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Incidence and predictors of atrial fibrillation episodes as detected by implantable loop recorder in patients at risk
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ABSTRACT

Background: Recent studies have suggested a high prevalence of subclinical atrial fibrillation (AF) in various patient populations, and interest in AF screening has increased. However, knowledge about episode-duration is scarce, and risk factors for short or long subclinical AF episodes have yet to be recognized.

Aims: To assess AF by long-term continuous screening, and to investigate predictors of episodes lasting ≥6 minutes, ≥5.5 hours or ≥24 hours, respectively.

Methods: A total of 597 patients aged ≥70 years and diagnosed with ≥1 of hypertension, diabetes, previous stroke, or heart failure, were recruited from the general population to receive implantable loop recorder with remote monitoring. Exclusion criteria included history of AF or cardiac implantable electronic device. AF episodes were adjudicated by senior cardiologists.

Results: During 40 [37;42] months of continuous monitoring, AF was detected in 209 (35%) of the patients. The cumulative incidences at 3 years were 33.8 (30.2-37.8), 16.1 (13.4-19.4), and 5.7 (4.1-7.9) % for AF episodes lasting ≥6 minutes, ≥5.5 hours and ≥24 hours, respectively. Slower resting sinus rate and higher body mass index, NT-proBNP, and troponin T at baseline were independently associated with AF detection. Addition of these markers to a model of sex, age, and comorbidities improved prediction of AF episodes ≥24 hours (time-dependent area under the receiver operating characteristic curve 79% vs. 65%, p=0.037).

Conclusion: A considerable burden of previously unknown AF was detected when long-term monitoring was applied in at-risk patients. Biomarkers were associated with AF incidence and improved prediction of long AF episodes.

Keywords: Atrial fibrillation; Implantable loop recorder; Remote monitoring; Screening; Risk factors

Highlights

- 35% of at-risk patients had new-onset AF during long-term continuous screening
- Episodes lasting ≥5.5 and ≥24 hours were seen in 16 and 6 %, respectively
- A model of sex, age, and comorbidities poorly identified participants at risk of AF
- BMI, heart rate, NT-proBNP, and troponin T improved prediction of long AF episodes
- These biomarkers could be used to select patients for screening

INTRODUCTION

Ischemic stroke is an increasing health problem world-wide.[1] At least 20% of ischemic strokes are attributable to atrial fibrillation (AF),[2] and another 30% of ischemic strokes are cryptogenic, possibly related to undiagnosed AF.[3] Oral anticoagulation (OAC) is well established as an effective treatment for stroke prevention in at-risk patients diagnosed with AF.[4] However, as AF is often asymptomatic, many patients remain undiagnosed. Approximately 30% of a general population of pacemaker or cardioverter defibrillator patients, will have new-onset AF during 2-3 years following implantation.[3,5] Although the majority of these AF episodes are short-lasting and asymptomatic, the *ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial* (ASSERT) and other studies have found that such AF episodes are associated with risk of stroke.[5,6] Since the ASSERT was published, screening for AF has received increasing attention.[7] Still, the bulk of our knowledge about AF and stroke risk is derived from patients with symptomatic or rather long-lasting AF episodes, and mass screening cannot yet be recommended.[4,7] One problem is that an appropriate screening population has yet to be recognized. A post-hoc analysis of ASSERT found that the increased risk of stroke was driven by patients with AF episodes lasting >24 hours,[8] and a recent consensus document suggested the compromise of OAC in patients with device-detected AF episodes lasting ≥5.5 hours.[9] Similarly, recent data from the Veterans Health Administration showed increasing rates of stroke with increasing episode duration.[10] Predictors for such AF episodes remain unknown.

The ongoing LOOP study randomizes individuals with CHA_2DS_2VASc score of ≥2 to AF screening with implantable loop recorder (ILR) screening or control.[11] The study's power calculation assumes that 30% of participants receiving ILR will have AF detected, and that stroke can be reduced by OAC in these patients. The primary endpoint will be published according to protocol, when the required number of events is reached.

The current substudy had two aims: First, we sought to assess incidence of AF using very long-term continuous monitoring in a large general population at risk. In this regard, we wished to validate if the AF detection rate among the earliest included participants in the LOOP study matched the study's power calculation. Second, we sought to investigate predictors of AF episodes of shorter and longer duration.

METHODS

Study design

The LOOP study is an ongoing, investigator-initiated, multicenter controlled trial. A detailed description of the study design has been published previously.[11] In brief, participants from the general population residing in 3 of the 5 administrative regions of Denmark are identified by administrative registries and receive a letter of invitation from one of the four study centers. Eligible subjects are ≥70 years old and have ≥1 of the following stroke risk factors; hypertension, diabetes, heart failure or previous stroke. Exclusion criteria include OAC or contraindication to OAC and any history of AF. At the initial screening visit, study eligibility is confirmed, and a baseline evaluation is performed including detailed medical history, height and weight, and blood pressure and sinus rate measurement after 10 minutes of supine rest. Prevalent AF is ruled out by 12-lead ECG. Blood is sampled for measurement of creatinine, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), and troponin T. In the smallest center, NT-proBNP was not routinely measured for logistic reasons, and in the two smallest centers, troponin I was measured instead of troponin T. Subjects are then randomized in a 1:3 ratio to receive ILR (Reveal LINQ™, Medtronic) with continuous electrocardiographic monitoring or control.

The programmable parameters of the ILRs are set to the standard for detection of "suspected AF" according to manufacturer's recommendations: AF detection "less sensitive", ectopy rejection "nominal", blank after sense 150 ms, sensing threshold decay delay 150 ms, and R-wave sensitivity

0.035 mV, though in participants with R-wave amplitude below 0.3 mV even after re-positioning, sensitivity would be re-programmed at the discretion of the implanting physician, and in participants with false AF alerts due to premature beats during follow-up, ectopy rejection would be re-programmed to "aggressive" on the discretion of the monitoring physician. All participants receiving ILR are followed by automated remote transmissions to an online database, where any new arrhythmia episodes are reviewed daily by an experienced medical doctor. AF adjudication is obtained by at least two senior cardiologists independently reviewing new-onset AF episodes lasting ≥6 minutes. The length of the rhythm strip used for adjudication is 2 minutes for all AF episodes. When AF is confirmed, OAC is initiated, and monitoring continues for further detection of longer AF episodes or other arrhythmias as adjudicated by minimum one experienced medical doctor. Patients are questioned about AF related symptoms at the index episode.

The heart rhythm monitoring continues until end of battery-life, study withdrawal or death, but is expected to last minimum 3 years according to the ILR manufacturer's projected battery longevity. In the current analysis, all LOOP study participants receiving ILR until June 1st 2015 were included, and data acquisition and AF adjudication concluded on December 1st 2018. Thus, the time-span from implantation to last day of possible interrogation was minimum 42 months.

The primary endpoint of the current analysis was time to first adjudicated AF episode lasting ≥6 minutes, while time to first AF episode lasting ≥30 minutes, ≥1 hour, ≥5.5 hours, ≥12 hours, and ≥24 hours were secondary endpoints. In this way, participants reaching the endpoint of AF lasting 6 minutes at one day were subsequently followed for AF episodes of longer durations, while participants who debuted with AF lasting 24 hours at one day also reached the endpoints of AF ≥12 hours, ≥5.5 hours, ≥1 hour etc. on that day. Participants were censored on the date of the last ILR interrogation.

All study participants gave written informed consent. A centralized, online case report file system was used for storage of study data. The LOOP study was approved by the Ethics Committee of the

Capital Region of Denmark (H-4-2013-025) and the Danish Data Protection Agency (2007-58-0015). The trial is registered at ClinicalTrials.gov (NCT02036450).

Statistics

Continuous variables were presented as means and standard deviations (sd) for normally distributed variables, and medians and quartiles 1 and 3 [Q1;Q3] for non-normally distributed variables, while categorical variables were presented as frequencies and corresponding percentages. Any prevalences, cumulative incidences, or rates were presented as percentage (95% confidence interval (CI)) and ratios as ratio (95% CI).

A power calculation was conducted for analyses of association between baseline variables and time to event. Assuming that 30% of the population would reach the primary end-point during follow-up, inclusion of 600 participants would yield 80% power to detect a hazard ratio (HR) of 1.5 or higher for the half of the population with the predictor (e.g. biomarker above median) compared to without the predictor (e.g. biomarker below median), with 2-sided equality and 5% risk of type I error.

Incidence rates and exact confidence intervals were derived from a Poisson distribution. To account for the competing risk of death, the cumulative incidences were estimated, plotted and group-wise compared in a multi-state fashion.[12]

To assess potential predictors of AF, association analyses were performed. Baseline variables were analyzed with univariate cause-specific Cox regression, and after considering clinical and statistical significance ($p<0.1$) in the univariate analyses, multivariable Cox regression models were constructed to investigate the association between baseline variables and AF episodes lasting ≥6 minutes, ≥5.5 hours, and ≥24 hours independently of sex, age, and comorbidities (heart failure, hypertension, diabetes, previous stroke, cardiac valvular disease, and previous acute myocardial infarction and/or coronary arterial bypass graft surgery (CABG)), constituting a basic model. Schoenfeld and Martingale residuals were assessed to validate the proportional hazards and linearity assumption, respectively.

To comply with these assumptions for valid Cox regression, CHA_2DS_2VASc and $CHADS_2$ score were grouped as ≤3 and >3, and ≤1 and >1, respectively. NT-proBNP and hs-CRP were logaritmized to normalize the distribution.

Additionally, to evaluate the added discriminative value over the basic model from the physical and biochemical markers identified in the association studies as possible predictors, risk prediction analyses were conducted for the endpoints of AF episodes lasting ≥6 minutes, ≥5.5 hours, and ≥24 hours. The 42-months risk of AF was predicted using cause-specific Cox regression. Receiver operating characteristics (ROC) curves were drawn and the time-dependent area under the ROC curve (AUC) was calculated for each model. Differences in AUC between models were calculated, while Brier scores were used to assess model calibration.[13] Furthermore, to extrapolate the predictive value of the models from the study population, the risk prediction analyses were repeated after splitting the dataset in training and test sets. The training set comprised 2/3 of the population, and analyses were repeated in 1001 splits at random. The split corresponding to the median AUC of the models without the predictors was used to analyze the difference between the basic model and the model with the predictors. All association and risk prediction was performed as complete-case analyses, meaning that missing variables in the proposed model were dropped.

Lastly, to further evaluate the relationship between continuous variables and AF episodes ≥6 minutes, a sliding-windows approach was used to plot the incidence rate against the median value of the variable in subgroups comprising 10% of the study population with sequentially overlapping steps the size of 2.5% of the population.[14]

For supplementary analyses, in the association analyses instead of adjusting for sex, age and all individual comorbidities, CHA_2DS_2VASc and $CHADS_2$ score, respectively, were entered into a model adjusting for each of the following baseline variables: body mass index (BMI), resting sinus rate, NT-proBNP and troponin T.

Analyses were performed using the R software, https://www.R-project.org/, R Core Team (2017), including the *survival*, *cmprsk*, *epiR*, *evobiR*, *timereg, pec*, *riskRegression*, and *ggplot2* packages.

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RESULTS

Population and follow-up

A total of 597 study participants received ILR from February 26th 2014 until June 1st 2015 and were included in the current analysis. Mean age was 76 (±4) years, 57% were men, and mean CHA_2DS_2VASc score was 3.9 (±1.2) (Table 1). NT-proBNP was missing in 65, troponin T in 198, blood pressure in 1, resting sinus rate in 3, hs-CRP in 1, and creatinine in 2 participants.

Time from device implantation to last interrogation was median 40 [37;42] months, and 81% were monitored for minimum 3 years, yielding a total of 1897 person-years of continuous monitoring. During this time 30 deaths occurred, and the mortality rate was 1.6 (1.1-2.2) per 100 person-years.

