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# Atrial fibrillation burden and cognitive decline in elderly patients undergoing continuous monitoring

Mathias Pinto BONNESEN, MSc [a], Søren Zöga DIEDERICHSEN, MD, PhD [a], Jonas L. ISAKSEN, MSc [b], Kristian Steen FREDERIKSEN, MD, PhD [c], Steen Gregers HASSELBALCH, MD, DMSc [c,d], Ketil Jørgen HAUGAN, MD, PhD [e], Christian KRONBORG, PhD [f], Claus GRAFF, PhD [g], Søren HØJBERG, MD, PhD [h], Lars KØBER, MD, DMSc [a,d], Derk W. KRIEGER, MD, PhD [i,j], Axel BRANDES, MD, DMSc [k,l,m], and Jesper Hastrup SVENDSEN, MD, DMSc [a,d]
*Copenhagen, Denmark; Roskilde, Denmark; Odense, Denmark*

**Aims** To study the relationship between subclinical atrial fibrillation (AF) and changes in cognitive function in a large cohort of individuals with stroke risk factors.

**Methods** : Individuals with no prior AF diagnosis but with risk factors for stroke were recruited to undergo annual cognitive assessment with the Montreal Cognitive Assessment (MoCA) along with implantable loop recorder (ILR) monitoring for AF for 3 years. If AF episodes lasting ≥6 minutes were detected, oral anticoagulation (OAC) treatment was initiated.

**Results** : A total of 1194 participants (55.2 % men, mean age 74.5 (±3.9)) had a combined duration of heart rhythm monitoring of ≈1.3 million days. Among these, 339 participants (28.3%) had adjudicated AF, with a median AF burden of 0.072% (0.02, 0.39), and 324 (96%) initiated OAC. When stratifying the participants into AF burden groups (No AF, $AF_{low}$ (AF burden <0.25%), and $AF_{high,}$ (AF burden >0.25%)), only participants in the $AF_{low}$ group had a decrease in MoCA score over time ($P = .03$), although this was not significant after adjustment for stroke risk factors. A subgroup analysis of 175 participants (14.6%) with a MoCA <26 at 3 years found no association to AF diagnosis or burden.

**Conclusions** : In a high-risk population, subclinical AF detected by continuous monitoring and subsequently treated with OAC was not associated with a significant change in MoCA score over a 3-year period. (Am Heart J 2021;242:15–23.)

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with a prevalence between 2% and 4% in the adult general population, rising to above 16% in individuals >70 years.[1] AF is associated with an increased risk of stroke and all-cause mortality, while also being an independent risk factor for cognitive impairment.[2]

Since cognitive impairment/dementia and AF share risk factors and are dominant in the same age group, numerous studies have sought to explain the underlying pathways and mechanisms.[2-4] AF increases the risk of ischemic stroke 4-5 fold and especially ischemic stroke is a risk factor for cognitive impairment and dementia.[5] However, studies have also found that AF increases the risk of dementia even in the absence of stroke,[6] indicating a link between AF, subclinical brain damage, and cognitive function. While previous studies have come closer to understanding the mechanisms causing cognitive decline, unknown aspects include the impact of AF burden, subclinical AF, and anticoagulation.[7]

The LOOP study provides a unique opportunity to investigate the relationship between AF burden and cognitive decline with continuous heart rhythm monitoring along with annual assessment of cognitive function in a large sample of individuals at risk.[8]

*From the [a]Department of Cardiology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, [b]Laboratory of Experimental Cardiology, Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark, [c]Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, [d]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, [e]Department of Cardiology, Zealand University Hospital Roskilde, Roskilde Denmark, [f]Department of Business and Economics, University of Southern Denmark, Odense, Denmark, [g]Department of Health Science and Technology, Aalborg University, Aalborg, Denmark, [h]Department of Cardiology, Copenhagen University Hospital Bispebjerg, Copenhagen Denmark, [i]Department of Neurology, Mediclinic City Hospital, Dubai, United Arabic Emirates, [j]Department of Neuroscience, Mohammed Bin Rashid University of Medicine and Health Science, Dubai, United Arabic Emirates, [k]Department of Cardiology, Odense University Hospital, Odense, Denmark, [l]Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense C, Denmark, [m]Department of Internal Medicine – Cardiology, University Hospital of Southern Denmark – Esbjerg, Esbjerg, Denmark*

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Reprint requests: *Mathias Pinto BONNESEN, MSc, Department of Cardiology, Copenhagen University Hospital - Rigshospitalet, Inge Lehmanns Vej 7, 2100, Copenhagen, Denmark*

*E-mail address: Mathias.Pinto.Bonnesen@regionh.dk.*

*0002-8703*



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The aim of the current sub-study was to investigate the relationship between subclinical AF and cognitive function in 2 steps; First, to correlate subclinical AF with cognitive decline and compare the findings with prior research, and second, to extend the analysis by stratifying by AF burden. From now on, all further mentions of AF episodes analyzed in this study should be considered *subclinical* AF episodes.

