JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 74, NO. 22, 2019

PUBLISHED BY ELSEVIER

Natural History of Subclinical Atrial Fibrillation Detected by Implanted Loop Recorders

Søren Zöga Diederichsen, MD,[a] Ketil Jørgen Haugan, MD, PhD,[b] Axel Brandes, MD, DMSc,[c,d] Mathias Buus Lanng, MSE,[e] Claus Graff, PhD,[e] Derk Krieger, MD, PhD,[f,g] Christian Kronborg, PhD,[h] Anders Gaarsdal Holst, MD, PhD,[i] Lars Køber, MD, DMSc,[a,j] Søren Højberg, MD, PhD,[k] Jesper Hastrup Svendsen, MD, DMSc[a,i,j]

ABSTRACT

BACKGROUND As new heart rhythm monitoring technologies emerge, subclinical atrial fibrillation (AF) signifies a future challenge to health care systems. The pathological characteristics of this condition are largely unknown.

OBJECTIVES This study sought to characterize the natural history of subclinical AF in at-risk patients from the general population.

METHODS The authors studied 590 individuals ≥70 years of age with ≥1 of hypertension, diabetes, previous stroke, or heart failure, without history of AF, undergoing long-term implantable loop recorder monitoring as part of the LOOP (Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals) study. Baseline assessments included N-terminal pro-B-type natriuretic peptide (NT-proBNP). All day-to-day heart rhythm and symptom data were extracted from the device. Endpoints included AF burden, AF progression, symptom reports, and heart rate during AF.

RESULTS A total of 685,445 monitoring days were available for analysis. Adjudicated AF episodes lasting ≥6 min were detected in 205 participants (35%). The AF burden was median 0.13% (interquartile range: 0.03% to 1.05%) of the monitoring time and changed by a factor of 1.31 (95% CI: 1.02 to 1.68) per doubling of NT-proBNP. AF episodes were present 2.7% (interquartile range: 1.0% to 15.7%) of monitoring days after debut. Progression to 24-h episodes was seen in 33 of the AF patients (16%), whereas 46 (22%) had no AF episodes in the last 6 months of monitoring or longer. Symptoms were absent in 185 (90%) at debut, and 178 (87%) never reported AF-related symptoms during follow-up. The averaged heart rate during AF was 96 (interquartile range: 83 to 114) beats/min, 24 (interquartile range: 9 to 41) beats/min faster than daytime sinus rates.

CONCLUSIONS Although previously unknown AF was highly prevalent, the burden was low, and progression was limited. In addition, symptoms were scarce, and the heart rate was only modestly elevated. (Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals [LOOP]; NCT02036450) (J Am Coll Cardiol 2019;74:2771–81) © 2019 by the American College of Cardiology Foundation.

From the [a]Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [b]Department of Cardiology, Zealand University Hospital, Roskilde, Denmark; [c]Department of Cardiology, Odense University Hospital, Odense, Denmark; [d]Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark; [e]Department of Health Science and Technology, Aalborg University, Aalborg, Denmark; [f]University Hospital Zurich, University of Zurich, Zurich, Switzerland; [g]Stroke Unit, Mediclinic City Hospital, Dubai, United Arab Emirates; [h]Department of Business and Economics, University of Southern Denmark, Odense, Denmark; [i]Laboratory for Molecular Cardiology, Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [j]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; and the [k]Department of Cardiology, Bispebjerg Hospital, Copenhagen University Hospital, Copenhagen, Denmark. This investigator-initiated study was supported by The Innovation Fund Denmark grant 12-135225, The Research Foundation for the Capital Region of Denmark, The Danish Heart Foundation grant 11-04-R83-A3363-22625, Aalborg University Talent Management Programme, Arvid Nilssons Fond, Skibsreder Per Henriksen, R. og Hustrus Fond, and Medtronic. The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources. Dr. Haugan has received travel and educational grants from Medtronic, Boston Scientific, Abbott, and Biotronik not related to this work; and has received speaker fees from Boehringer Ingelheim not related to this work. Dr. Brandes has received a research grant from Gilead; and has received lecture fees from Bayer, Boehringer Ingelheim, Merck Sharp and Dohme, and Bristol-Myers Squibb not related to this work. Dr. Krieger has been a Medtronic Focus Group member. Dr. Holst is an employee of Novo Nordisk, not related to this work. Dr. Køber has received speaker honoraria from Bayer, AstraZeneca,

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.09.050

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BMI = body mass index

CIED = cardiac implantable electronic device

ILR = implantable loop recorder

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SR = sinus rhythm

Atrial fibrillation (AF) is a major risk factor for ischemic stroke, heart failure, dementia, and death, and can also require symptomatic treatment (1–3). AF patients can benefit from guideline-driven treatment if the diagnosis is established (4). Studies have shown that even short, subclinical episodes of AF as detected by cardiac implantable electronic devices (CIEDs) are associated with increased risk of stroke (5). This has resulted in a growing interest in AF screening (6). Recent studies have shown that continuous electrocardiographic monitoring with implantable loop recorders (ILRs) will find previously undetected AF in approximately 30% of patients with risk factors (7–9). Still, the pathophysiology of the condition is largely unknown. New technologies to detect subclinical AF are currently spreading from the clinic and into the consumer market (10,11), which will likely increase the patient population diagnosed with this new entity.

SEE PAGE 2782

In the current study, we undertook a detailed characterization of subclinical AF in terms of AF burden, risk factors for AF burden, progression of AF, and symptoms and heart rate during AF.

METHODS

STUDY DESIGN. The LOOP (Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals) study is an ongoing, investigator-initiated, randomized, controlled trial for which the inclusion has been finalized and detailed methods have been published (12). The trial is registered at ClinicalTrials.gov (NCT02036450). In brief, individuals from the general population were identified by administrative registries and received a letter of invitation from 1 of 4 study centers. Eligible subjects were ≥70 years of age and had ≥1 of the following stroke risk factors; hypertension, diabetes, heart failure, or previous stroke. Exclusion criteria included any history of AF (12).

Eligible subjects were randomized in a 1:3 ratio to receive an ILR (Reveal LINQ; Medtronic, Dublin, Ireland) with continuous electrocardiographic monitoring via the CareLink Network, or to control.

New-onset ILR-detected AF episodes lasting ≥6 min were independently adjudicated by at least 2 senior cardiologists (K.J.H., A.B., S.H, J.H.S.). If AF was confirmed, individuals were contacted by phone and offered clinical follow-up with initiation of oral anticoagulation. Furthermore, these participants were asked about presence of any AF-related symptoms at debut, and received the Reveal LINQ Patient Assistant to report future symptoms. Rhythm monitoring continued until end of device battery life, death, or other end-of-study event. Further treatment, for example, rhythm or frequency regulation, was not initiated per study protocol, but was based on standard care.