AF detection rate

The primary endpoint of an adjudicated AF episode lasting ≥6 minutes was reached in 209 participants, corresponding to a prevalence of 35% during the entire follow-up period. A total of 22

patients (11% of all with AF) reported symptoms at the index episode. The cumulative incidences at 3 years were 33.8 (30.2-37.8), 16.1 (13.4-19.4), and 5.7 (4.1-7.9)% for AF episodes lasting ≥6 minutes, ≥5.5 hours and ≥24 hours, respectively (Figure 1).

The incidence rate of AF ≥6 minutes was 14.5 (12.7-16.6) per 100 person-years, and most incident cases of short episodes were detected during the first year after implantation, while the incidence rate was more stable for longer AF episodes (Supplementary Figure 1). Time to detection was median 5.5 [1.4;17], 14 [4.8;26], and 20 [6.4;30] months for the first AF episode lasting ≥6 minutes, ≥5.5 hours and ≥24 hours, respectively (Figure 2).

Association analyses and risk prediction

Table 1 shows baseline characteristics of the study population according to AF detection. Univariate Cox regressions of association between baseline variables and time to AF detection are shown in Supplementary Table 2, and cumulative incidence of AF of different durations by groups of baseline markers are shown in Supplementary Figure 2. After multivariate adjustment higher age, NT-proBNP, troponin T, hs-CRP, and slower resting sinus rate were independently associated with detection of time to AF ≥6 minutes (Figure 3). For longer episodes, also higher BMI and previous CABG were associated with AF, whereas age and hs-CRP did not reach statistical significance.

Supplementary Table 1 presents baseline characteristics according to whether any markers required for risk prediction analyses were missing. There were no relevant differences among patients included in risk prediction analyses or not. In the risk prediction analyses, the basic model of sex, age, and comorbidities had poor discriminative value for screen-detected AF, while addition of baseline BMI, resting sinus rate, NT-proBNP and troponin T significantly increased AUC for AF episodes ≥24 hours, 79% vs. 65%, p=0.037 (Figure 4). This was also true after the data was split in training and test sets (Supplementary Table 3). For all models, Brier score was lower when the markers where included.

The sliding-windows approach showed decreased incidence rate of AF episodes ≥24 hours in participants with BMI <26 kg/m^2, resting sinus rate >62 beats per minute, NT-proBNP <12 pmol/L, troponin T <12 ng/L (Figure 5). Comparable results were seen for shorter episodes, though not as discernible.

In the supplementary Cox regression models adjusted for markers of BMI, resting sinus rate, NT-proBNP, and troponin T, CHA_2DS_2VASc score group was not associated with AF of any duration, and $CHADS_2$ score >1 was only associated with AF ≥6 minutes (HR 1.59 (1.02-2.5)).

DISCUSSION

The present study is the first to investigate AF in a large general population at risk using long-term monitoring corresponding to the lifetime of a modern ILR device. First, we found that AF was detected in 35% of participants, which is in agreement with the assumptions of the LOOP study protocol. Second, approximately 16% of all participants had episodes exceeding the debatable duration-threshold for OAC in device-detected AF,[9] and 50% of these episodes were detected after more than 14 months of monitoring. Third, slower resting sinus rate and higher BMI, NT-proBNP, and troponin T at baseline were independently associated with AF detection, and addition of these markers to a model of sex, age, and comorbidities significantly improved prediction of AF episodes ≥24 hours.

ILR screening studies

The low frequency of symptoms at AF debut (11%) underlines that we have indeed investigated a subclinical arrhythmia. The detection rates in the current study can be compared to findings in recent ILR screening studies.[3,14–16] However, these studies were not powered to investigate predictors of AF. The CRYSTAL-AF study monitored 221 patients with recent cryptogenic stroke or transient ischemic attack and found AF in 12% at 12 months.[3] The ASSERT-II study recruited 256 patients with risk

factors from cardiology and neurology clinics and monitored them during approximately 12 months in which 31% reached the endpoint of AF episodes lasting ≥5 minutes.[14] Age and left atrial diameter were associated with time to AF, while higher blood pressure was inversely associated with AF detection, possibly indicating selection bias. The PREDATE AF study found AF ≥6 minutes in 55 of 245 patients (22%) during approximately 15 months,[15] while the REVEAL-AF study monitored 326 patients for at least 18 months at which an estimated cumulative rate of 29% was reported.[16]

The lower rate of AF detection in CRYSTAL-AF compared to ASSERT-II, PREDATE AF, REVEAL-AF, and the current study, respectively, could be due to lower age; mean 61.5 years compared to 73.9, 74.3, 71.6, and 76.4 years, respectively. Furthermore, all patients in CRYSTAL-AF were monitored with a device with inferior sensitivity compared to the devices used in most patients in the other studies, increasing the risk of false-negatives.[17–19]

While the participants included in the LOOP study and the ASSERT-II, PREDATE AF, and REVEAL-AF were rather similar in terms of conventional risk factors (CHA_2DS_2VASc score was mean 4.1, 4.6, and 4.4 in ASSERT-II, PREDATE AF, and REVEAL-AF, respectively), the current study is unique in having recruited participants from home as opposed to a clinical setting, which arguably decreases selection bias. Secondly, the current study provides a larger sample size and longer follow-up, yielding enough person-years to investigate AF predictors. Keeping in mind that detection of longer episodes required very long-term monitoring, the current study enables investigation of AF burden of different durations opposed to short AF episodes in general. The outcomes of AF episode duration were chosen to reflect the controversies in the current understanding of duration-threshold for increased stroke risk in subclinical AF; "any" AF (≥6 minutes),[6] the duration in the European Heart Rhythm Association consensus statement (≥5.5 hours),[9] or the duration that upheld the increased risk in ASSERT (≥24 hours).[8]

Predictors of AF episodes of different durations

To the best of our knowledge, the current study is the first to demonstrate an association between troponin and screen-detected AF, while a recent study inferred that NT-proBNP and BMI are useful in selection of patients for short-term screening for prevalent AF.[20] Both NT-proBNP, troponin, and BMI are established markers in clinically diagnosed AF.[21–23] The inverse association between incident AF and resting sinus rate at baseline in our population can be compared to epidemiological findings of higher risk of clinical AF in both slower and faster sinus rates.[24] When we modelled resting sinus rate as a categorical variable, participants in the fastest tertile still had significantly lower risk than those with slowest rates, and this was independent of BMI as well as other risk factors. The sliding-windows approach confirmed the inverse relationship (Figure 5). Possible explanations for this finding could be good physical condition, or subclinical sinus node or AV conduction dysfunction leading to relative bradycardia and increased atrial preload in these patients.[25,26] Furthermore, in this elderly population, we did not find an association between height and screen-detected AF, oppositely to what is known from clinical AF.[27]

Of demographic variables, sex was not a risk factor for AF in our study, which is in agreement with recently evaluated risk models for clinical AF.[28] Furthermore, we did find an association between age and AF, though not as strong as what is described in clinical AF.[28] This could be due to the fact that we only included participants ≥70 years of age.

Interestingly, previous CABG was associated with AF episodes lasting ≥24 hours, as 7 of 41 patients (17%) with previous CABG had such episodes during follow-up (Table 1). However, most of the CHA_2DS_2VASc components and medical treatments did not show association with AF (Figure 3 and Supplementary Table 2). Likewise, in agreement with the above described ILR studies, higher CHA_2DS_2VASc score did not by itself predict screen-detected AF. This could be due to the fact that we only included participants with CHA_2DS_2VASc score ≥2, and thus, a possible risk attributed to one CHA_2DS_2VASc component could be clouded by presence of other risk-attributes in participants

without that component. Arguably, instead of predicting AF from traditional risk factors among patients with increased risk of stroke, an important goal would be to identify easily available biomarkers to accompany the traditional risk factors in selection of patients for screening.

We performed risk prediction analyses to evaluate whether the physical and biochemical markers from the association studies improved prediction over a model considering only sex, age, and previous diagnoses. These analyses revealed that this basic model was indeed poor at identifying participants at risk of AF, while addition of NT-proBNP, troponin, BMI, and resting sinus rate improved prediction for episodes lasting ≥24 hours. This holds important implications if the ongoing trials[11,29,30] find that very low AF burden does not merit OAC, and future screening should thus aim at identifying patients with longer AF episodes. Indeed, a relationship between AF burden and stroke risk has been suggested.[8] Our study shows that a consideration of biomarkers could reduce the number needed to screen.

In summary, we have presented findings from a large general population of AF-naïve participants with risk factors for stroke screened during the full life-span of a standard ILR. The data suggests that a considerable AF burden is detected when long-term continuous monitoring is applied, and that physical and biochemical markers can improve prediction of these AF episodes.

Limitations

The current study has several limitations. First, since the LOOP study invited subjects by letter, our results could possibly be affected by healthy user bias, meaning that persons with better health status are more inclined to participate. However, the rates of AF we found were comparable to those in studies of patients with cardiac implantable electronic devices.[5] Second, the ILR device is capable of monitoring for minimum 3 years, and thus all participants receiving ILR in the LOOP study at least 3.5 years before December 2018 were included. This provided a long follow-up duration and sufficient sample size to assess predictors, although increased statistical power would likely have

revealed more variables associated with AF of different durations, and would enable investigation of which individual markers would improve AUC for AF in risk prediction analyses, as opposed to a set of markers. Furthermore, a subset of participants had missing NT-proBNP and Troponin T due to logistic reasons, and analyses including these variables have limited power. In spite of this, the biomarkers did in fact constitute a significant addition to the discriminative value of a basic model in identifying patients with increased risk of long AF episodes. Further studies are needed to confirm biomarker cutoffs in selection of patients to screening.

Our findings rely on the capability of the ILR to detect AF. The algorithm used has been shown to have a sensitivity of approximately 95%, although specificity might be decreased, especially for short episodes.[17,31] Thus, to avoid false positives, a rigorous adjudication regimen was applied. Finally, the current results are limited to a discussion about AF detection and predictors of AF in at-risk patients recruited from the general population, and we cannot yet report on the health benefits of the screening. We anticipate further investigation when the LOOP study has been finalized, including studies of additional risk markers from magnetic resonance imaging for atrial fibrosis and function, echocardiographic measures, genetics and more, along with the main studies of impact on stroke risk and cost-effectiveness in ILR screening for AF.[11]

Conclusion

A considerable burden of previously unknown AF was detected when long-term monitoring was applied in at-risk patients from the general population. Sex, age, and comorbidities had poor discriminative value in prediction of AF in these patients. Markers of BMI, resting sinus rate, NT-proBNP, and troponin T were associated with AF incidence and improved prediction of long AF episodes. These findings may hold important implications for future screening programs.

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CONFLICTS OF INTEREST

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FIGURE LEGENDS

Figure 1

Title: Cumulative incidence of AF episodes

Legend: The figure presents cumulative incidence of AF detection plotted with the Aalen-Johansen method.

Figure 2

Title: Time to detection of AF episodes

Legend: The figure presents boxplots of months from device implantation to AF detection. The vertical lines represent quartile 1, median and quartile 3, while the horizontal line represents the range and the diamond represents the mean.

Figure 3

Title: Association between baseline variables and time to AF after multivariate adjustment

Legend: The figure represents hazard ratios and confidence intervals for the association between baseline markers and time to AF episodes lasting ≥6 minutes, ≥5.5 hours, and ≥24 hours in cause-specific Cox models adjusting for sex, age, and comorbidities (heart failure, hypertension, diabetes, previous stroke, cardiac valvular disease, and previous acute myocardial infarction and/or CABG). The models of age, previous stroke, previous CABG, and BMI included 597 patients, while the models of resting sinus rate, NT-proBNP, troponin T and hs-CRP included 594, 532, 399, and 596 patients, respectively. The CABG model did not include previous acute myocardial infarction. The previous stroke model was unchanged when stroke and/or transient ischemic attack was included instead of stroke alone. The resting sinus rate model further included body mass index, which did not change the estimates, and the results were similar when resting sinus rate was modelled as a categorical variable of tertiles. Finally, the estimates for AF ≥ 6 minutes and 5.5 hours were unchanged when the models of resting sinus rate were applied only to patients not treated with betablockers or cardiac calcium blockers (n=440), while for AF ≥ 24 hours significance was not reached in this strata.

