | | | | |
| **>1mm** | 14 (33%) | 95 (34%) | 8 (53%) | 11 (42%) |
| **IMT max–all segments (mm)** | 1.04 (0.93-1.20) | 0.98 (0.84-1.16) | 1.00 (0.88-1.20) | 1.02 (0.88-1.14) |
| **IMT max-all segments** | | | | |
| **>1mm** | 24 (57%) | 130 (47%) | 7 (47%) | 13 (50%) |
| **Pulse wave velocity (m/s)** | 8.60 (6.98-10.00) | 8.49 (7.45-10.20) | 8.46 (7.66-10.25) | 9.20 (8.14-10.26) |
| **Plaques** | 23 (64%) | 102 (48%) | 6 (60%) | 9 (60%) |
| **Plaques >3** | 2 (4%) | 10 (3%) | 2 (12%) | 3 (9%) |

Data are presented as mean±standard deviation, number of patients (%), or median (interquartile range). Abbreviations: ACE=angiotensin-converting enzyme; AF=atrial fibrillation; BMI=body mass index; CCA= common carotid artery; eGFR=estimated glomerular filtration rate; EHRA= European Heart Rhythm Association class for symptoms; HFpEF= heart failure with preserved ejection fraction; HFrEF= heart failure with reduced ejection fraction; IMT=intima media thickness; NOAC= novel oral anticoagulation; NT-proBNP=N-terminal pro-brain natriuretic peptide; *Atherosclerosis is presence of history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, ischemic cerebral infarction, peripheral vascular disease, Agatston score >400 or plaque; **The number of comorbidities was calculated by awarding points for hypertension, heart failure, age >65 years, diabetes mellitus; coronary artery disease, BMI>25kg/m2, moderate or severe mitral valve regurgitation and kidney dysfunction (eGFR<60); ***The CHA2DS2-VASc score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A2=age ≥75 years; D=diabetes mellitus; S2=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc=sex category (female sex). ). [a]Left atrial and ventricle strain measurements could not be performed in 75 patients. Measurements of right atrial strain could not be done in 123 patients. [b]Agatston score was not available for 10 patients, epicardial and pericardial fat could not be analysed for 21 patients. [c]IMT CCA was not available for 55 patients, IMT all segments for le for 56 patients and pulse wave velocity could not be measured in 78 patients and amount of plaques could not be measured in 145 patients.