## Methods

### Study design

This analysis is part of the LOOP study; a randomized controlled trial conducted in 4 centers in Denmark. The primary aim of the LOOP study was to investigate if screening for subclinical AF with an Implantable LOOP Recorder (ILR) could reduce the risk of stroke in individuals with known risk factors. Detailed methods have been published previously.[8] Written informed consent was obtained for all participants, and the study was approved by the regional ethics committee (H-4-2013-025) and data protection agency (2007-58-0015), and the trial was registered at ClinicalTrials.gov (NCT02036450).

Briefly, individuals from the general population were identified by administrative registries and invited by letter to participate. Eligible individuals had to be ≥70 years old and be diagnosed with ≥1 of the following stroke risk factors: hypertension, diabetes, heart failure or previous stroke. Individuals with any history of AF or cardiac electronic implantable device (CIED) were excluded from the study. Participants were invited to a baseline visit at the hospital where a 12-lead ECG was obtained to exclude patients with ongoing AF. At the end of the visit, the participants were randomized in a 1:3 ratio to receive an ILR (Reveal LINQ®, Medtronic). New AF episodes were reviewed daily by an experienced physician. Any new-onset episode suspicious of AF lasting ≥6 minutes was independently adjudicated by 2 senior cardiologists. Dispute was resolved by a majority decision after involving a third senior cardiologist. A confirmed AF event resulted in the participant being contacted and offered initiation of oral anticoagulation treatment (OAC).[8] Transmission of data from the ILR continued until end of device battery-life (minimum 3 years), device explantation or death. Further treatment, i.e., rate or rhythm control, was initiated at the discretion of the local investigator according to current guidelines.

The current substudy included all LOOP study participants who had complete ILR data available for the current study and who underwent Montreal Cognitive Assessment (MoCA) at baseline and at annual follow-up during 3 years. The present study was planned prior to the finalization of the main study.

### Montreal cognitive assessment

MoCA is a tool used to assess general cognitive function in the elderly population,[9] which has been used in studies of AF and cognitive function following findings of positive correlation between MoCA score and heart failure and vascular disease.[7,10] The test covers 6 different cognitive aspects: executive functions (4 points); visuospatial abilities (4 points); short-term memory (5 points); language (5 points); attention, concentration, and working memory (6 points); and temporal and spatial orientation (6 points). The output is a score ranging from 0 to 30 (+1 if ≤12 years education), where lower scores indicate more severe cognitive impairment. A threshold of MoCA < 26 was used to introduce a binary cognitive decline parameter, by recommendation from the Danish Health Authority in a 2018 report, claiming a 98% sensitivity of detecting a substantial reduction in cognitive function.[11] In the LOOP study the test was administered by study nurses at each hospital visit, without any changes in test format between the visits. In this paper MoCA score will be reported as MoCA score at baseline ($MoCA_{baseline}$), MoCA at year 3 follow-up ($MoCA_{y3}$) and the difference between the two, ΔMoCA defined as $MoCA_{y3}$ subtracted by $MoCA_{baseline}$.

### Data handling

All information was registered in and acquired from an online database. MoCA scores were calculated based on published guidelines. All AF events ≥6 minutes were included, from 7 days prior to the AF diagnosis and to the end of the study, due to a possible uploading delay of 7 days. Furthermore, final MoCA assessment determined end of follow-up for loop recorder monitoring and participants who did not attend all 3 follow-up visits were removed. Finally, participant information such as age, gender, medication, and disease history were taken at the baseline visit. AF burden was defined as cumulative duration of AF episodes divided by the cumulative duration of monitoring. In this study we defined $AF_{low}$ as AF burden below 0.25% and $AF_{high}$ as AF burden above or equal to 0.25% in accordance with previous definitions.[12] Tests with different thresholds for AF burden can be found in Supplementary Table 1.