Figure 4

Title: Prediction of AF using the basic model or the model including additional markers

Legend: The figure presents time-dependent receiver operating curves for two models in prediction of AF episodes lasting ≥6 minutes, ≥5.5 hours, and ≥24 hours along with P-values for difference. The *Basic model* is a cause-specific Cox model including sex, age, and comorbidities, while the *Basic model + markers* further included N-terminal pro-brain natriuretic peptide, troponin T, body mass index and resting sinus rate. These analyses were performed in exactly the same population, and due to missing blood biomarker information, the sample comprised a total of 397 patients.

Figure 5

Title: Relationship between baseline markers and incidence rate of AF

Legend: The y-axis presents exact %/year incidence rate (points) and confidence intervals (colored ribbon) for AF episodes lasting ≥6 minutes, ≥5.5 hours, and ≥24 hours in sequentially overlapping subgroups comprising 10% of the population on the x-axis. The curve represents a moving average using local polynomial regression fitting, while the dashed line represents the average incidence rate for the entire population.

Table 1

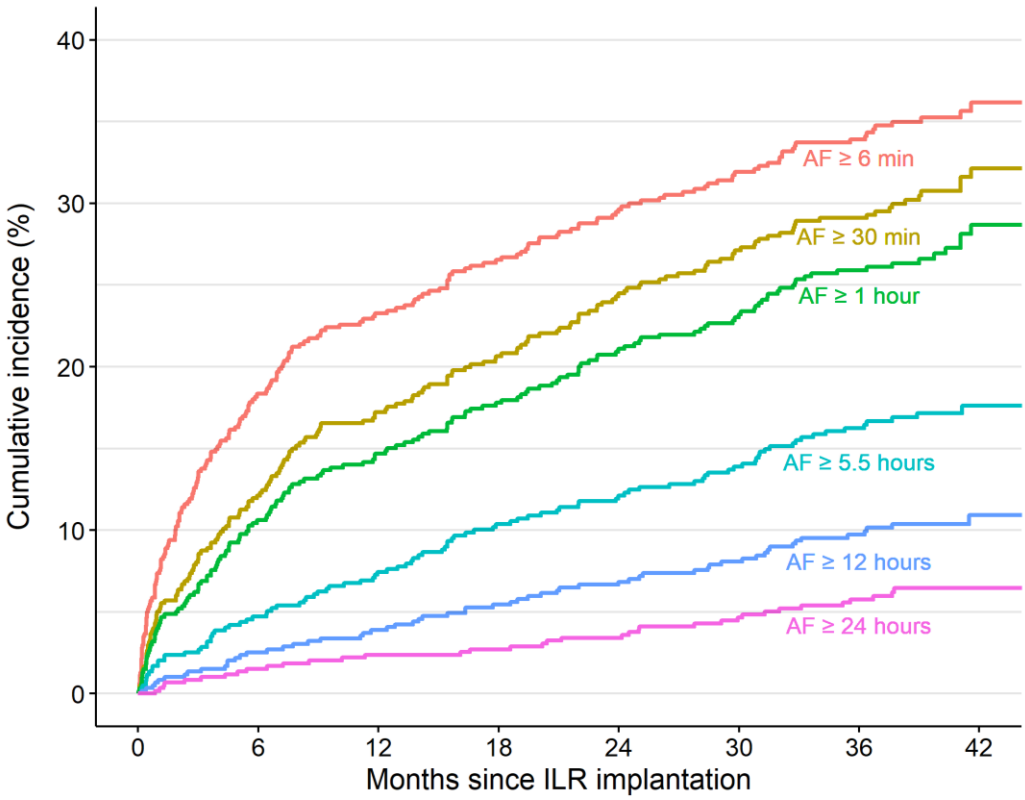
Baseline characteristics for patients without AF and AF episodes of different durations

AF during follow-up n (% of all)	No AF 388 (65)	AF ≥ 6 min 209 (35)	AF ≥ 30 min 180 (30)	AF ≥ 1 hour 159 (27)	AF ≥ 5.5 hours 99 (17)	AF ≥ 12 hours 61 (10)	AF ≥ 24 hours 37 (6)	All 597 (100)
Male sex (%)	218 (56)	123 (59)	105 (58)	91 (57)	63 (64)	42 (69)	25 (68)	341 (57.1)
Age, years (sd)	76.0 (4.0)	77.1 (4.5)	77.0 (4.4)	77.1 (4.6)	77.1 (4.7)	76.8 (4.4)	77.2 (4.6)	76.4 (4.2)
CHA_2DS_2VASc score (sd)	3.9 (1.2)	4.1 (1.2)	4.0 (1.2)	4.1 (1.2)	4.1 (1.2)	4.0 (1.1)	4.0 (1.1)	3.9 (1.2)
$CHADS_2$ score (sd)	2.2 (1.1)	2.4 (1.1)	2.4 (1.1)	2.4 (1.0)	2.5 (1.0)	2.4 (1.0)	2.4 (1.0)	2.3 (1.1)
Heart failure (%)	19 (4.9)	6 (2.9)	5 (2.8)	4 (2.5)	2 (2.0)	2 (3.3)	1 (2.7)	25 (4.2)
Hypertension (%)	350 (90)	190 (91)	165 (92)	146 (92)	90 (91)	56 (92)	34 (92)	540 (90.5)
Diabetes (%)	114 (29)	60 (29)	51 (28)	46 (29)	30 (30)	18 (30)	11 (30)	174 (29.1)
Previous stroke (%)	64 (16)	43 (21)	37 (21)	34 (21)	23 (23)	16 (26)	9 (24)	107 (17.9)
Previous transient ischemic attack, n (%)	46 (11.9)	21 (10.0)	19 (10.6)	16 (10.1)	10 (10.1)	5 (8.2)	3 (8.1)	67 (11.2)
Previous systemic embolism, n (%)	25 (6.4)	17 (8.1)	15 (8.3)	14 (8.8)	10 (10.1)	5 (8.2)	2 (5.4)	42 (7.0)
Previous AMI (%)	38 (9.8)	20 (9.6)	17 (9.4)	16 (10.1)	12 (12.1)	8 (13.1)	5 (13.5)	58 (9.7)
Previous CABG (%)	27 (7.0)	14 (6.7)	14 (7.8)	13 (8.2)	11 (11.1)	9 (14.8)	7 (18.9)	41 (6.9)
Valvular heart disease (%)	13 (3.3)	13 (6.2)	8 (4.4)	6 (3.8)	4 (4.0)	2 (3.3)	1 (2.7)	26 (4.4)
Beta blockers, n (%)	95 (24)	49 (23)	45 (25.0)	41 (25.8)	29 (29.3)	23 (37.7)	15 (40.5)	144 (24.1)
Calcium channel blockers, n (%)	124 (32)	85 (41)	72 (40.0)	63 (39.6)	43 (43.4)	32 (52.5)	17 (45.9)	209 (35.0)
Non-dihydropyridine type, n (%)	5 (1.3)	9 (4.3)	8 (4.4)	6 (3.8)	3 (3.0)	2 (3.3)	0 (0.0)	14 (2.3)
ACEi, ARB, or renin inhibitors, n (%)	235 (61)	121 (58)	105 (58.3)	93 (58.5)	57 (57.6)	35 (57.4)	24 (64.9)	356 (59.6)
Lipid-lowering drugs, n (%)	201 (52)	121 (58)	107 (59.4)	97 (61.0)	65 (65.7)	39 (63.9)	23 (62.2)	322 (53.9)
Diuretics, n (%)	112 (29)	65 (31)	57 (31.7)	52 (32.7)	34 (34.3)	19 (31.1)	12 (32.4)	177 (29.6)
Platelet inhibitors, n (%)	188 (48)	107 (51)	93 (51.7)	84 (52.8)	54 (54.5)	36 (59.0)	23 (62.2)	295 (49.4)
Glucose-lowering drugs, n (%)	98 (25)	51 (24)	45 (25.0)	40 (25.2)	27 (27.3)	17 (27.9)	11 (29.7)	149 (25.0)
Systolic BP, mmHg (sd)	151.9 (19)	151.6 (18)	151.7 (18)	152.2 (18)	151.9 (17)	149.6 (18)	153.4 (17)	151.8 (18.7)
Diastolic BP, mmHg (sd)	85.0 (12)	84.6 (11)	84.7 (11)	84.6 (11)	84.5 (11)	84.1 (11)	86.0 (12)	84.9 (11.6)
Resting sinus rate, bpm (sd)	72.5 (13)	68.8 (11)	68.7 (12)	68.6 (12)	68.0 (12)	68.2 (13)	67.1 (13)	71.2 (12.4)
Height, cm (sd)	170.5 (8.7)	171.3 (8.7)	171.2 (8.8)	171.0 (8.8)	171.6 (8.5)	172.9 (8.6)	172.9 (9.0)	170.8 (8.7)
Body mass index, kg/m^2 (sd)	27.4 (4.4)	27.8 (4.8)	27.6 (4.5)	27.8 (4.6)	28.3 (4.8)	28.4 (4.7)	29.3 (4.9)	27.6 (4.6)
Creatinine, µmol/L (sd)	86.7 (23)	87.9 (24)	88.3 (25)	87.9 (24)	89.8 (24)	92.1 (25)	91.7 (24)	87.1 (23.6)
NT-proBNP, pmol/L [Q1;Q3]	14 [8;26]	20 [12;34]	20 [12;34]	21 [12;34]	21 [12;34]	24 [13;38]	24 [13;44]	16 [9;28]
hs-CRP, mg/L [Q1;Q3]	2 [1;3]	2 [1;4]	2 [1;4]	2 [1;4]	2 [1;4]	2 [1;4]	2 [1;4]	2 [1;4]
Troponin T, ng/L (sd)	13.8 (5.4)	15.8 (7.3)	15.8 (7.9)	15.9 (8.3)	16.4 (8.9)	17.5 (10.4)	19.0 (12.1)	14.6 (6.48)

The table presents baseline characteristics of the study participants according to presence of AF.

Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein.

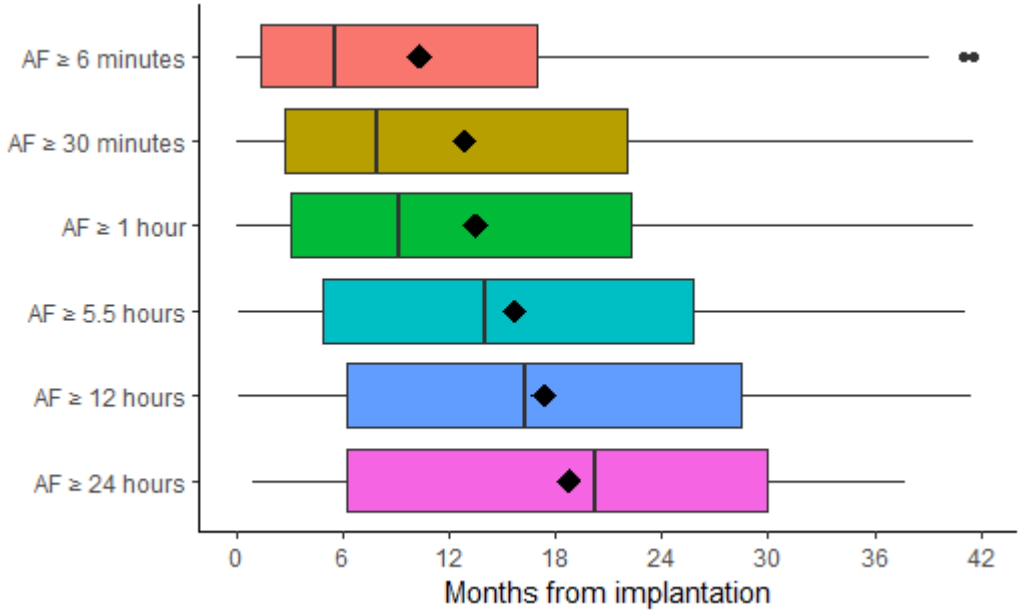
Figure 1 Cumulative incidence of AF episodes



AF duration	No. at risk							
≥ 6 min	597	483	449	427	404	382	326	107
≥ 30 min	597	519	484	460	432	408	348	110
≥ 1 hour	597	528	498	476	451	430	363	115
≥ 5.5 hours	597	562	540	518	501	479	409	129
≥ 12 hours	597	575	561	544	529	510	437	135
≥ 24 hours	597	581	570	560	549	530	459	138

Legend: The figure presents cumulative incidence of AF detection plotted with the Aalen-Johansen method.
Abbreviations: AF, atrial fibrillation; ILR, implantable loop recorder; min, minutes.