All study participants gave written informed consent. The LOOP study has been approved by the Ethics Committee of the Capital Region of Denmark (H-4-2013-025) and the Danish Data Protection Agency (2007-58-0015).

For the current analysis, data acquisition and AF adjudication concluded December 1, 2018. Because the ILR battery life is a minimum of 3 years, we included all LOOP study participants receiving ILRs until June 1, 2015, in order to maximize monitoring duration.

DATA COLLECTION AND DEFINITIONS. For each day of monitoring, the ILR calculates the following day-to-day heart rhythm data: time in AF in minutes, mean heart rate during AF, if AF is present in beats per minute, and mean heart rate during sinus rhythm (SR) in beats/min calculated separately for daytime (hours 8 AM to 8 PM) and nighttime (midnight to 4 AM). Every night, this information is automatically and wirelessly transferred via the CareLink Network along with electrocardiographic documentation on any arrhythmias or symptom reports since last transmission. For the current analysis, all of the aforementioned variables were extracted each day, for each participant.

To investigate the natural history of subclinical AF, participants were censored at the first of the following events: Last day of ILR monitoring (e.g., device end of service, device explantation, death, or other end-of-study event), December 1, 2018 (end of data acquisition for the current study), or date of initiation of antiarrhythmic treatment, defined as any of: AF ablation, direct current cardioversion, or Class I or III drugs. Data about daily heart rates were censored at

Orion Pharma, Novartis, and Sanofi, not related to this work; and has served on steering committees for trials sponsored by Novartis. Dr. Svendsen has been a member of Medtronic advisory boards; and has received speaker honoraria and research grants from Medtronic in relation to this work, in addition to a research grant from Gilead, not related to this work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 8, 2019; revised manuscript received September 2, 2019, accepted September 13, 2019.

initiation of beta-blocker, non-dihydropyridine calcium antagonist, or digoxin during follow-up.

The primary endpoint was AF burden, defined as cumulative duration of all AF episodes lasting ≥6 min from the first adjudicated AF episode onward, divided by total duration of monitoring.

Secondary endpoints included cumulative duration of AF, number of AF episodes, duration per AF episode, number of days with AF, number of days without AF. Furthermore, AF progression was investigated as follows: First, progression was defined as reaching AF episodes lasting ≥24 h (13), and progression until this point was investigated by counting days with shorter episodes preceding the long episode. Second, progression over time was investigated by means of the monitoring time starting from the first adjudicated AF episode until censoring. The proportion of AF burden that occurred in the first one-half of this timespan was calculated, and AF decrease was defined as a lower AF burden in the second one-half than in the first one-half. Finally, AF remission was defined as exactly zero AF in the last 6 months of monitoring or longer.

Additional secondary endpoints to further characterize AF included patient-reported symptoms at AF debut, and after debut using the Patient Assistant, on days with and without AF, respectively. Symptoms were investigated as a binary entity depicting whether any or no symptoms were reported. Finally, to characterize heart rate parameters during AF versus SR, average values were calculated for sinus rate nighttime (considered resting sinus rate) and daytime, and rate during AF, weighted by time per day in SR or AF, respectively.

TABLE 1 Baseline Characteristics of the Study Population (N = 590)

Male	337 (57.1)
Age, yrs	76.3 ± 4.2
Alcohol consumption, U/week	5.0 (1.0–12.0)
Smoking pack yrs	9.0 (0.0–28.0)
Heart failure	24 (4.1)
Previous myocardial infarction	55 (9.3)
Previous CABG	39 (6.6)
Hypertension	533 (90.3)
Diabetes	172 (29.2)
Previous stroke	107 (18.1)
CHA_2DS_2-VASc score	3.9 (1.2)
Medications	
Beta-blockers	141 (23.9)
Calcium antagonists	207 (35.1)
Non-dihydropyridine calcium antagonists	14 (2.4)
Renin-angiotensin inhibitors	352 (59.7)
Statins	316 (53.6)
Diuretic agents	176 (29.8)
Platelet inhibitors	291 (49.3)
Antidiabetic drugs	147 (24.9)
Biomarkers	
Systolic blood pressure, mm Hg	151.7 ± 18.8
Diastolic blood pressure, mm Hg	84.8 ± 11.6
Height, cm	170.8 ± 8.7
Weight, kg	80.5 ± 15.2
Body mass index, kg/m^2	27.5 ± 4.5
Creatinine, μmol/l	87.2 ± 23.6
Troponin T, ng/l	14.6 ± 6.5
NT-proBNP, pmol/l	16.0 (9.0–28.0)
hs-CRP, mg/l	2.0 (1.0–4.0)

Values are n (%), mean ± SD, or median (interquartile range).

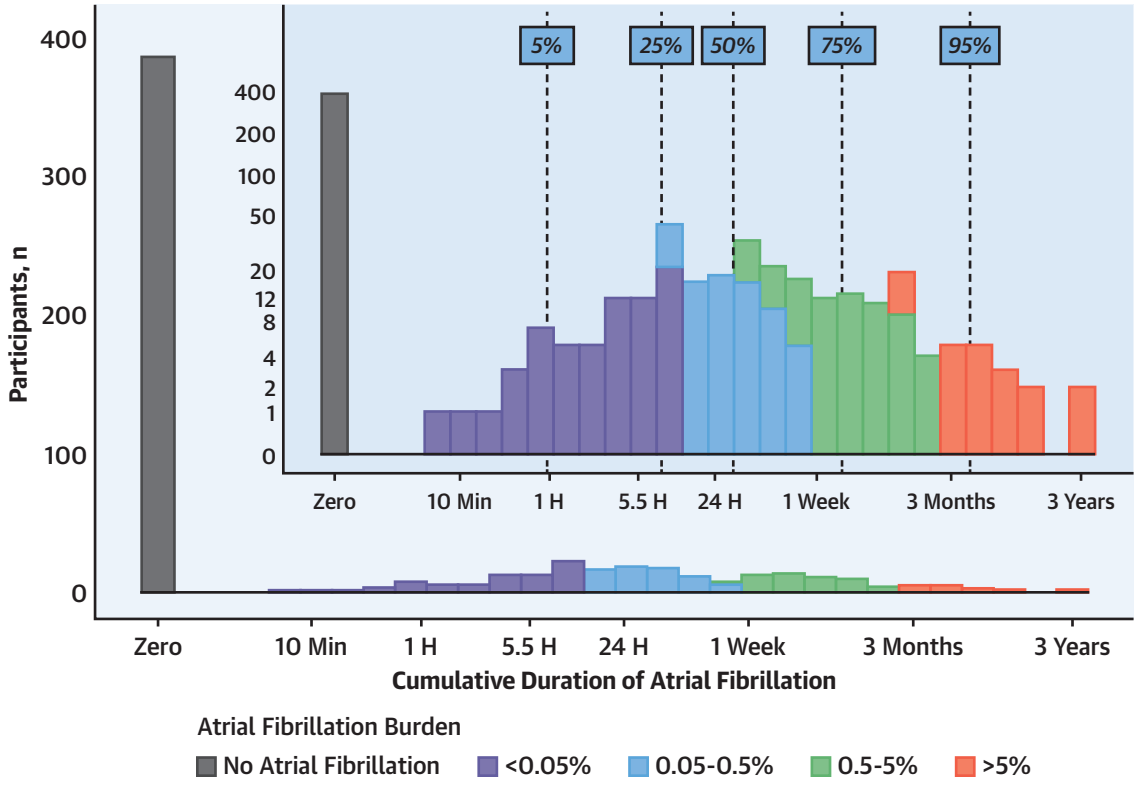
CABG = coronary artery bypass grafting; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