**Supplementary Table S5. Olink biomarkers at baseline**

| Characteristic | AF progression (N=51) | No AF progression (N=366) | Total (N=417) | *P*-value |
|---|---|---|---|---|
| ALCAM | 6.06 (5.82 - 6.20) | 6.07 (5.84 - 6.22) | 6.07 (5.84 - 6.22) | 0.772 |
| AP-N | 5.46 (5.26 - 5.69) | 5.53 (5.33 - 5.76) | 5.53 (5.33 - 5.76) | 0.107 |
| AXL | 9.44 (9.24 - 9.63) | 9.39 (9.16 - 9.60) | 9.39 (9.16 - 9.60) | 0.168 |
| AZU1 | 4.59 (4.33 - 5.16) | 4.61 (4.28 - 5.03) | 4.61 (4.28 - 5.03) | 0.298 |
| BLM hydrolase | 6.26 (6.02 - 6.56) | 6.21 (5.91 - 6.48) | 6.21 (5.91 - 6.48) | 0.181 |
| CASP-3 | 8.32 (7.56 - 9.40) | 8.52 (7.31 - 9.49) | 8.45 (7.36 - 9.49) | 0.883 |
| CCL15 | 8.08 (7.90 - 8.38) | 8.04 (7.78 - 8.36) | 8.04 (7.78 - 8.36) | 0.259 |
| CCL16 | 7.45 (7.09 - 7.71) | 7.44 (7.07 - 7.71) | 7.44 (7.07 - 7.71) | 0.929 |
| CCL24 | 6.37 (5.46 - 6.88) | 6.24 (5.64 - 6.87) | 6.24 (5.63 - 6.87) | 0.926 |
| CD163 | 8.02 (7.65 - 8.39) | 7.96 (7.60 - 8.25) | 7.96 (7.61 - 8.27) | 0.323 |
| CD93 | 11.82 (11.57 - 12.00) | 11.79 (11.56 -12.00) | 11.79 (11.56 - 12.00) | 0.690 |
| CDH5 | 4.34 (4.06 - 4.59) | 4.38 (4.08 - 4.59) | 4.38 (4.08 - 4.59) | 0.849 |
| CHI3L1 | 7.46 (6.87 - 7.95) | 7.22 (6.68 - 7.89) | 7.22 (6.68 - 7.89) | 0.128 |
| CHIT1 | 7.29 (6.69 - 8.12) | 7.16 (6.46 - 7.75) | 7.16 (6.46 - 7.75) | 0.281 |
| CNTN1 | 4.75 (4.40 - 4.89) | 4.78 (4.47 - 5.04) | 4.78 (4.45 - 5.03) | 0.161 |
| COL1A1 | 3.45 (3.12 - 3.71) | 3.47 (3.20 - 3.71) | 3.46 (3.20 - 3.71) | 0.446 |
| CPA1 | 6.67 (6.34 - 7.20) | 6.62 (6.21 - 7.02) | 6.62 (6.21 - 7.02) | 0.379 |
| CPB1 | 6.61 (6.26 - 7.07) | 6.53 (6.08 - 6.88) | 6.53 (6.08 - 6.88) | 0.130 |
| CSTB | 5.54 (5.19 - 5.80) | 5.38 (5.05 - 5.76) | 5.38 (5.05 - 5.76) | 0.176 |
| CTSD | 5.22 (5.06 - 5.67) | 5.11 (5.06 - 5.40) | 5.11(5.06- 5.40) | 0.021 |
| CTSZ | 5.97 (5.68 - 6.20) | 5.91 (5.68 - 6.10) | 5.92 (5.68 - 6.11) | 0.259 |
| CXCL16 | 5.85 (5.71 - 6.04) | 5.90 (5.66 - 6.12) | 5.90 (5.67 - 6.12) | 0.489 |
| DLK-1 | 7.01 (6.71 - 7.34) | 6.95 (6.58 - 7.35) | 6.95 (6.59 - 7.35) | 0.435 |
| EGFR | 3.52 (3.38 - 3.75) | 3.62 (3.45 - 3.82) | 3.62 (3.45 - 3.82) | 0.060 |
| Ep-CAM | 6.40 (5.91 - 7.39) | 6.66 (5.91 - 7.50) | 6.66 (5.91 - 7.50) | 0.382 |
| EPHB4 | 5.18 (4.89 - 5.31) | 5.12 (4.89 - 5.32) | 5.12 (4.89 - 5.32) | 0.501 |
| FABP4 | 6.64 (6.07 - 7.23) | 6.40 (5.94 - 6.96) | 6.40 (5.94 - 6.96) | 0.107 |
| FAS | 6.14 (5.95 - 6.45) | 6.14 (5.89 - 6.35) | 6.14 (5.89 - 6.35) | 0.188 |
| Gal-3 | 6.61 (6.20 - 6.82) | 6.51 (6.27 - 6.75) | 6.51 (6.27 - 6.75) | 0.281 |
| Gal-4 | 4.17 (3.80 - 4.44) | 4.14 (3.79 - 4.42) | 4.14 (3.79 - 4.42) | 0.475 |
| GDF-15 | 6.60 (6.21 - 6.99) | 6.38 (6.00 - 6.75) | 6.38 (6.00 - 6.75) | 0.010 |
| GP6 | 3.10 (2.60 - 3.62) | 3.12 (2.55 - 3.71) | 3.13 (2.55 - 3.71) | 0.904 |
| GRN | 6.92 (6.76 - 7.16) | 6.93 (6.69 - 7.14) | 6.93 (6.70 - 7.14) | 0.331 |
| ICAM-2 | 5.75 (5.42 - 5.96) | 5.70 (5.38 - 5.97) | 5.70 (5.39 - 5.97) | 0.532 |
| IGFBP-1 | 4.80 (3.99 - 5.56) | 4.71 (3.82 - 5.66) | 4.71 (3.82 - 5.66) | 0.610 |
| IGFBP-2 | 8.45 (7.82 - 8.90) | 8.32 (7.65 - 8.83) | 8.32 (7.65 - 8.83) | 0.182 |
| IGFBP-7 | 8.30 (8.07 - 8.66) | 8.25 (7.99 - 8.50) | 8.25 (7.99 - 8.50) | 0.093 |
| IL-17RA | 4.36 (4.09 - 4.63) | 4.41 (4.03 - 4.70) | 4.40 (4.05 - 4.69) | 0.879 |
| IL-18BP | 6.73 (6.53 - 6.99) | 6.68 (6.44 - 6.95) | 6.69 (6.45 - 6.96) | 0.197 |