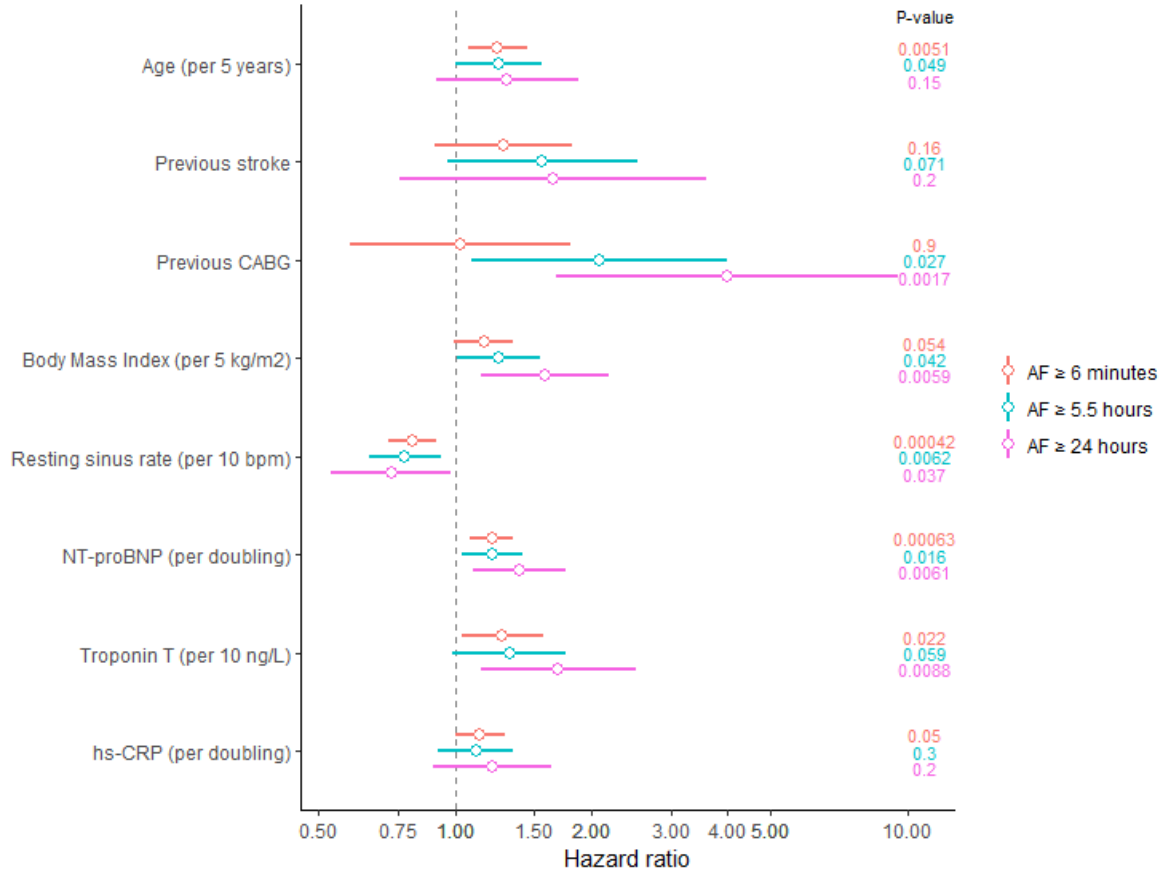
Figure 2 Time to detection of AF episodes



Legend: The figure presents boxplots of months from device implantation to AF detection. The vertical lines represent quartile 1, median and quartile 3, while the horizontal line represents the range and the diamond represents the mean.

Abbreviations: AF, atrial fibrillation.

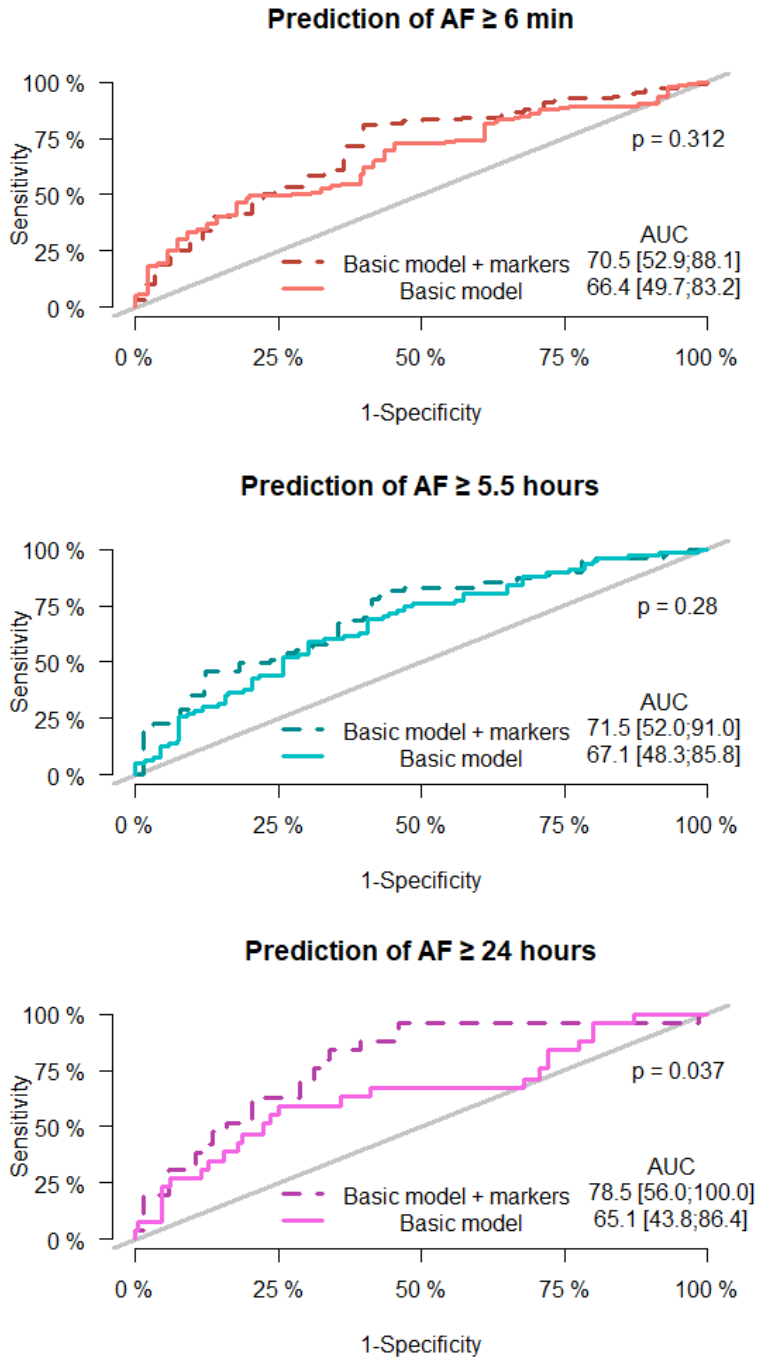
Figure 3 Association between baseline variables and time to AF after multivariate adjustment



Legend: The figure represents hazard ratios and confidence intervals for the association between baseline markers and time to AF episodes lasting ≥6 minutes, ≥5.5 hours, and ≥24 hours in cause-specific Cox models adjusting for sex, age, and comorbidities (heart failure, hypertension, diabetes, previous stroke, cardiac valvular disease, and previous acute myocardial infarction and/or CABG). The models of age, previous stroke, previous CABG, and BMI included 597 patients, while the models of resting sinus rate, NT-proBNP, troponin T and hs-CRP included 594, 532, 399, and 596 patients, respectively. The CABG model did not include previous acute myocardial infarction. The previous stroke model was unchanged when stroke and/or transient ischemic attack was included instead of stroke alone. The resting sinus rate model further included body mass index, which did not change the estimates, and the results were similar when resting sinus rate was modelled as a categorical variable of tertiles. Finally, the estimates for AF ≥6 minutes and ≥5.5 hours were unchanged when the models of resting sinus rate were applied only to patients not treated with betablockers or non-dihydropyridine calcium blockers (n=440), while significance was not reached in this strata for AF ≥24 hours.

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass graft surgery; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

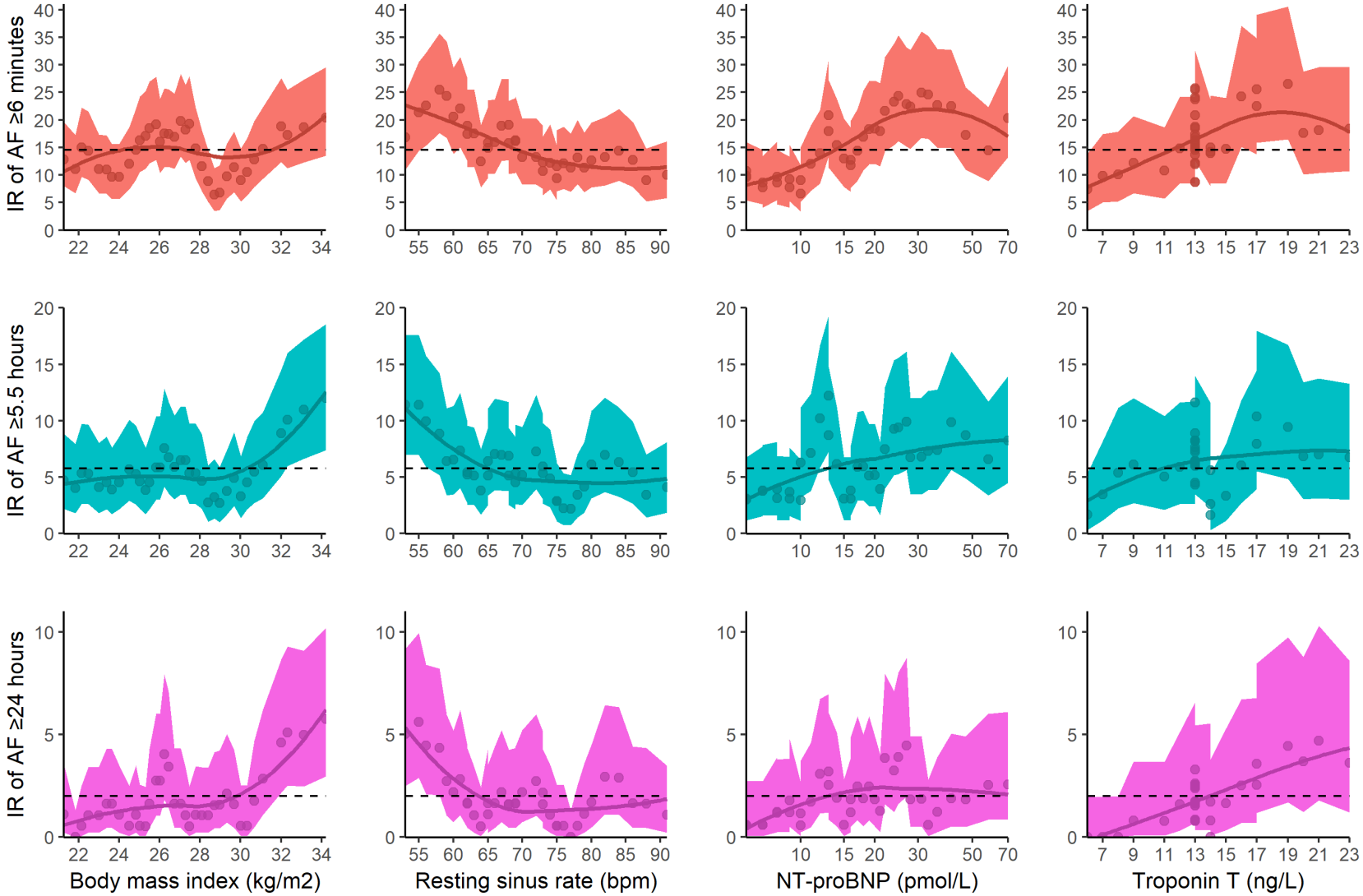
Figure 4 Prediction of AF using the basic model or the model including additional markers