### Statistical analysis

For summary statistics, continuous variables were presented as mean ± standard deviation for normally distributed variables compared by t-tests, and median (interquartile range) for non-normally distributed variables compared by Wilcoxon rank sum tests, while categorical variables were presented as frequency and percentage compared by chi-squared tests. For analysis of data with more than 2 groups such as AF burden group, Kruskal Wallis method was used and in case of significance, the inter-group significance was assessed using

Turkey and Kramer method. The linear regression models had ΔMoCA or $MoCA_{y3}$ as the dependent variable, always adjusted for $MoCA_{baseline}$, and a logistic regression model was used in case of a binary outcome. Both linear and logistic regression models were tested in 2 variations: one only adjusted by baseline MoCA score (M1) and another one (M2) further adjusted by known risk factors for cognitive impairment: age, gender, hypertension, diabetes, stroke. A 2 -sided *P*-value <.05 was considered statistically significant. The analysis of association between MoCA < 26 and AF burden was conducted using M1 and M2 with the outcome changed to MoCA < 26 and using a $\chi^2$-test investigating the association between frequency of MoCA < 26 and AF burden. Data handling and analysis were performed using R version 4.0.1 (https://www.R-project.org/, R Core Team (2019)) including *tidyverse* version 1.3.0. [13]

## Results

### Study population and data overview

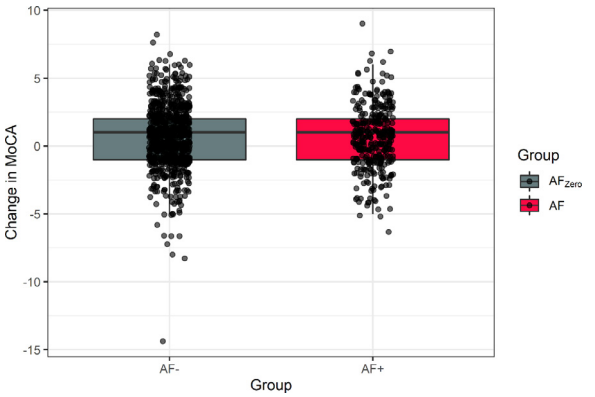
A total of 1501 participants were randomized into the ILR arm, and 1402 had complete ILR data available for this study: data for all of monitoring from baseline to 3 years or until device explantation or death.

Of the 1402 participants with complete ILR data, 1401 (99.9%) underwent MoCA at baseline, 1356 (96.7%) at 1 year, 1301 (92.8%) at 2 years, and 1252 (89.4%) at 3 years. One-thousand one-hundred ninety-four of these (85.2% of all with ILR data) had MoCA at all 3 years and comprised the current study population; 659 (55.2 %) were men, and the mean age was 77 (±4) years. A comprehensive overview of baseline characteristics of the study population can be seen in Table I. The mean MoCA score at 3 years was 27.9 (±2.5), mean ΔMoCA was -0.7 (±2.3), and 174 participants (14.6%) had MoCA < 26 at 3 years. An overview of the MoCA score distribution at baseline and year 3 visit, can be found in the Supplementary Figure 1.

### AF

The duration of continuous heart rhythm monitoring was median 1072 (1057,1086) days, and 339 (28.3%) participants were diagnosed with AF during the study, of which 38 (11.2%) had symptoms on their first AF episode. Of those with AF, the AF burden was median 0.072% (0.02,0.39), mean 1.63% (±6.6), and the median number of AF episodes per person was 20 (4,70). A total of 324 (96%) received OAC after the diagnosis onwards. The distribution of AF burden is illustrated in Figure 2(A) using a histogram colored by burden group, while the year 3 characteristics for each group can be seen in Table II. Supplementary Figure 3 shows the same figure, using only patients with a baseline MoCA score of >27. For more detailed overview of AF episodes with respect to the number of episodes grouped by the various durations of the episodes, please see the online Supplementary Table 5 and the online Supplementary Figure 5.

**Figure 1**




AF diagnosis and cognition Caption: Boxplots showing difference in change of MoCA score from baseline to year 3, for all 1194 participants grouped by AF diagnosis; No AF (*n* = 855) and AF (*n* = 339). A t-test of the MoCA change from baseline to year 3 follow-up showed no statistical difference (*P*=.4) between the two groups. Abbreviations: AF, Atrial Fibrillation; MoCA, Montreal Cognitive Assessment.