STATISTICAL ANALYSIS. Continuous variables were presented as mean ± SD for normally distributed variables, and median (interquartile range) for non-normally distributed variables, whereas categorical variables were presented as frequency and percentage.

To assess risk factors for increased AF burden, the cumulative duration of AF (count of minutes in AF) was entered as the dependent variable into a zero-inflated regression model for count data via maximum likelihood, using duration of monitoring as offset to adjust for differences in how long the participants were monitored. This model included a negative binomial regression (with log link) and a binomial zero-inflation regression (with logit link) in which identical variables were used as regressors. For all individuals, the zero part of this model computed the odds of having AF detected, whereas for individuals with AF, the count part computed the incidence rate ratio for the amount of AF. A multivariate model adjusting for age, sex, heart failure, hypertension, diabetes, ischemic heart disease (coronary artery bypass grafting and/or previous myocardial infarction), and previous stroke was established. The following baseline variables were included 1 by 1: systolic and diastolic blood pressure, height, weight, body mass index (BMI), and blood tests; creatinine, N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), and troponin T. The following model diagnostics were applied: The marginal distribution of the data was investigated by comparing the observed and fitted frequencies for counts of cumulative AF duration via the rootogram (14), and the distribution of the residuals was visualized in Q-Q plots using randomized quantile residuals (15).

Supplementary analyses among individuals with AF included linear regression models of heart rate during AF, and ratio of heart rate during AF to resting sinus rate, and logistic regression models of AF

CENTRAL ILLUSTRATION **Natural History of Subclinical Atrial Fibrillation: Histogram of Cumulative Duration of Atrial Fibrillation**



Diederichsen, S.Z. et al. J Am Coll Cardiol. 2019;74(22):2771–81.

Evaluation of 590 patients continuously monitored during a median of 40.2 (37.6 to 42.4) months. The x-axis presents a logarithmic scale of cumulative AF duration, and the y-axis shows the number of participants. The **inset** shows the same data on a logarithmic y-axis. The **broken vertical lines** denote the 5th, 25th, 50th, 75th, and 95th percentiles of cumulative AF duration among the 205 patients with AF, which are at 57 min, 9 h, 34 h, 11 days, and 131 days, respectively.

remission, and progression to 24-h AF episodes. Furthermore, the ratio of AF burden during the last to first 6 months after the first adjudicated AF episode (logarithm transformed) was investigated in a linear regression model. These models were adjusted for the same risk factors as the model described earlier in the text. Diagnostics were applied to appropriately test for linearity of the data, and normality and homoscedasticity of residuals in linear regression models, and for logit linearity, outliers, and multicollinearity in logistic models. Finally, after 1 year of monitoring, mortality rates were investigated according to AF detection during the first year. In all regressions, NT-proBNP and hs-CRP were logarithm transformed to normalize the distribution.

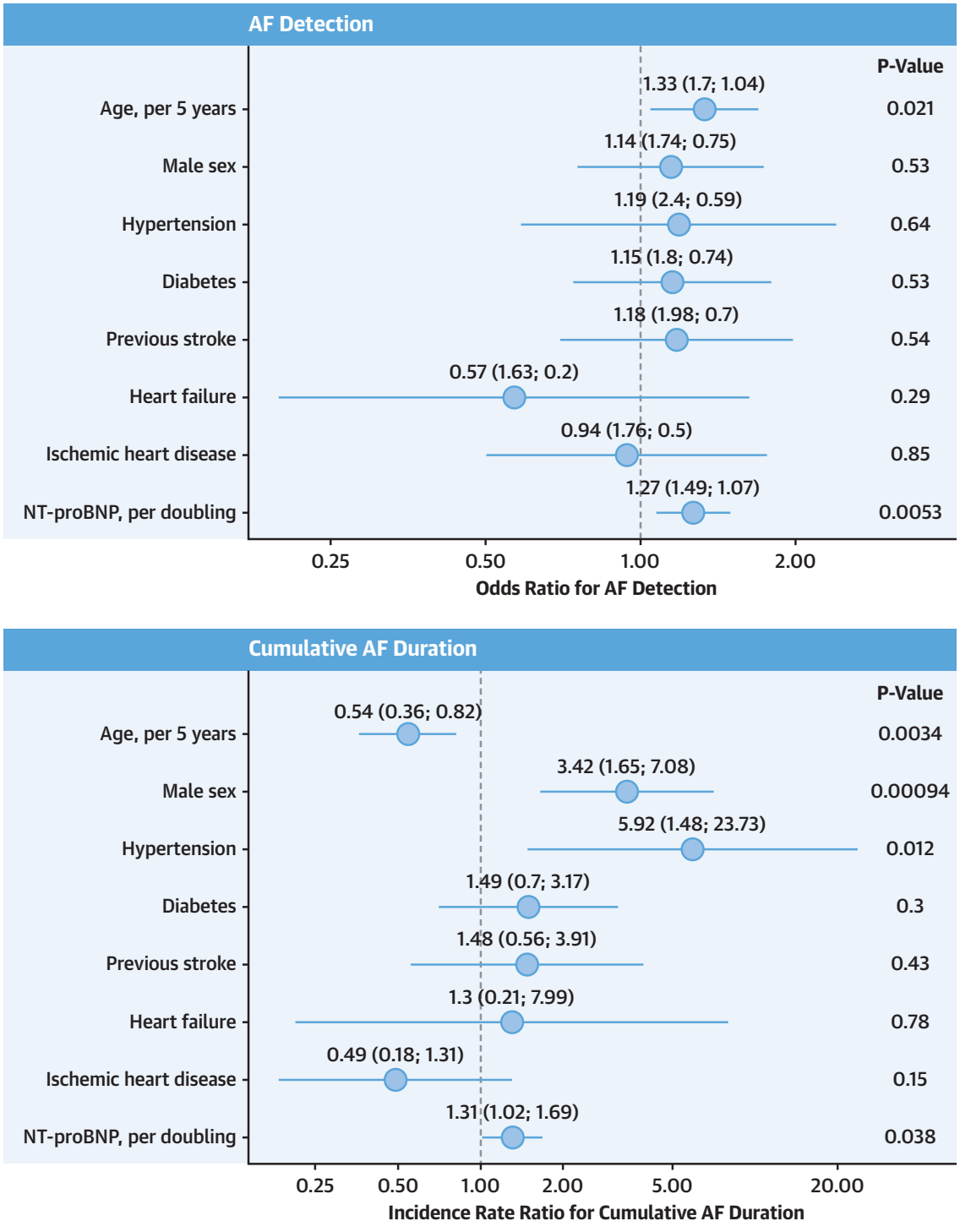
R software version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for data access and management, and statistical analysis and presentation.