Legend: The figure presents time-dependent receiver operating curves for two models in prediction of AF episodes lasting ≥6 minutes, ≥5.5 hours, and ≥24 hours along with P-values for difference. The *Basic model* is a cause-specific Cox model including sex, age, and comorbidities, while the *Basic model + markers* further included N-terminal pro-brain natriuretic peptide, troponin T, body mass index and resting sinus rate. These analyses were performed in exactly the same population, and due to missing blood biomarker information, the sample comprised a total of 397 patients.

Abbreviations: AF, atrial fibrillation; AUC, area under the receiver operating curve; BMI, body mass index; CABG, coronary artery bypass graft surgery.

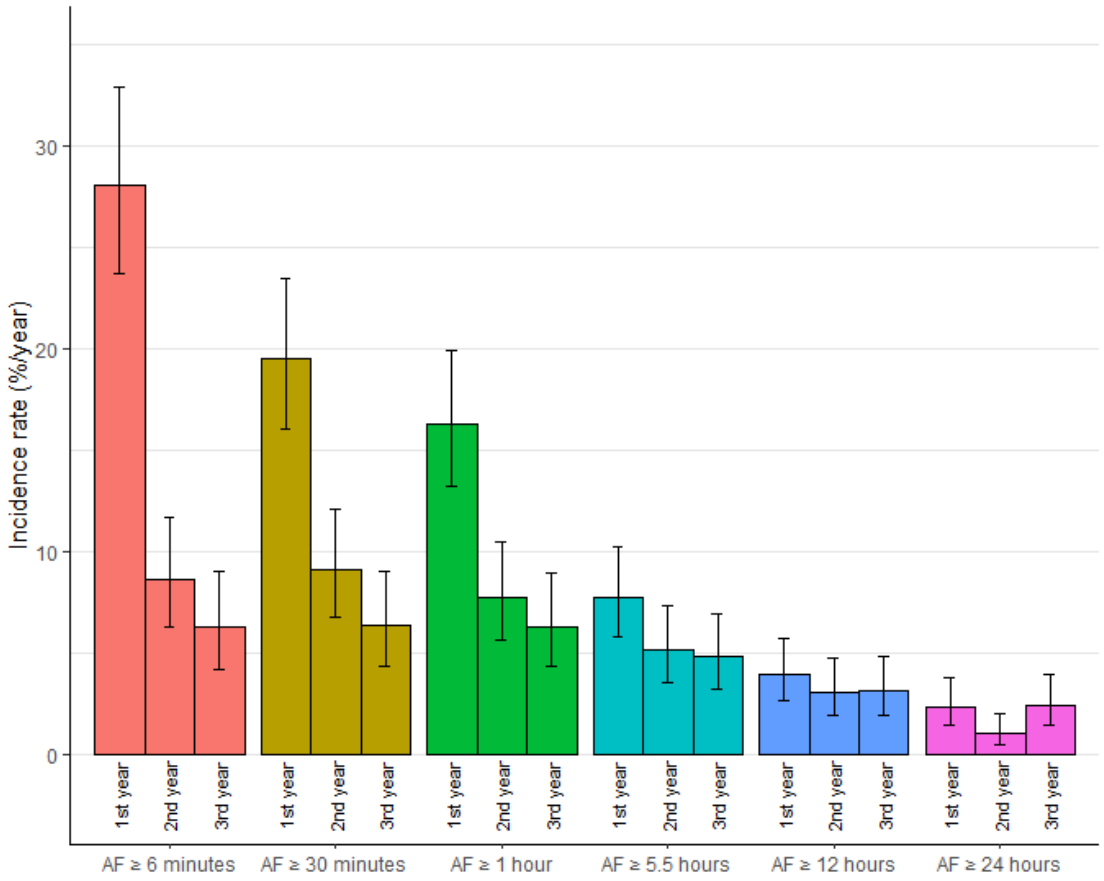
Figure 5 Relationship between baseline markers and incidence rate of AF



Legend: The y-axis presents exact incidence rate (points) and confidence intervals (colored ribbon) for AF episodes lasting ≥6 minutes, ≥5.5 hours, and ≥24 hours in sequentially overlapping subgroups comprising 10% of the population on the x-axis. The curve represents a moving average using local polynomial regression fitting, while the dashed line represents the average incidence rate for the entire population.

Abbreviations: AF, atrial fibrillation; bpm, beats per minute; IR, incidence rate (%/year); NT-proBNP, N-terminal pro-brain natriuretic peptide.

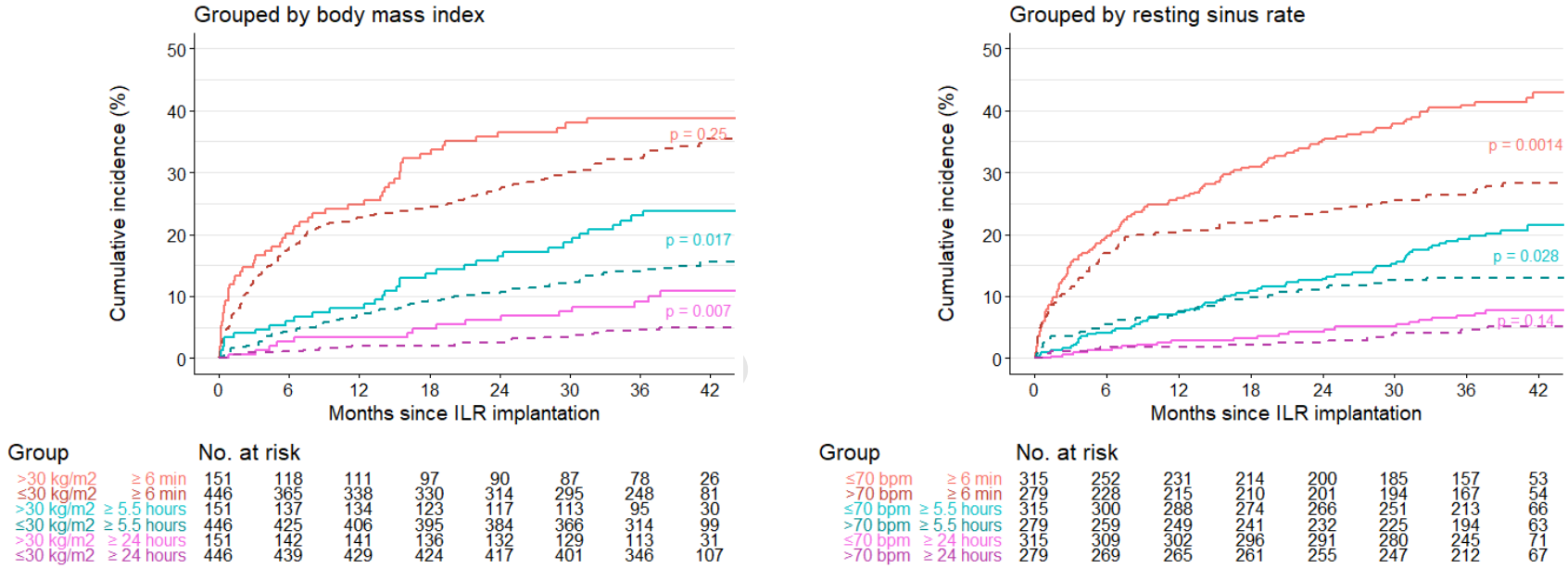
Supplementary Figure 1
Incidence rate of new AF episodes of different durations according to year of monitoring



Legend: The figure presents detection rate and exact confidence intervals for new AF episodes of different durations for each of the first three years after device implantation.
Abbreviations: AF, atrial fibrillation.

Supplementary Figure 2a

Cumulative incidence of AF episodes lasting ≥ 6 minutes, 5.5 hours and 24 hours grouped by baseline characteristics

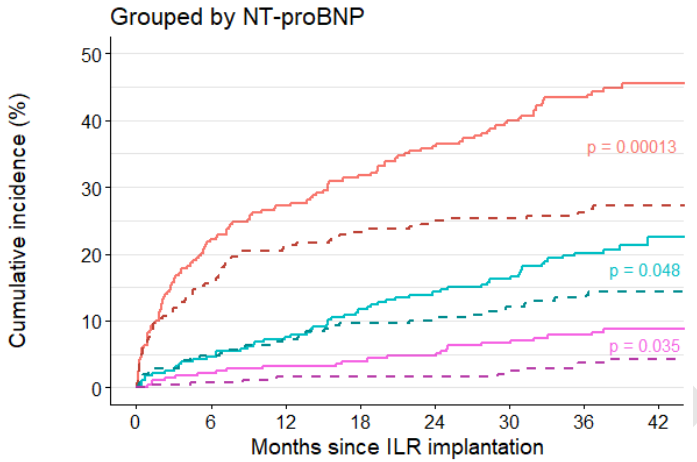


Legend: The figure presents cumulative incidence of AF detection plotted with the Aalen-Johansen method, grouped by BMI and resting sinus rate.

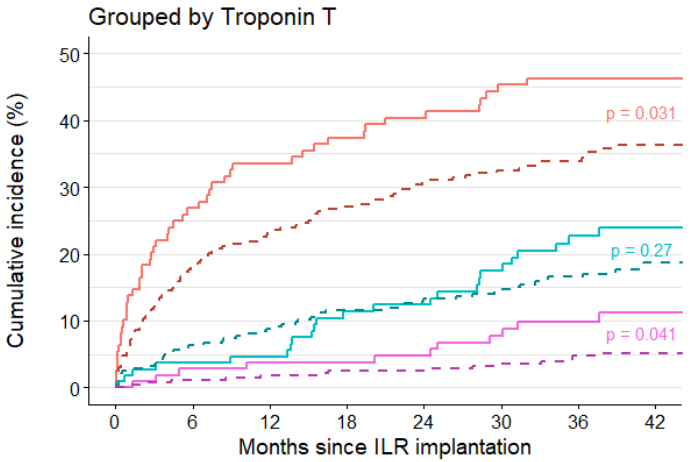
Abbreviations: AF, atrial fibrillation; BMI, body mass index.