| | | | | |
|---|---|---|---|---|
| IL-1RT1 | 6.90 (6.74 - 7.12) | 6.92 (6.68 - 7.11) | 6.92 (6.68 - 7.11) | 0.697 |
| IL-1RT2 | 5.60 (5.44 - 5.80) | 5.63 (5.41 - 5.85) | 5.63 (5.41 - 5.84) | 0.448 |
| IL2-RA | 4.75 (4.51 - 5.14) | 4.66 (4.332 - 4.93) | 4.66 (4.33 - 4.92) | 0.054 |
| IL-6RA | 12.82 (12.50 - 13.05) | 12.85 (12.50 - 13.13) | 12.84 (12.49 - 13.12) | 0.634 |
| ITGB2 | 6.42 (6.12 - 6.72) | 6.35 (6.047 - 6.66) | 6.35 (6.05 - 6.66) | 0.250 |
| JAM-A | 6.82 (6.15 - 7.77) | 6.95 (6.11 - 7.92) | 6.95 (6.11 - 7.92) | 0.738 |
| KLK6 | 6.16 (5.89 - 6.40) | 6.11 (5.84 - 6.33) | 6.11 (5.86 - 6.34) | 0.250 |
| LDL receptor | 5.42 (5.01 - 5.84) | 5.52 (5.10 - 5.90) | 5.52 (5.10 - 5.90) | 0.385 |
| LTBR | 4.685 (4.38 - 4.98) | 4.68 (4.40 - 4.91) | 4.68 (4.40 - 4.92) | 0.683 |
| MB | 7.36 (7.04 - 7.68) | 7.23 (6.82 - 7.60) | 7.23 (6.82 - 7.60) | 0.060 |
| MCP-1 | 4.42 (4.15 - 4.63) | 4.44 (4.20 - 4.65) | 4.44 (4.20 - 4.65) | 0.455 |
| MEPE | 6.24 (5.86 - 6.55) | 6.15 (5.88 - 6.45) | 6.16 (5.87 - 6.46) | 0.429 |
| MMP-2 | 4.58 (4.34 - 4.80) | 4.54 (4.27 - 4.79) | 4.56 (4.29 - 4.79) | 0.232 |
| MMP-3 | 7.35 (6.82 - 7.66) | 7.05 (6.58 - 7.50) | 7.08 (6.59 - 7.54) | 0.042 |
| MMP-9 | 4.91 (4.45 - 5.30) | 4.86 (4.27 - 5.48) | 4.86 (4.27 - 5.48) | 0.668 |
| MPO | 4.15 (3.93 - 4.56) | 4.078 (3.83 - 4.37) | 4.078 (3.83 - 4.37) | 0.075 |
| Notch 3 | 5.32 (4.88 - 5.65) | 5.30 (4.95 - 5.62) | 5.30 (4.95 - 5.62) | 0.926 |
| NT-proBNP | 5.65 (4.75 - 6.41) | 4.94 (4.02 - 5.69) | 4.99 (4.09 - 5.78) | <0.001 |
| OPG | 4.570 (4.21 - 4.77) | 4.50 (4.20 - 4.74) | 4.50 (4.20 - 4.74) | 0.488 |
| OPN | 7.00 (6.49 - 7.33) | 6.82 (6.50 - 7.17) | 6.82 (6.50 - 7.17) | 0.211 |
| PAI | 5.70 (5.19 - 6.29) | 5.78 (5.21 - 6.43) | 5.77 (5.20 - 6.41) | 0.714 |