RESULTS

POPULATION AND FOLLOW-UP. In all, 597 study participants received an ILR between February 2014 and June 2015. Of these, 7 were excluded from the current analysis because day-to-day ILR data were not retrieved (Online Table 1). Thus, the study population comprised 590 individuals for which the baseline characteristics are presented in **Table 1**. These participants were continuously monitored during a median of 40.2 (37.6 to 42.4) months. A total of 30 deaths occurred, and the most frequent cause of death was cancer (53%) followed by cardiovascular disease (33%). The mortality rate was 1.6 (1.1 to 2.2) per 100 person-years.

A total of 205 participants (35%) had adjudicated AF episodes lasting ≥6 min, and of these, 188 (92%) started oral anticoagulation. The mortality rate was higher among patients with AF detected during the first year

FIGURE 1 Association Between Baseline Variables and AF Detection and Cumulative AF Duration, N = 590



The figure displays the results of a zero-inflated regression model for count data. The dependent variable is the patients' cumulative duration of AF. The **upper panel** presents odds ratios for having any AF (the zero inflation part of the model), and the **lower panel** presents incidence rate ratios for the cumulative duration of AF (the count part of the model). The model is adjusted for monitoring duration, age, sex, hypertension, diabetes, previous stroke, heart failure, ischemic heart disease (defined as previous coronary artery bypass grafting and/or myocardial infarction), and NT-proBNP. AF = atrial fibrillation; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

TABLE 2 Characteristics of AF Burden Among 205 Patients With AF

	All with AF (n = 205)	AF Burden Group <0.05% (n = 68)	0.05%–0.5% (n = 66)	0.5%–5% (n = 53)	>5% (n = 18)
AF burden, %	0.13 (0.03–1.05)	0.02 (0.006–0.30)	0.14 (0.08–0.18)	1.70 (0.90–2.80)	15.3 (8.7–36.5)
AF episodes, n	24 (5–105)	5 (2–11)	21 (9–49)	126 (82–284)	266 (51–676)
Median episode duration, h	0.4 (0.2–1.5)	0.2 (0.1–1.0)	0.4 (0.2–1.6)	0.4 (0.2–1.5)	0.7 (0.3–11.7)
Mean episode duration, h	0.9 (0.3–3.1)	0.6 (0.2–1.5)	1.1 (0.3–3.5)	1.3 (0.4–5.7)	7.8 (0.9–26.4)
Maximum episode duration, h	6.7 (2.7–17.1)	1.8 (0.9–3.6)	7.2 (4.7–12.6)	18.2 (11.2–48)	576 (30–3498)
Monitoring days with AF	20 (5–127)	4 (2–10)	16 (8–38)	142 (71–271)	650 (239–947)
Proportion of days with AF					
Of all monitoring days, %	1.9 (0.5–11.3)	0.3 (0.2–0.9)	1.4 (0.6–3.5)	13.3 (6.5–24.9)	57.8 (23.1–84.2)
Of days after first adjudicated AF episode, %	2.7 (1.0–15.7)	0.6 (0.4–1.6)	1.9 (1.1–5.2)	15.7 (8.6–27.5)	72.2 (47.8–91.3)
Any day with AF ≥5.5 h	118 (57.6)	8 (12.1)	43 (63.2)	49 (92.5)	18 (100.0)
Any episode ≥24 h	33 (16.1)	0 (0.0)	2 (2.9)	17 (32.1)	14 (77.8)
Any episode ≥7 days	13 (6.3)	0 (0.0)	0 (0.0)	3 (5.7)	10 (55.6)
AF in first one-half of monitoring, %*	56.2 (30.0–94.3)	97.8 (60.2–100)	58.4 (34.0–89.3)	36.9 (20.7–57.7)	35.1 (15.4–48.0)
AF decrease†	113 (55.1)	53 (77.9)	40 (60.6)	16 (30.2)	4 (22.2)
AF remission‡	46 (22.4)	33 (48.5)	11 (16.7)	1 (1.9)	1 (5.6)

Values are median (interquartile range) or n (%). *Percentage of cumulative AF duration that occurred in the first one-half of the monitoring time from AF debut to end of monitoring. †Presence of AF decrease, defined as reduced AF burden in the last one-half compared with the first one-half of the monitoring time from AF debut to end of monitoring. ‡Presence of AF remission, defined as zero AF in the last 6 months of monitoring or longer.

AF = atrial fibrillation.

(hazard ratio: 4.51; 95% CI: 2.08 to 9.58). Seven participants (1.2%) were censored at initiation of antiarrhythmic treatment during monitoring (5 at cardioversion, 2 at ablation), with median time to censoring 30 (21 to 32) months. This left a total of 685,445 days of continuous day-to-day heart rhythm data for analysis. The number of days with missing data during monitoring was 1,412 (0.2% of all monitoring days).

In 132 participants (22%; 75 with AF, 57 without AF), new treatment with a beta-blocker, non-dihydropyridine calcium antagonist, or digoxin was initiated after a median of 12 (5.7 to 22) months, and heart rate data specifically was censored from that point.

AF BURDEN AND RISK FACTORS. The distribution of cumulative duration of AF per person is shown in the **Central Illustration**. Among the 205 subjects with AF, the AF burden was <0.05%, 0.05% to 0.5%, 0.5% to 5%, and >5% in 66 (32%), 68 (33%), 53 (26%), and 18 (9%), respectively, whereas the mean AF burden was 2.98 ± 11.24%, and the median was 0.13% (0.03% to 1.05%) (Online Figure 1). There was no difference in anticoagulation initiation across AF burden groups (chi-square p = 0.2).