Supplementary Figure 2b

Cumulative incidence of AF episodes lasting ≥ 6 minutes, 5.5 hours and 24 hours grouped by baseline characteristics



Group	No. at risk							
>15 pmol/L ≥ 6 min	281	216	198	186	171	157	126	36
0-15 pmol/L ≥ 6 min	251	209	195	188	183	179	155	46
>15 pmol/L ≥ 5.5 hours	281	263	251	238	227	215	175	48
0-15 pmol/L ≥ 5.5 hours	251	237	229	221	217	210	182	52
>15 pmol/L ≥ 24 hours	281	270	263	257	251	239	202	52
0-15 pmol/L ≥ 24 hours	251	247	243	240	238	233	201	54



Group	No. at risk							
>14 ng/L ≥ 6 min	109	77	69	65	60	55	49	12
0-14 ng/L ≥ 6 min	290	235	219	208	196	187	154	44
>14 ng/L ≥ 5.5 hours	109	102	99	91	88	81	67	15
0-14 ng/L ≥ 5.5 hours	290	269	260	251	243	234	194	54
>14 ng/L ≥ 24 hours	109	103	100	98	95	90	77	15
0-14 ng/L ≥ 24 hours	290	284	280	275	272	264	222	58

Legend: The figure presents cumulative incidence of AF detection plotted with the Aalen-Johansen method, grouped by NT-proBNP and troponin T.

Abbreviations: AF, atrial fibrillation; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

Supplementary Table 1

Baseline characteristics for patients included vs. not included in prediction analyses

Included in prediction analyses n (% of all)	Included 397 (66)	Not included 200 (34)	p
Male sex (%)	235 (59.2)	106 (53.0)	0.18
Age, years (sd)	76.53 (4.40)	75.99 (3.77)	0.14
CHA_2DS_2VASc score (sd)	3.94 (1.24)	3.89 (1.21)	0.6
$CHADS_2$ score (sd)	2.32 (1.06)	2.23 (1.08)	0.3
Heart failure (%)	18 (4.5)	7 (3.5)	0.3
Hypertension (%)	357 (89.9)	183 (91.5)	0.11
Diabetes (%)	120 (30.2)	54 (27.0)	0.7
Previous stroke (%)	73 (18.4)	34 (17.0)	0.6
Previous transient ischemic attack, n (%)	51 (12.8)	16 (8.0)	0.5
Previous systemic embolism, n (%)	25 (6.3)	17 (8.5)	0.8
Previous AMI (%)	46 (11.6)	12 (6.0)	0.10
Previous CABG (%)	21 (5.3)	20 (10.0)	0.4
Valvular heart disease (%)	19 (4.8)	7 (3.5)	0.042
Beta blockers, n (%)	91 (22.9)	53 (26.5)	0.048
Calcium channel blockers, n (%)	129 (32.5)	80 (40.0)	0.6
Nondihydropyridine type, n (%)	9 (2.3)	5 (2.5)	0.4
ACEi, ARB, or renin inhibitors, n (%)	232 (58.4)	124 (62.0)	0.09
Lipid-lowering drugs, n (%)	211 (53.1)	111 (55.5)	1.0
Diuretics, n (%)	118 (29.7)	59 (29.5)	0.5
Platelet inhibitors, n (%)	199 (50.1)	96 (48.0)	0.6
Glucose-lowering drugs, n (%)	102 (25.7)	47 (23.5)	1.0
Systolic BP, mmHg (sd)	151.31 (18.20)	152.70 (19.77)	0.7
Diastolic BP, mmHg (sd)	84.25 (11.31)	86.12 (12.03)	0.6
Resting sinus rate, bpm (sd)	71.14 (11.80)	71.32 (13.58)	0.4
Height, cm (sd)	171.50 (9.20)	169.44 (7.48)	0.06
Body mass index, kg/m^2 (sd)	27.68 (4.74)	27.28 (4.16)	0.87
Creatinine, µmol/L (sd)	88.53 (22.72)	84.35 (25.02)	0.006
NT-proBNP, pmol/L [Q1;Q3]	16.00 [9.00, 28.00]	18.00 [9.00, 32.00]	0.3
hs-CRP, mg/L [Q1;Q3]	2.00 [1.00, 4.00]	2.00 [1.00, 4.00]	0.041
Troponin T, ng/L (sd)	14.58 (6.50)	13.00 (0.00)	0.6

The table presents baseline characteristics of the study participants according to inclusion in prediction analyses (Figure 4 and Supplementary Table 3). Patients could not be included in prediction analyses if they had any missing information about resting sinus rate (3 missing), body mass index (0 missing), NT-proBNP (65 missing), or troponin T (198 missing). Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein.

Supplementary Table 2
Univariate Cox regressions

	AF ≥ 6 minutes	p	AF ≥ 30 minutes	p	AF ≥ 1 hour	p	AF ≥ 5.5 hours	p	AF ≥ 12 hours	p	AF ≥ 24 hours	p
Male sex	1.1 (0.83-1.4)	0.5	1.0 (0.78-1.4)	0.8	1.0 (0.72-1.3)	0.9	1.3 (0.88-2)	0.18	1.7 (0.98-2.9)	0.058	1.6 (0.79-3.1)	0.2
Age (per 5 years)	1.3 (1.1-1.5)	0.0031	1.2 (1-1.4)	0.018	1.3 (1.1-1.5)	0.006	1.2 (1-1.6)	0.046	1.2 (0.87-1.5)	0.3	1.3 (0.9-1.8)	0.2
CHA_2DS_2VASc >3	1.3 (1-1.8)	0.043	1.2 (0.91-1.7)	0.18	1.4 (1-1.9)	0.044	1.4 (0.94-2.2)	0.099	1.4 (0.8-2.3)	0.3	1.5 (0.74-2.9)	0.3
$CHADS_2$ >1	1.6 (1.1-2.3)	0.0068	1.5 (1-2.1)	0.046	1.6 (1.1-2.4)	0.024	1.6 (0.96-2.7)	0.068	1.8 (0.89-3.5)	0.1	1.5 (0.64-3.3)	0.4
Heart failure	0.62 (0.28-1.4)	0.3	0.59 (0.24-1.4)	0.2	0.52 (0.19-1.4)	0.2	0.44 (0.11-1.8)	0.3	0.74 (0.18-3)	0.7	0.62 (0.085-4.5)	0.6
Hypertension	1.2 (0.74-1.9)	0.5	1.2 (0.73-2.1)	0.4	1.2 (0.7-2.2)	0.5	1.1 (0.55-2.2)	0.8	1.2 (0.49-3)	0.68	1.2 (0.38-4)	0.7
Diabetes	1.0 (0.74-1.4)	1.0	0.96 (0.7-1.3)	0.8	1 (0.71-1.4)	1.0	1.1 (0.69-1.6)	0.8	1.0 (0.58-1.7)	1.0	1.0 (0.51-2.1)	0.9
Previous stroke	1.2 (0.88-1.7)	0.2	1.2 (0.85-1.7)	0.3	1.3 (0.9-1.9)	0.16	1.5 (0.92-2.3)	0.11	1.7 (0.98-3.1)	0.057	1.5 (0.73-3.3)	0.3
Previous AMI	1.0 (0.65-1.6)	0.9	1 (0.63-1.7)	0.9	1.1 (0.66-1.8)	0.7	1.4 (0.74-2.5)	0.3	1.5 (0.7-3.1)	0.3	1.5 (0.58-3.9)	0.4
Previous CABG	0.97 (0.56-1.7)	0.9	1.2 (0.68-2)	0.6	1.2 (0.7-2.2)	0.5	1.8 (0.97-3.4)	0.06	2.7 (1.3-5.4)	0.0069	3.5 (1.5-8.1)	0.003
Valvular disease	1.6 (0.9-2.8)	0.11	1 (0.49-2)	1.0	0.82 (0.36-1.8)	0.6	0.85 (0.31-2.3)	0.8	0.73 (0.18-3)	0.6	0.59 (0.081-4.3)	0.6
Beta blockers	0.95 (0.69-1.3)	0.7	1.1 (0.76-1.5)	0.7	1.1 (0.79-1.6)	0.5	1.4 (0.88-2.1)	0.17	2.0 (1.2-3.4)	0.0078	2.2 (1.2-4.3)	0.02
Calcium channel blockers	1.3 (0.99-1.7)	0.06	1.3 (0.94-1.7)	0.11	1.3 (0.91-1.7)	0.17	1.5 (0.99-2.2)	0.055	2.1 (1.3-3.5)	0.0035	1.6 (0.83-3.0)	0.2
Non-dihydropyridine type	2.1 (1.1-4)	0.033	2.2 (1.1-4.6)	0.025	1.9 (0.82-4.2)	0.14	1.4 (0.43-4.3)	0.6	1.4 (0.34-5.7)	0.7	NA	NA
ACEi, ARB, or renin inhibitors	0.97 (0.73-1.3)	0.8	0.96 (0.71-1.3)	0.8	0.96 (0.7-1.3)	0.8	0.9 (0.61-1.3)	0.6	0.91 (0.55-1.5)	0.7	1.3 (0.64-2.5)	0.5
Lipid-lowering drugs	1.3 (0.95-1.6)	0.11	1.3 (0.98-1.8)	0.064	1.4 (1-1.9)	0.037	1.7 (1.1-2.6)	0.011	1.6 (0.93-2.7)	0.088	1.4 (0.74-2.8)	0.3
Diuretics	1.1 (0.85-1.5)	0.4	1.2 (0.84-1.6)	0.4	1.2 (0.88-1.7)	0.2	1.3 (0.85-1.9)	0.2	1.1 (0.63-1.9)	0.8	1.2 (0.58-2.3)	0.7
Platelet inhibitors	1.1 (0.88-1.5)	0.3	1.2 (0.88-1.6)	0.3	1.2 (0.9-1.7)	0.18	1.3 (0.87-1.9)	0.2	1.6 (0.95-2.6)	0.081	1.8 (0.91-3.4)	0.09
Glucose-lowering drugs	0.98 (0.71-1.3)	0.9	1 (0.71-1.4)	1.0	1 (0.71-1.4)	1.0	1.1 (0.72-1.7)	0.6	1.2 (0.66-2)	0.6	1.3 (0.63-2.6)	0.5
Systolic BP (per 5 mmHg)	0.99 (0.92-1.1)	0.7	1.0 (0.93-1.1)	1.0	1.0 (0.93-1.1)	0.8	1.0 (0.9-1.1)	1.0	0.94 (0.82-1.1)	0.3	1 (0.88-1.2)	0.6
Diastolic BP (per 5 mmHg)	0.97 (0.86-1.1)	0.6	0.98 (0.86-1.1)	0.8	0.97 (0.85-1.1)	0.7	0.98 (0.82-1.2)	0.8	0.95 (0.76-1.2)	0.6	1.1 (0.84-1.4)	0.5
Resting sinus rate (per 5 bpm)	0.83 (0.74-0.94)	0.0021	0.83 (0.73-0.94)	0.0028	0.82 (0.71-0.94)	0.0033	0.79 (0.66-0.94)	0.0075	0.81 (0.65-1)	0.06	0.74 (0.55-0.99)	0.04

Height (per 10 cm)	1.1 (0.93-1.3)	0.3	1.1 (0.89-1.3)	0.5	1.0 (0.85-1.2)	0.8	1.1 (0.89-1.4)	0.4	1.3 (0.99-1.8)	0.06	1.3 (0.9-1.9)	0.2
Body mass index (per 5 kg/m^2)	1.1 (0.96-1.3)	0.17	1 (0.89-1.2)	0.7	1.1 (0.93-1.3)	0.3	1.2 (0.98-1.5)	0.08	1.2 (0.94-1.6)	0.13	1.5 (1.1-2.0)	0.01
Creatinine (per 20 µmol/L)	1.0 (0.94-1.2)	0.4	1.1 (0.94-1.2)	0.3	1.0 (0.92-1.2)	0.5	1.1 (0.95-1.3)	0.2	1.2 (0.99-1.4)	0.06	1.2 (0.93-1.4)	0.2
NT-proBNP (per doubling)	1.2 (1.1-1.3)	0.00018	1.2 (1.1-1.4)	0.00028	1.2 (1.1-1.4)	0.00093	1.2 (1.1-1.4)	0.0043	1.4 (1.2-1.6)	0.00035	1.4 (1.1-1.8)	0.002
hs-CRP (per doubling)	1.1 (1-1.3)	0.039	1.1 (0.94-1.2)	0.3	1.1 (0.95-1.3)	0.2	1.1 (0.91-1.3)	0.4	1.0 (0.8-1.3)	0.8	1.2 (0.88-1.6)	0.3
Troponin T (per 10, ng/L)	1.4 (1.1-1.7)	0.00068	1.3 (1.1-1.6)	0.0067	1.4 (1.1-1.7)	0.0042	1.5 (1.1-1.9)	0.0045	1.6 (1.2-2.2)	0.00078	1.9 (1.4-2.7)	0.0002