| PCSK9 | 3.11 (2.96 - 3.36) | 3.07 (2.81 - 3.38) | 3.07 (2.81 - 3.38) | 0.214 |
| PDGF subunit A | 4.48 (4.00 - 4.89) | 4.46 (3.87 - 5.17) | 4.46 (3.87 - 5.13) | 0.718 |
| PECAM-1 | 5.76 (5.37 - 6.44) | 5.86 (5.33 - 6.46) | 5.86 (5.33 - 6.46) | 0.978 |
| PGLYRP1 | 8.43 (8.12 - 8.72) | 8.20 (7.90 - 8.55) | 8.20 (7.90 - 8.55) | <0.001 |
| PI3 | 4.59 (4.29 - 4.89) | 4.39 (4.00 - 4.80) | 4.39 (4.00 - 4.80) | 0.011 |
| PLC | 7.35 (7.19 - 7.59) | 7.30 (7.11 - 7.53) | 7.30 (7.11 - 7.53) | 0.080 |
| PON3 | 5.69 (5.28 - 6.27) | 6.01 (5.53 - 6.47) | 6.01 (5.53 - 6.47) | 0.004 |
| PRTN3 | 5.62 (5.41 - 6.15) | 5.50 (5.20 - 5.87) | 5.50 (5.20 - 5.87) | 0.019 |
| PSP-D | 3.48 (2.99 - 3.85) | 3.29 (2.81 - 3.80) | 3.29 (2.82 - 3.80) | 0.142 |
| RARRES2 | 12.19 (11.97 - 12.44) | 12.26 (12.01 - 12.44) | 12.26 (12.01 - 12.44) | 0.477 |
| RETN | 7.03 (6.75 - 7.42) | 6.876 (6.60 - 7.22) | 6.88 (6.60 - 7.22) | 0.013 |
| SCGB3A2 | 3.19 (2.80 - 3.72) | 3.15 (2.67 - 3.63) | 3.15 (2.67 - 3.63) | 0.756 |
| SELE | 13.30 (12.95 - 13.78) | 13.23 (12.77 - 13.59) | 13.24 (12.78 - 13.59) | 0.324 |
| SELP | 11.11 (10.61 - 11.76) | 11.10 (10.56 - 11.76) | 11.10 (10.56 - 11.76) | 0.799 |
| SHPS-1 | 3.84 (3.63 - 4.06) | 3.87 (3.66 - 4.12) | 3.87 (3.65 - 4.12) | 0.541 |
| SPON1 | 1.21 (0.99 - 1.39) | 1.15 (0.89 - 1.38) | 1.146 (0.89 - 1.38) | 0.152 |
| ST2 | 4.97 (4.58 - 5.26) | 4.94 (4.58 - 5.25) | 4.94 (4.58 - 5.25) | 0.888 |
| TFF3 | 6.00 (5.76 - 6.25) | 5.85 (5.589 - 6.08) | 5.85 (5.58 - 6.08) | 0.002 |
| TFPI | 10.16 (9.96 - 10.44) | 10.33 (10.09 - 10.55) | 10.29 (10.08 - 10.54) | 0.012 |
| TIMP4 | 4.25 (4.03 - 4.55) | 4.17 (3.90 - 4.54) | 4.20 (3.91 - 4.54) | 0.248 |
| TLT-2 | 5.40 (5.14 - 5.70) | 5.44 (5.12 - 5.74) | 5.44 (5.13 - 5.74) | 0.921 |
| TNF-R1 | 7.08 (6.78 - 7.32) | 6.91 (6.67 - 7.16) | 6.91 (6.67 - 7.16) | 0.021 |