In the multivariable model, older age and higher NT-proBNP were associated with increased odds of having AF detected (**Figure 1** upper panel), whereas among subjects in which AF was detected, younger age, male sex, history of hypertension, and higher NT-proBNP were associated with increased incidence rate ratio of cumulative AF duration (**Figure 1** lower panel). This was also illustrated by higher AF burden in subjects who were younger (<76 years), male, hypertensive, or had higher NT-proBNP (≥40 pmol/l), respectively (Online Table 2). Other markers were not associated with amount of AF.

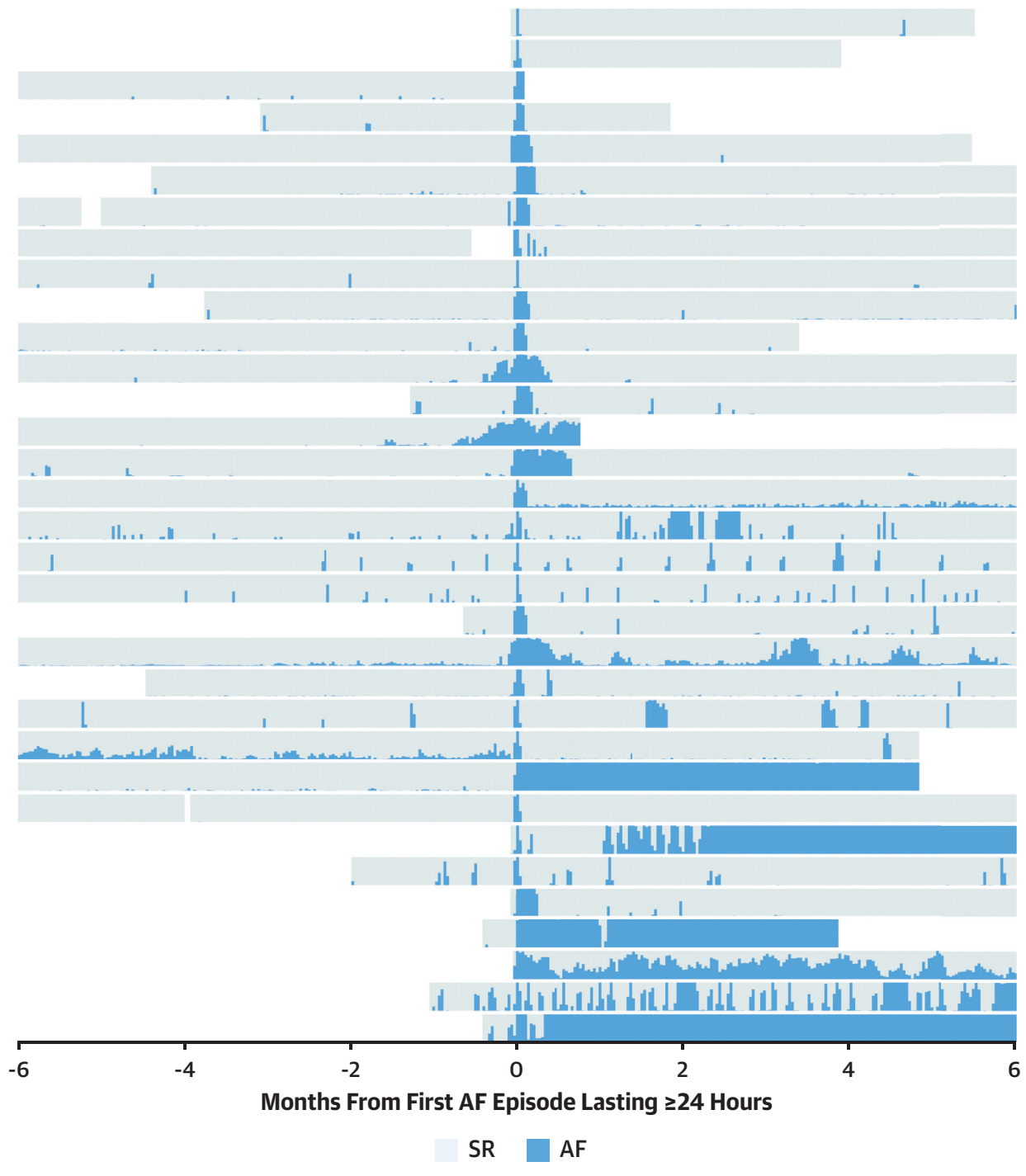
AF EPISODE DURATION AND PROGRESSION. The total number of AF episodes in the dataset was 23,591, and the number of monitoring days with AF was 24,259. **Table 2** lists AF characteristics grouped by AF burden.

A total of 33 subjects (5.6% of all patients, 16.1% of patients with AF) reached the endpoint of AF lasting ≥24 h, and this was in 28 cases (85%) preceded by shorter AF episodes; median 20 (7 to 51) days with short episodes preceding the first 24-h AF episode. In 18 of these subjects (55%), short episodes had been detected >6 months before the first 24-h AF episode. **Figure 2** presents the heart rhythm in the 6 months before and after the first 24-h AF episode per patient.

In terms of progression over time, 113 subjects (55.1% of all with AF) had a reduced burden in the last one-half compared with the first one-half of the monitoring time from debut to end of monitoring (**Table 2**). A total of 46 subjects (22.4% of all with AF) had spontaneous, complete remission of AF, meaning that they had no further AF in the last 6 months of monitoring or longer. The development of AF for each person is shown in **Figure 3** and Online Figure 2.