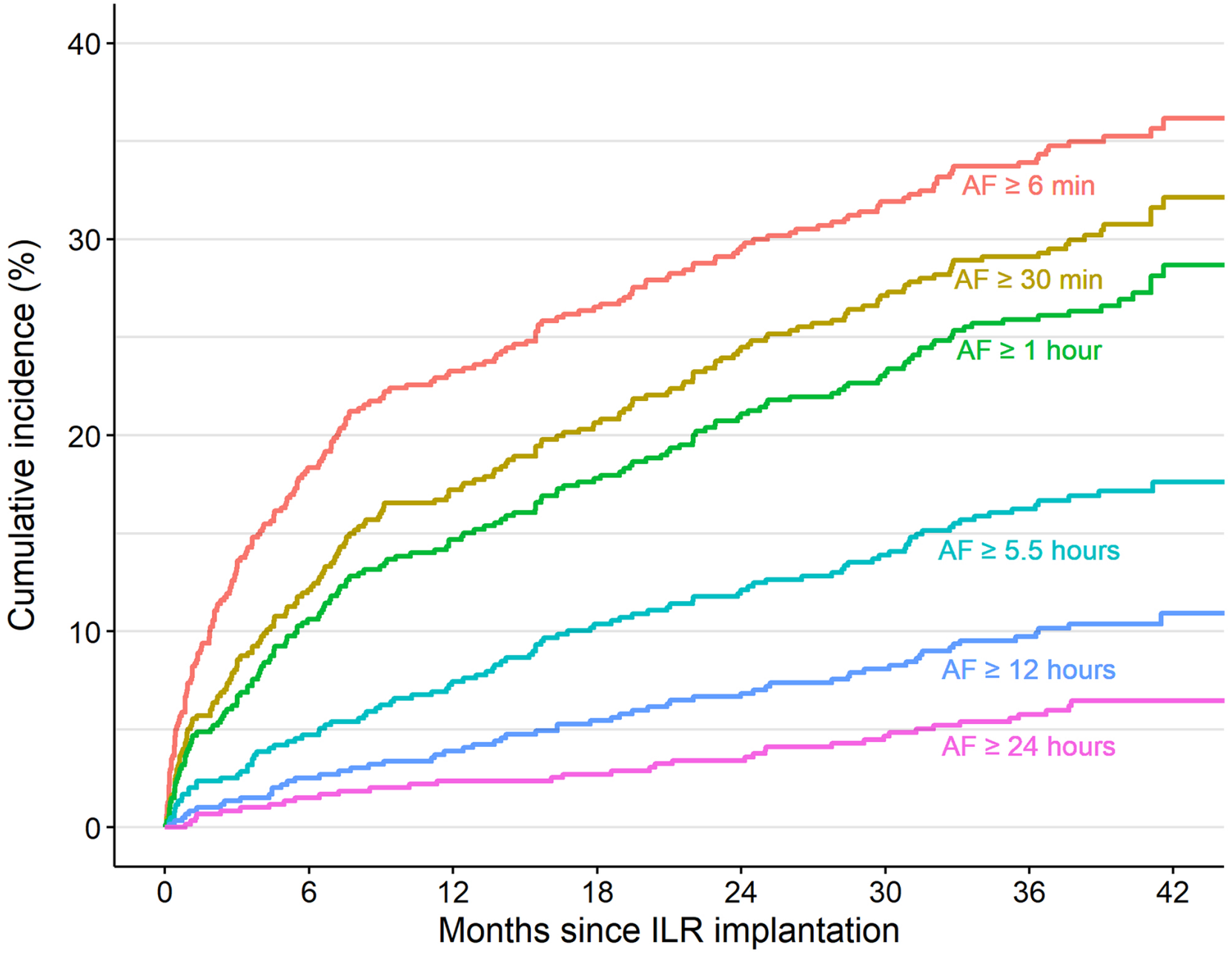
The table presents hazard ratios (with 95% confidence intervals) and p-values from univariate Cox regressions with time to AF of different durations as endpoint.
Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; BP, blood pressure; CABG, coronary artery bypass graft surgery; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; NA, not applicable.

Supplementary Table 3

AUC for prediction of AF after split in training and test sets

Endpoint	Model	AUC	ΔAUC	P
AF ≥ 6 min	Basic model	0.594 [0.45;0.74]	0.045 [-0.06;0.15]	0.4
AF ≥ 6 min	Basic model + markers	0.638 [0.49;0.79]		
AF ≥ 5.5 hours	Basic model	0.569 [0.40;0.74]	0.056 [-0.07;0.17]	0.3
AF ≥ 5.5 hours	Basic model + markers	0.614 [0.44;0.79]		
AF ≥ 24 hours	Basic model	0.499 [0.18;0.82]	0.221 [0.08;0.36]	0.002
AF ≥ 24 hours	Basic model + markers	0.719 [0.46;0.98]		

The table presents time-dependent area under the receiver operating characteristics curve (AUC) for two models in prediction of atrial fibrillation applied in the same test dataset, along with differences between AUC (ΔAUC) and P-values for difference. The *Basic model* is a cause-specific Cox model sex, age, and comorbidities, while the *Basic model + markers* further included N-terminal pro-brain natriuretic peptide, troponin T, body mass index and resting sinus rate.
Abbreviations: AF, atrial fibrillation; AUC, area under the time-dependent receiver operating curve; CABG, coronary artery bypass graft surgery.



AF duration	No. at risk							
≥ 6 min	597	483	449	427	404	382	326	107
≥ 30 min	597	519	484	460	432	408	348	110
≥ 1 hour	597	528	498	476	451	430	363	115
≥ 5.5 hours	597	562	540	518	501	479	409	129
≥ 12 hours	597	575	561	544	529	510	437	135
≥ 24 hours	597	581	570	560	549	530	459	138

Figure 1

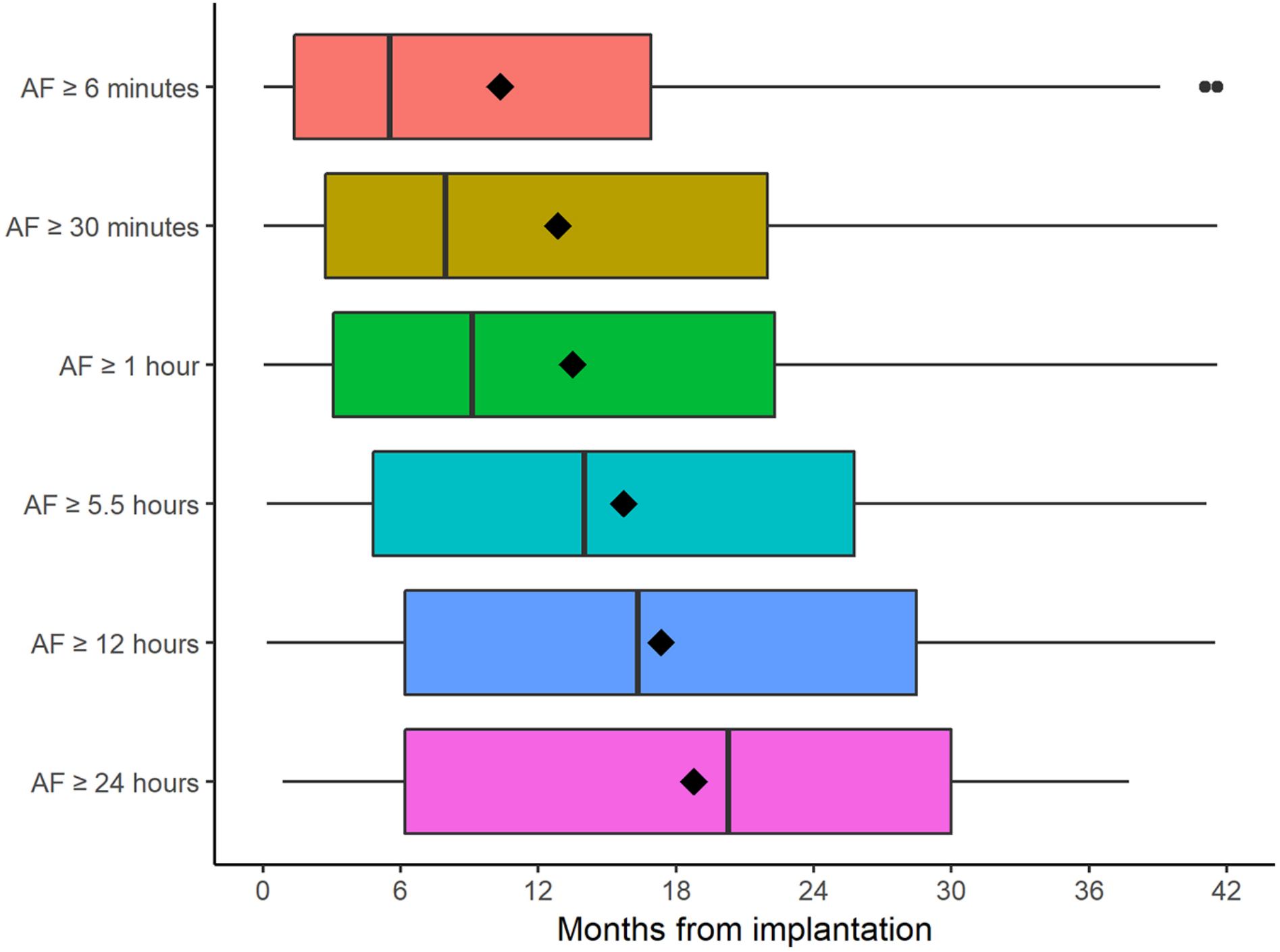

AF ≥ 6 minutes
AF ≥ 30 minutes
AF ≥ 1 hour
AF ≥ 5.5 hours
AF ≥ 12 hours
AF ≥ 24 hours
0
6
12
18
24
30
36
42
Months from implantation