Supplemental material

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*Heart*

| | | | | |
|---|---|---|---|---|
| TNF-R2 | 5.87 (5.56 - 6.11) | 5.68 (5.41 - 5.96) | 5.68 (5.41 - 5.96) | 0.005 |
| TNFRSF10C | 7.01 (6.65 - 7.38) | 6.88 (6.50 - 7.24) | 6.88 (6.50 - 7.24) | 0.036 |
| TNFRSF14 | 5.41 (5.07 - 5.60) | 5.27 (5.012 - 5.52) | 5.27 (5.01 - 5.52) | 0.204 |
| TNFSF13B | 7.595 (7.35 - 7.88) | 7.58 (7.34 - 7.83) | 7.58 (7.34 - 7.83) | 0.820 |
| t-PA | 7.77 (7.40 - 8.36) | 7.84 (7.26 - 8.74) | 7.84 (7.26 - 8.74) | 0.790 |
| TR | 5.54 (5.02 - 5.80) | 5.29 (4.88 - 5.74) | 5.29 (4.88 - 5.74) | 0.115 |
| TR-AP | 4.73 (4.46 - 4.97) | 4.81 (4.55 - 5.03) | 4.79 (4.54 - 5.02) | 0.136 |
| uPA | 6.33 (6.07 - 6.59) | 6.30 (6.09 - 6.57) | 6.31 (6.08 - 6.57) | 0.873 |
| U-PAR | 5.91 (5.66 - 6.16) | 5.81 (5.55 - 6.05) | 5.81 (5.55 - 6.05) | 0.061 |
| vWF | 7.85 (7.05 - 9.10) | 7.91 (7.05 - 9.09) | 7.91 (7.05 - 9.09) | 0.965 |

Data is presented in a log2 scale in median (interquartile range).

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**Supplementary Table S6. Coagulation markers at baseline**

| Coagulation markers | Total (N=417) |
| --- | --- |
| Factor XIIa:C1inh (pM) | 862.64 (747.28- 989.81) |
| Factor XIIa:antithrombin (pM) | 11.28 (11.28-36.06) |
| Plasma Kallikrein:C1inh (nM) | 0.30 (0.3-1.45) |
| Factor XIa:C1inh (pM) | 72.04 (72.04-197.22) |
| Factor XIa:AT (pM) | 7.90 (7.90-7.90) |
| Factor XIa:a1AT (pM) | 56.17 (56.17-92.04) |
| Factor Xa:AT (pM) | 421.62 (348.16- 497.15) |
| Factor IXa:AT (pM) | 170.20 (170.20- 170.20) |
| Thrombin:AT (ug/L) | 2.04 (2.04-3.54) |

Data is presented in median (interquartile range). AT= antithrombin; a1AT= alpha-1-antitrypsin; C1inh=C1-Esterase inhibitor; nM=nanomolar; pM=picomolar

**Supplementary Table S7. Age and sex adjusted of clinical factors related to AF progression**

| | OR | 95% CI | *P*-value |
|---|---|---|---|
| **Female sex** | 0.48 | 0.25-0.91 | 0.024 |
| **CHA$_2$DS$_2$-VASc score >1** | 3.73 | 1.40-9.95 | 0.009 |
| **Heart failure with reduced ejection fraction** | 4.31 | 1.12-16.58 | 0.034 |
| **Plaques >3** | 5.54 | 1.59-19.36 | 0.008 |
| **Peripheral artery disease** | 11.98 | 1.05-136.78 | 0.046 |
| **Waist circumference** (per SD) | 1.46 | 1.06-2.02 | 0.022 |
| **PR interval** (per SD) | 1.45 | 1.10-1.92 | 0.009 |
| **Left atrial contractile function** (per SD) | 0.60 | 0.39-0.92 | 0.019 |
| **Left atrium end diastolic volume** (per SD) | 1.46 | 1.08-1.97 | 0.014 |
| **Left atrium end diastolic volume indexed for BSA** (per SD) | 1.44 | 1.07-1.95 | 0.017 |
| **Right atrium end systolic volume** (per SD) | 1.53 | 1.05-2.23 | 0.026 |
| **Right atrium end systolic volume indexed for BSA** (per SD) | 1.44 | 1.01-2.04 | 0.044 |

Logistic regression adjusted for age and sex. BSA= body surface area; CI=confidence interval; OR=odds ratio. CHA$_2$DS$_2$-VASc score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A$_2$=age ≥75 years; D=diabetes mellitus; S$_2$=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc=sex category (female sex).