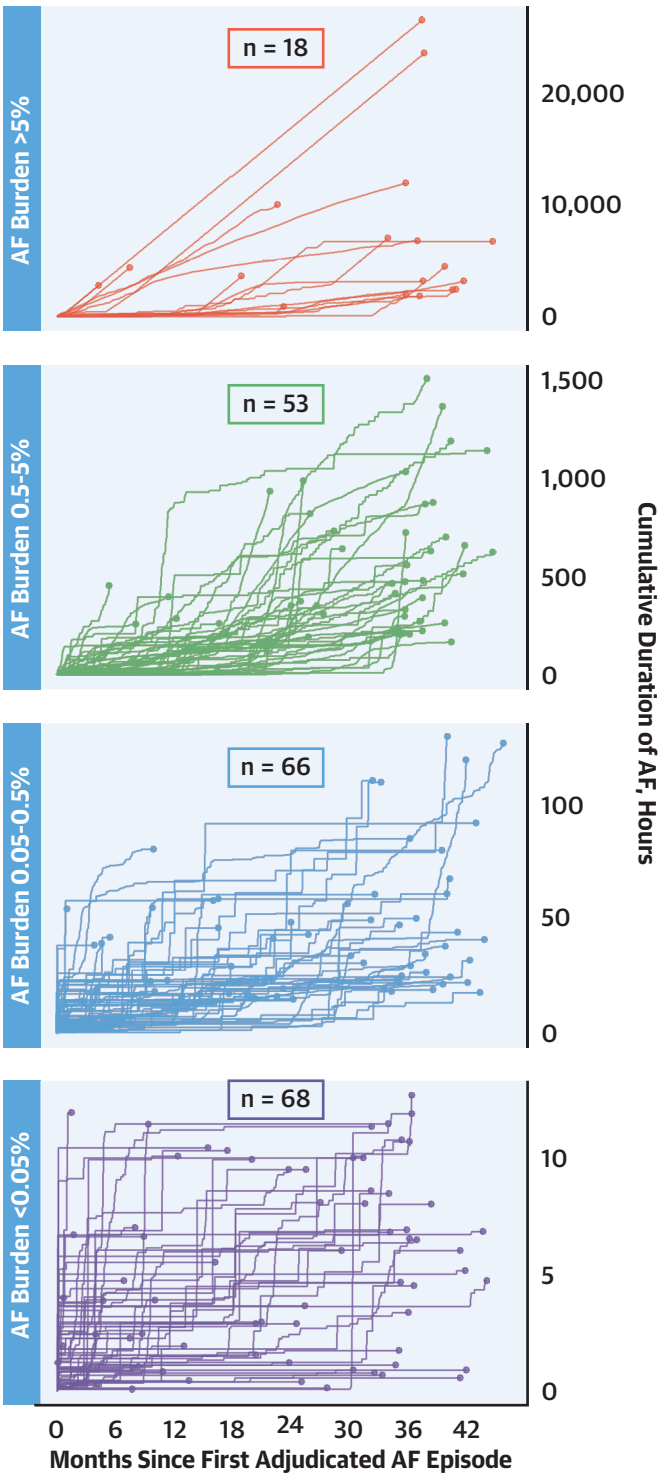
In the supplementary analyses, no variables were associated with 24-h AF episodes, whereas

FIGURE 2 **Heart Rhythm Before and After the First 24-h AF Episode (n = 33)**



The figure displays continuous monitoring data from all subjects with AF episodes lasting ≥24 h. The 6 months preceding and following the first 24-h AF episode are shown. The **height of each blue bar** represents time per day in AF, from 0 to 24 h, whereas **gray** represents sinus rhythm. **Blank areas** represent time without continuous monitoring, for example before device implantation, after censoring or other end-of-study, or missing remote transmissions. AF = atrial fibrillation; SR = sinus rhythm.

FIGURE 3 Progression of AF Over Time (n = 205)



Each **line** represents one participant's cumulative duration of AF, from debut until the last day of monitoring (marked with a **dot**). The x-axis denotes time since first adjudicated AF episode, and the y-axis denotes cumulative hours of AF. A **horizontal line** thus represents sinus rhythm. AF = atrial fibrillation.

hypertension and previous stroke were associated with decreased odds of AF remission, and hypertension, previous stroke, and heart failure were associated with a higher ratio of AF burden during the last to first 6 months after the first adjudicated AF episode (Online Table 3).

AF SYMPTOMS AND HEART RATE. The overall symptom burden is depicted in **Figure 4**, showing that 185 of all subjects with AF (90.2%) denied any symptoms at debut, and 178 (86.8%) never used the Patient Assistant to report symptoms during AF after debut.

The weighted daytime sinus heart rate was lower in subjects with AF than subjects without AF, median 74 (67 to 79) beats/min versus 76 (70 to 82) beats/min; $p = 0.0007$ (Online Figure 3). Among those with AF, the heart rate was lowest during resting SR, whereas the heart rate increased by 10 (6 to 14) beats/min during daytime and by an additional 24 (9 to 41) beats/min during AF, reaching a median of 96 (83 to 114) beats/min (**Figure 5**). Subjects with a larger AF burden had lower heart rates during AF (Online Figures 4 and 5). Subjects without symptoms at debut had a lower heart rate during AF than subjects with symptoms: median 95 (81 to 109) versus 122 (109 to 135) beats/min ($p < 0.0001$) (Online Figures 6 and 7). Higher baseline BMI and NT-proBNP were independently associated with a lower heart rate during AF and a lower ratio of rate during AF to resting sinus rate (Online Table 3).

DISCUSSION

KEY FINDINGS. We investigated the heart rhythm of 590 participants with stroke risk factors, but without history of AF, recruited from the general population. During continuous monitoring for a median of 40.2 months, we found that: 1) although AF was detected in 35% of participants, the median AF burden was only 0.13%, and only 2.7% of days after the first adjudicated AF episode had any AF; 2) the AF burden was higher in participants with lower age, male sex, history of hypertension, and higher NT-proBNP at baseline; 3) AF progression was heterogeneous, because 16% and 6.3% of participants with AF developed episodes lasting ≥24 h and ≥7 days, respectively, whereas AF only appeared transiently in many patients; 4) very few patients received antiarrhythmic treatment despite AF monitoring, and symptoms were almost always absent, both at AF debut and during further monitoring; and 5) the heart rate during subclinical AF was relatively slow (median 96 beats/min), only modestly increased compared with daytime sinus rates.

AF BURDEN. Previous studies have investigated the prevalence of subclinical AF in patients with risk

factors (7-9). In addition to AF detection, the current study reports AF burden as a percentage of monitoring time. Apart from this burden being low, the episodes were usually short-lasting, and only a small proportion of monitoring days after the first episode had any AF (**Table 2**). Because continuous monitoring is required to assess all time in AF, previous studies mostly concern patients with CIEDs, although the AF burden per week (8) or month (9) was touched upon in the above mentioned studies. A post hoc analysis of the TRENDS (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics) and OMNI (Assessing Therapies in Medtronic Pacemaker, Defibrillator, and Cardiac Resynchronization Therapy Devices) cohorts, which investigated conventional CIED patients of which 20% to 27% had a history of AF at baseline, reported a mean AF burden of 3 ± 7% among those with paroxysmal AF as annotated by the device (16). In our study, AF patients had a mean burden of 3 ± 11%, though the median of 0.13% (0.03% to 1.05%) was more representative (Online Figure 1).

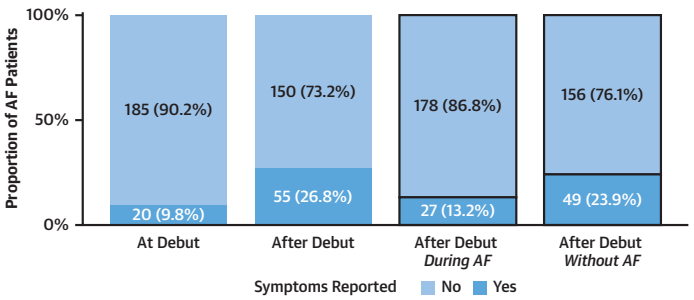
Furthermore, we report whether baseline markers are associated with AF burden. Notably, NT-proBNP was associated not only with the occurrence of AF, but also with the amount of AF.