Figure 2

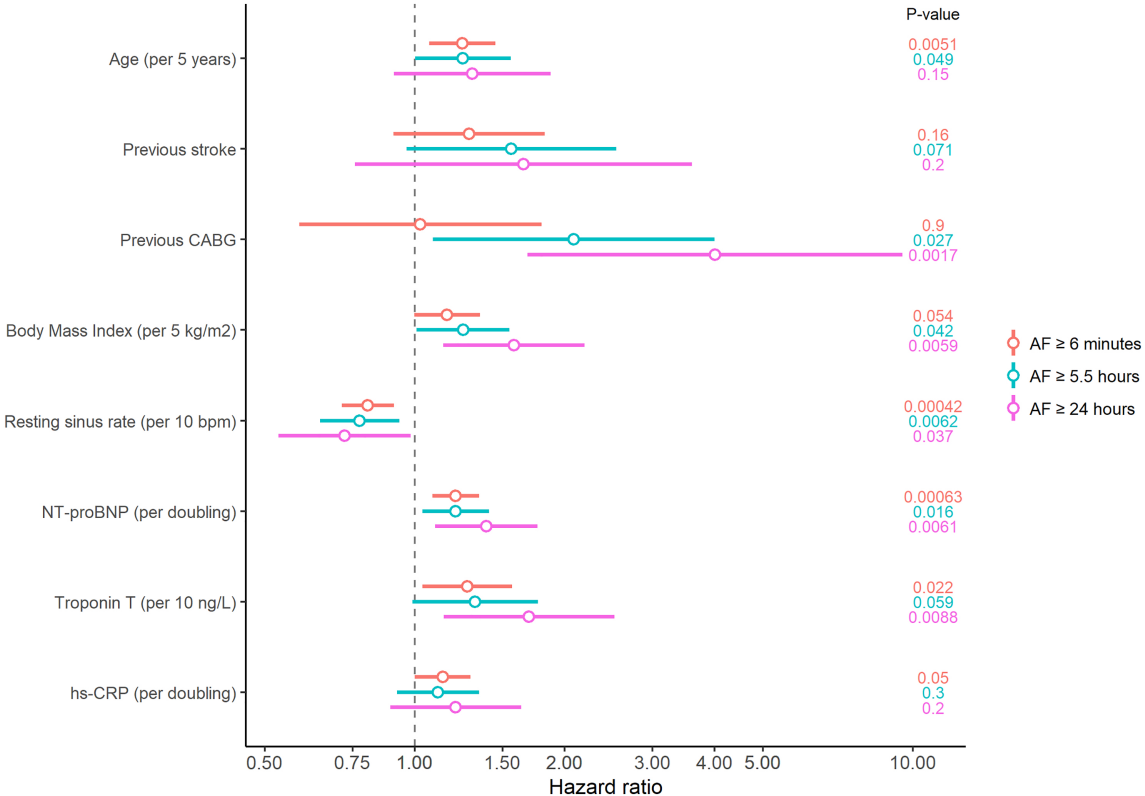
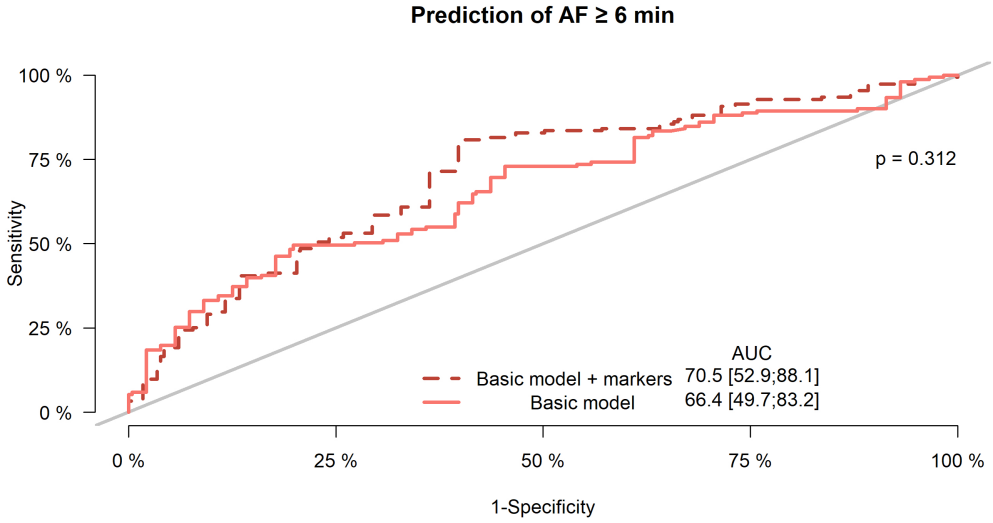
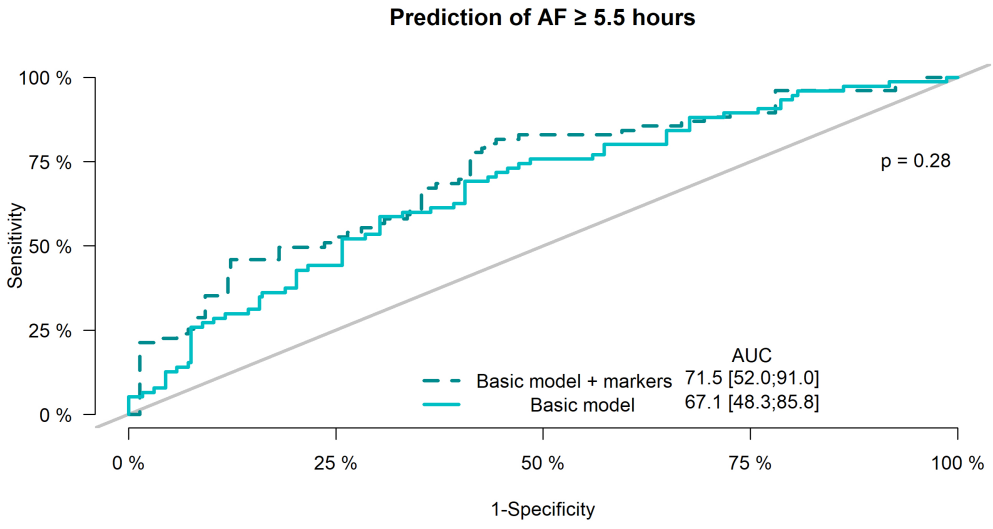

P-value
Age (per 5 years)
0.0051
0.049
0.15
Previous stroke
0.16
0.071
0.2
Previous CABG
0.9
0.027
0.0017
Body Mass Index (per 5 kg/m2)
0.054
0.042
0.0059
Resting sinus rate (per 10 bpm)
0.00042
0.0062
0.037
NT-proBNP (per doubling)
0.00063
0.016
0.0061
Troponin T (per 10 ng/L)
0.022
0.059
0.0088
hs-CRP (per doubling)
0.05
0.3
0.2
AF ≥ 6 minutes
AF ≥ 5.5 hours
AF ≥ 24 hours
0.50
0.75
1.00
1.50
2.00
3.00
4.00
5.00
10.00
Hazard ratio

Figure 3


Prediction of AF ≥ 6 min
100 %
75 %
50 %
25 %
0 %
Sensitivity
p = 0.312
AUC
Basic model + markers
70.5 [52.9;88.1]
Basic model
66.4 [49.7;83.2]
0 %
25 %
50 %
75 %
100 %
1-Specificity


Prediction of AF ≥ 5.5 hours
100 %
75 %
50 %
25 %
0 %
Sensitivity
p = 0.28
AUC
Basic model + markers
71.5 [52.0;91.0]
Basic model
67.1 [48.3;85.8]
0 %
25 %
50 %
75 %
100 %
1-Specificity

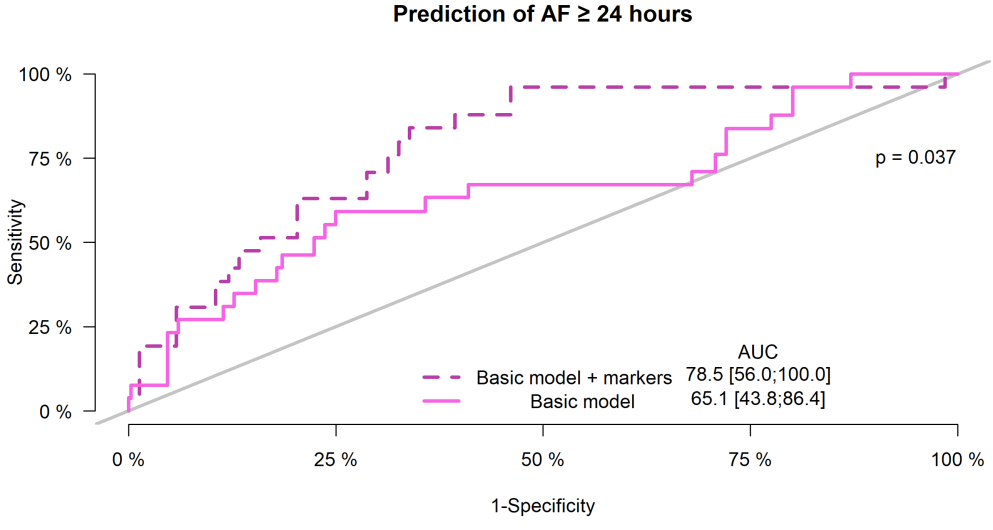

Prediction of AF ≥ 24 hours
100 %
75 %
50 %
25 %
0 %
Sensitivity
p = 0.037
AUC
Basic model + markers
78.5 [56.0;100.0]
Basic model
65.1 [43.8;86.4]
0 %
25 %
50 %
75 %
100 %
1-Specificity

Figure 4

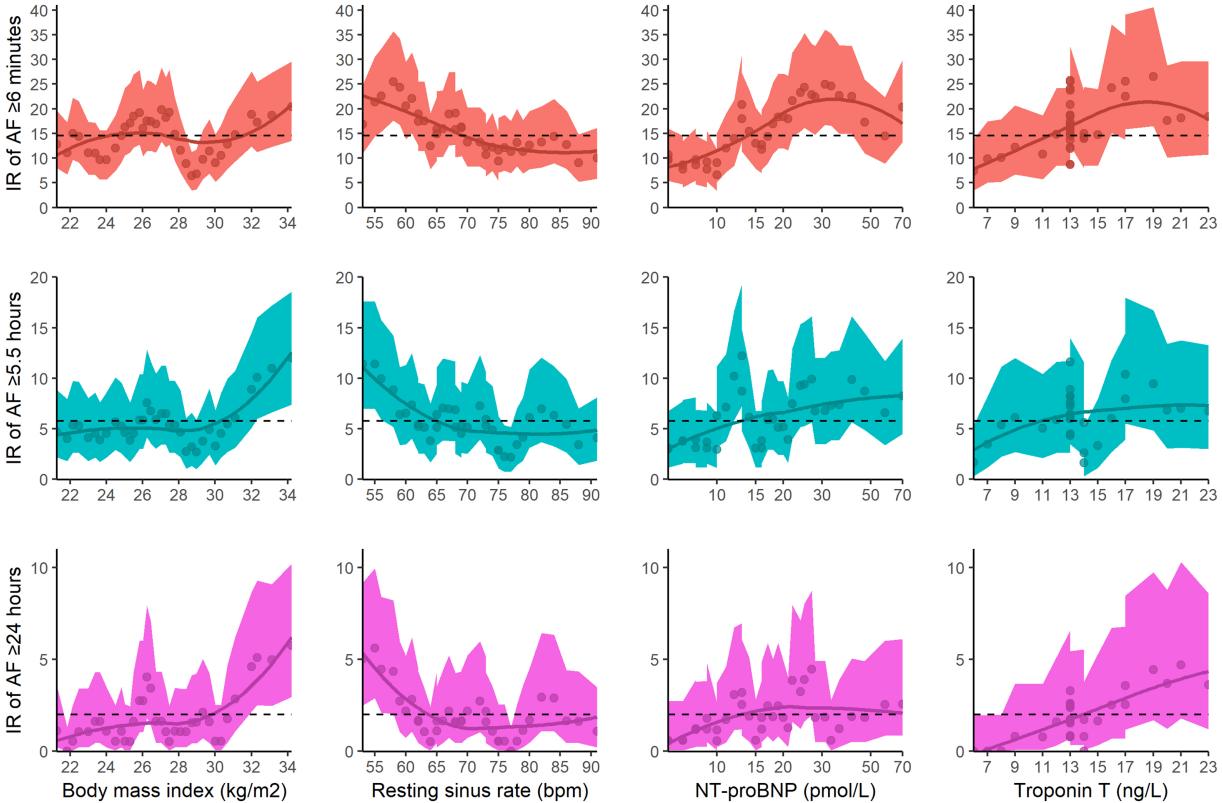

IR of AF ≥6 minutes
IR of AF ≥5.5 hours
IR of AF ≥24 hours
Body mass index (kg/m2)
Resting sinus rate (bpm)
NT-proBNP (pmol/L)
Troponin T (ng/L)

Figure 5