**Supplementary Table S8. Age and sex adjusted analysis including biomarkers**

| | OR | 95% CI | *P*-value |
|---|---|---|---|
| **Female sex** | 0.48 | 0.25-0.91 | 0.024 |
| **CHA$_2$DS$_2$-VASc score >1** | 3.73 | 1.40-9.95 | 0.009 |
| **Heart failure with reduced ejection fraction** | 4.31 | 1.12-16.58 | 0.034 |
| **Plaques >3** | 5.54 | 1.59-19.36 | 0.008 |
| **Peripheral artery disease** | 11.98 | 1.05-136.78 | 0.046 |
| **Waist circumference** (per SD) | 1.46 | 1.06-2.02 | 0.022 |
| **PR interval** (per SD) | 1.45 | 1.10-1.92 | 0.009 |
| **Left atrial contractile function** (per SD) | 0.60 | 0.39-0.92 | 0.019 |
| **Left atrial end diastolic volume** (per SD) | 1.46 | 1.08-1.97 | 0.014 |
| **Left atrium end diastolic volume indexed for BSA** (per SD) | 1.44 | 1.07-1.95 | 0.017 |
| **Right atrium end systolic volume** (per SD) | 1.53 | 1.05-2.23 | 0.026 |
| **Right atrium end systolic volume indexed for BSA**(per SD) | 1.44 | 1.01-2.04 | 0.044 |
| **CTSD** (per SD) | 1.32 | 1.01-1.73 | 0.043 |
| **FABP4** (per SD) | 1.47 | 1.06-2.05 | 0.021 |
| **NTproBNP** (per SD) | 2.05 | 1.43-2.94 | <0.001 |
| **PCSK9** (per SD) | 1.37 | 1.03-1.81 | 0.030 |
| **PGLYRP1**(per SD) | 1.44 | 1.09-1.91 | 0.011 |
| **PON3** (per SD) | 0.72 | 0.54-0.96 | 0.027 |
| **PRTN3** (per SD) | 1.29 | 1.00-1.66 | 0.046 |
| **RETN** (per SD) | 1.34 | 1.01-1.76 | 0.041 |
| **TFPI** (per SD) | 0.72 | 0.53-0.97 | 0.030 |
| **TNF-R2** (per SD) | 1.49 | 1.11-2.01 | 0.009 |
| **TNFRSF10C** (per SD) | 1.43 | 1.03-1.98 | 0.033 |
| **Factor XIIa:antithrombin** *(> median)* | 0.39 | 0.17-0.91 | 0.030 |

| | | | |
|---|---|---|---|
| **Factor XIIa:C1-esterase inhibitor** *(> median)* | 0.38 | 0.20-0.75 | 0.005 |

Logistic regression adjusted for age and sex, with imputation. BSA= body surface area; CI=confidence interval; CTSD=capthesin D; FABP4=fatty acid binding protein 4; NTproBNP=N-terminal pro-brain natriuretic peptide; OR=odds ratio; PCSK9= Proprotein convertase subtilisin/kexin type 9; PGLYRP1= peptidoglycan recognition protein 1; PON3= paraoxonase 3; PRTN3=myeloblastin; RETN=resistin; TFPI= tissue factor pathway inhibitor; TNF-R2=tumor necrosis factor receptor 2; TNFRSF10C=tumor necrosis factor receptor superfamily member 10C. $CHA_2DS_2$-VASc score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; $A_2$=age ≥75 years; D=diabetes mellitus; $S_2$=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc=sex category (female sex).