Several definitions of AF burden have been suggested. Often, AF burden is defined by the longest observed AF episode (8,9) or the longest cumulative amount of AF during a day (7,17,18) or a week (19). The aforementioned TRENDS study initially defined AF burden by the longest daily AF duration per 30 days in sliding windows with 1-day overlaps (20). Arguably, the percentage of time in AF is a more intuitive definition of AF burden (21). Finally, we investigated AF as a risk factor for mortality. Although detection of AF during the first year was associated with increased mortality, the event rate was insufficient to analyze a possible dose-response relationship with AF burden. Future follow-up will facilitate investigation into which threshold for AF burden increases the risk of complications.

PROGRESSION OF AF OVER TIME. AF is often understood as a progressive disease in accordance with the "AF begets AF" principle as derived from experimental studies (22), and the concept of structural and electrical atrial remodeling causing AF progression is well-established (23). One of the most interesting findings in our study was that opposed to being progressive, subclinical AF was often a self-limiting or transient entity.

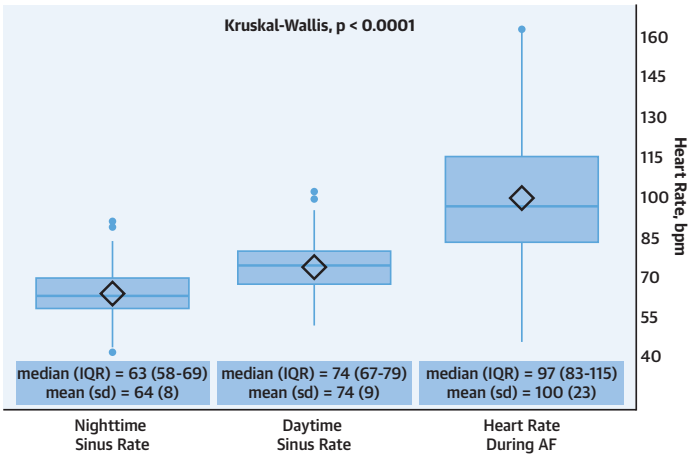
CIED cohort studies including both patients with and without clinical AF have defined progression as transition from short episodes to a single, longer episode (13,17), or to a certain cumulative AF duration within a specified monitoring period (19). Using such definitions, progression will be observed quite frequently. In our study, 58% and 16% of the subjects with AF reached a 1-day AF burden of ≥5.5 and ≥24 h, respectively, mostly preceded by shorter episodes. However, taking advantage of our assessment of all-time AF burden, we demonstrated that 55% of subjects with AF had a spontaneous decrease in AF burden over time, whereas 22% had exactly zero AF in the last 6 months of monitoring or longer (**Table 2**). Thus, future patients presenting with subclinical AF as detected by modern continuous monitoring should not in general be regarded as having a

FIGURE 4 Frequency of Symptoms Among Participants With AF Detected (n = 205)



At debut of AF, patients were questioned about presence of any AF-related symptoms. After debut of AF, the patients received a Patient Assistant to report symptoms during the rest of the monitoring period. For patients reporting any symptoms after debut, symptoms were grouped by presence of AF. AF = atrial fibrillation.

FIGURE 5 Heart Rate Characteristics Among Participants With AF Detected, n = 205



The figure displays boxplots of weighted average heart rates per participant during the whole of monitoring. AF = atrial fibrillation; bpm = beats/min; IQR = interquartile range.

progressive disease. Still, the development of AF is highly heterogeneous across patients because some patients progressed after a long period of very low burden or after reaching a significant amount of AF (**Figure 3**, Online Figure 2).

Risk factor management has shown some promise in limiting AF progression in other populations (24). In our observational study, we found no impact from baseline BMI, NT-proBNP, or other markers, although hypertension, previous stroke, and heart failure were associated with progression of AF burden over time (Online Table 3). Previous CIED cohort studies have reported that male sex, higher age, BMI, and history of hypertension were associated with transition to longer episodes (13,18).

HEART RATE AND SYMPTOM BURDEN. Using day-to-day heart rhythm data, we were able to calculate the weighted mean of heart rate during all AF episodes, and during all time in SR, per participant. Though heart rate during subclinical AF was increased compared with sinus rates, it remained rather slow, particularly for subjects with AF burden >5%; 84 (77 to 96) beats/min (Online Figures 4 and 5).

One previous screening study specifically asked patients about symptoms at AF debut and found that 93% were asymptomatic (9), which is comparable to the 90% in our cohort. For those who did report symptoms, symptoms could be due to an increase in heart rate during AF (Online Figures 6 and 7). To our knowledge, the present study is the first to assess AF-related symptoms as reported via remote transmissions. Only 13% ever reported symptoms on a day with AF, whereas 24% reported symptoms on days with zero AF (**Figure 4**). This further highlights the fact that we did indeed investigate a subclinical arrhythmia. The low prevalence of AF-related symptoms should be kept in mind when considering patients presenting with short, device-detected AF episodes. That is, until it has been determined whether oral anticoagulation is warranted (4), the goal of possible treatment should be symptom reduction and risk-factor modification.

Previous studies in post-ablation patients have shown that presence of symptoms does not correlate well with presence of AF (1). This has also been shown in CIED cohorts. Glotzer et al. (25) investigated 312 patients with and without history of atrial arrhythmias and found that most patients reported at least a moderate level of symptoms at some time during follow-up: 82% for patients with subclinical AF on the device, 62% for patients without AF. However, this study recorded symptoms at follow-up visits, not via remote transmissions. Overall, the poor correlation between symptoms and AF points to the message that detection of AF by screening is highly dependent on the intensity of rhythm monitoring.

STUDY LIMITATIONS. First, for the modeling of risk factors for AF burden, the distribution of AF burden in percent, or cumulative AF duration in minutes, were both severely right-skewed, and had many zeros due to participants without AF detection (**Central Illustration**, Online Figure 1). Thus, we used zero-inflated count regression (cumulative AF duration) adjusted for monitoring duration to model the amount of AF per time. A negative binomial 2-part hurdle model was considered, but had inferior goodness of fit. Second, the findings depend on the device's capability for AF detection and monitoring. Although the algorithm used has very high sensitivity (>93%), the specificity could be decreased, especially for short episodes (26,27). Therefore, a rigorous adjudication regimen was applied. As a sensitivity analysis, we included the unadjudicated AF episodes lasting <6 min in the burden estimation for patients with AF: median 19 (4 to 60) episodes per participant. Inclusion of these episodes increased the median of AF burden from 0.13% to 0.14% and did not change any of the factors associated with cumulative AF (**Figure 1**). Third, because older age was associated with odds of having AF detected, though inversely associated with AF burden, despite adjustment for monitoring duration, this indicates possible selection bias, for example, that older individuals with larger AF burden did not survive to enter the study, were ineligible due to history of AF, or were reluctant to participate. Fourth, although subjects with AF were asked to mark any symptoms by use of the Patient Assistant, absence of symptom reports does not necessarily depict absence of symptoms. However, more subjects noted symptoms during SR than during AF.

CONCLUSIONS

Although previously unknown AF was often detected by long-term continuous monitoring in a general population at risk of stroke, the AF burden was low, and AF often constituted a self-limiting measure. Symptoms were scarce and frequently occurred without the presence of AF. Heart rate during subclinical AF was only modestly elevated compared with sinus rates.

ACKNOWLEDGMENTS The authors thank Prof. Dan Atar, University of Oslo and Oslo University Hospital Ullevål, Norway, Prof. Gregory Y.H. Lip, The University of Liverpool and Liverpool Heart and Chest Hospital, United Kingdom, and Prof. Mårten Rosenqvist, Karolinska Institutet and Danderyd Hospital, Sweden, for assisting the study with their expertise in

the study's international advisory committee. The authors thank the research nurses and other colleagues in the departments of cardiology, Rigshospitalet, Zealand University Hospital Roskilde, Bispebjerg Hospital, and Odense University Hospital, having assisted with patient inclusion, data collection, and implantable loop recorder procedures.

ADDRESS FOR CORRESPONDENCE: Dr. Søren Zöga Diederichsen, Department of Cardiology, The Heart Centre, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 København, Denmark. E-mail: Soeren.Zoega.Diederichsen@regionh.dk. Twitter: @SDiederichsen.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Subclinical AF can be detected by long-term continuous rhythm monitoring, but the burden of AF is often low and generally rises slowly over time. Risk factors for greater AF burden include male sex, hypertension, and higher blood levels of NT-proBNP.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine the type, timing and intensity of interventions that improve clinical outcomes of patients with subclinical AF detected by long-term rhythm monitoring.

REFERENCES

1. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–76.

2. Diener H-C, Hart RG, Koudstaal PJ, Lane DA, Lip GYH. Atrial fibrillation and cognitive function: JACC Review Topic of the Week. J Am Coll Cardiol 2019;73:612–9.

3. Carlisle MA, Fudim M, DeVore AD, Piccini JP. Heart failure and atrial fibrillation, like fire and fury. J Am Coll Cardiol HF 2019;7:447–56.

4. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74:104–32.

5. Mahajan R, Perera T, Elliott AD, et al. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. Eur Heart J 2018;39:1407–15.

6. Curry SJ, Krist AH, Owens DK, et al. Screening for atrial fibrillation with electrocardiography: US Preventive Services Task Force Recommendation Statement. JAMA 2018;320:478–84.

7. Reiffel JA, Verma A, Kowey PR, et al. Incidence of previously undiagnosed atrial fibrillation using insertable cardiac monitors in a high-risk population. JAMA Cardiol 2017;2:1120–7.

8. Healey JS, Alings M, Ha A, et al. Subclinical atrial fibrillation in older patients. Circulation 2017;136:1276–83.

9. Nasir JM, Pomeroy W, Marler A, et al. Predicting determinants of atrial fibrillation or flutter for therapy elucidation in patients at risk for thromboembolic events (PREDATE AF) study. Heart Rhythm 2017;14:955–61.

10. Li KHC, White FA, Tipoe T, et al. The current state of mobile phone apps for monitoring heart rate, heart rate variability, and atrial fibrillation: narrative review. JMIR Mhealth Uhealth 2019;7:e11606.

11. Turakhia MP, Desai M, Hedlin H, et al. Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: the Apple Heart Study. Am Heart J 2019;207:66–75.

12. Diederichsen SZ, Haugan KJ, Køber L, et al. Atrial fibrillation detected by continuous electrocardiographic monitoring using implantable loop recorder to prevent stroke in individuals at risk (the LOOP study): rationale and design of a large randomized controlled trial. Am Heart J 2017;187:122–32.

13. Wong JA, Conen D, Van Gelder IC, et al. Progression of device-detected subclinical atrial fibrillation and the risk of heart failure. J Am Coll Cardiol 2018;71:2603–11.

14. Kleiber C, Zeileis A. Visualizing count data regressions using rootograms. Am Stat 2016;70:296–303.

15. Dunn PK, Smyth GK. Randomized quantile residuals. J Comput Graph Stat 1996;5:236–44.

16. Charitos EI, Pürerfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. J Am Coll Cardiol 2014;63:2840–8.

17. Boriani G, Glotzer TV, Ziegler PD, et al. Detection of new atrial fibrillation in patients with cardiac implanted electronic devices and factors associated with transition to higher device-detected atrial fibrillation burden. Heart Rhythm 2018;15:376–83.

18. Boriani G, Glotzer TV, Santini M, et al. Device-detected atrial fibrillation and risk for stroke: an analysis of >10 000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). Eur Heart J 2014;35:508–16.

19. Piccini JP, Passman R, Turakhia M, Connolly AT, Nabutovsky Y, Varma N. Atrial fibrillation burden, progression, and the risk of death: a case-crossover analysis in patients with cardiac implantable electronic devices. Europace 2019;21:404–13.

20. Glotzer TV, Daoud EG, Wyse DG, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol 2009;2:474–80.

21. Chen LY, Chung MK, Allen LA, et al. Atrial fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American Heart Association. Circulation 2018;137:e623–44.

22. Rostock T. Atrial fibrillation begets atrial fibrillation in the pulmonary veins on the impact of atrial fibrillation on the electrophysiological properties of the pulmonary veins in humans. J Am Coll Cardiol 2008;51:2153–60.

23. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. J Am Coll Cardiol 2014;63:2335–45.

24. Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). J Am Coll Cardiol 2015;65:2159–69.

25. Glotzer TV, Hellkamp AS, Zimmerman J, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the atrial diagnostics ancillary study of the MOde Selection Trial (MOST). Circulation 2003;107:1614–9.

26. Sanders P, Pürerfellner H, Pokushalov E, et al. Performance of a new atrial fibrillation detection algorithm in a miniaturized insertable cardiac monitor: results from the Reveal LINQ Usability Study. Heart Rhythm 2016;13:1425–30.

27. Mittal S, Rogers J, Sarkar S, et al. Real-world performance of an enhanced atrial fibrillation detection algorithm in an insertable cardiac monitor. Heart Rhythm 2016;13:1624–30.

KEY WORDS atrial fibrillation burden, atrial fibrillation progression, continuous monitoring, heart rate, symptoms

APPENDIX For supplemental figures and tables, please see the online version of this paper.