### Participants excluded from the study population

Of the 1401 who underwent MoCA at baseline, 207 did not attend all yearly follow up visits. The excluded participants differed from the 1194 in the study population in several characteristics (Table I). The duration of continuous heart rhythm monitoring in the excluded participants was median 1008 (693, 1082) days, and 58 (28%) were diagnosed with AF. Of those with AF, the AF burden was median 0.16% (0.04%, 0.5%), mean 0.76% (±1.8). The median number of AF episodes per person was 20 (11, 63). Of the 58 who did all 4 MoCA tests, 54 (83%) received OAC after the diagnosis onwards.

While no association was found between frequency of AF episode onset (*P* = .6) between the 2 populations, an association was found between AF burden and population group (*P* = .03). A total of 135 (65%) of the excluded participants died during the study period.

### MoCA score according to burden of subclinical AF

No correlation between ΔMoCA score and a diagnosis of new-onset subclinical AF was found in the model only adjusted by baseline MoCA score (M1) (*P* = .1) or further adjusted by comorbidities (M2) (*P* = .4), see **Figure 1**. The spline trend line in **Figure 2**(B) showed that participants in the $AF_{low}$ group had a lower $MoCA_{y3}$ score, while the $AF_{high}$

**Table I.** Baseline characteristics of participants included or excluded in the current substudy ($n = 1401$).

| | Included ($n = 1194$) | Excluded ($n = 207$) | *P*-value |
|---|---|---|---|
| Age, years | 74.5 ± 3.9 | 75.8 ± 4.8 | < .01 |
| Male sex | 659 (55.2) | 93 (44.9) | < .01 |
| Body mass index, kg/m2 | 27.8 ± 4.5 | 28.2 ± 5 | .3 |
| MoCA score | 27.2 (2.4) | 25.9 (3.2) | < .01 |
| MoCA ≥ 26 | 937 (78.5) | 126 (60.9) | < .01 |
| Highest Education Achieved | | | |
| Primary school | 221 (18.5) | 50 (24.2) | |
| High school or technical | 488 (40.9) | 83 (40.1) | |
| Shorter undergraduate | 186 (15.6) | 23 (11.1) | |
| Bachelor's degree | 161 (13.5) | 21 (10.1) | |
| Master's degree | 121 (10.1) | 13 (6.3) | |
| Doctorate | 5 (0.4) | 0 (0.0) | |
| Unknown | 14 (1.2) | 17 (8.2) | |
| Missing | 1 | 0 | |
| >12 years of education | 1012 (84.8) | 186 (89.9) | .07 |
| Alcohol consumption, units/week | 5 [1, 11] | 3 [0, 9.5] | < .01 |
| Smoking pack years | 7 [0, 27] | 10 [0, 30] | .3 |
| Hypertension | 1091 (91.4) | 193 (93.2) | .5 |
| Diabetes | 326 (27.3) | 70 (33.8) | .1 |
| Heart failure | 48 (4.0) | 12 (5.8) | .3 |
| Previous stroke or TIA | 238 (19.9) | 54 (26.1) | .1 |
| Previous myocardial infarction | 102 (8.5) | 24 (11.6) | .2 |
| Previous CABG | 65 (5.4) | 17 (8.2) | .2 |
| Valvular heart disease | 46 (3.9) | 15 (7.2) | .04 |
| PAD | 30 (2.5) | 9 (4.3) | .2 |
| COPD | 84 (7.0) | 19 (9.2) | .4 |
| CHA2DS2-VASc score | | | |
| 2 | 177 (14.8) | 16 (7.7) | |
| 3 | 425 (35.6) | 58 (28.0) | |
| 4 | 337 (28.2) | 54 (26.1) | |
| 5 | 182 (15.2) | 44 (21.3) | |
| ≥6 | 73 (6.1) | 35 (16.9) | |
| Treatment with beta blockers | 275 (23.0) | 49 (23.7) | .9 |
| Treatment with calcium channel blockers | 420 (35.2) | 78 (37.7) | .5 |
| Treatment with renin-angiotensin inhibitors | 751 (62.9) | 132 (63.8) | .9 |
| Treatment with statins | 668 (55.9) | 114 (55.1) | .9 |
| Treatment with diuretics | 356 (29.8) | 78 (37.7) | .03 |
| Treatment with platelet inhibitors | 521 (43.6) | 108 (52.2) | .03 |
| Treatment with insulin | 89 (7.5) | 22 (10.6) | .2 |
| Treatment with other antidiabetic drugs | 245 (20.5) | 52 (25.1) | .2 |

Values are presented as *n* (%), mean ±SD, or median [Q1, Q3]. Included participants had implantable loop recorder data and annual MoCA score during three years, whereas the excluded participants had one or more missing MoCA scores.

Abbreviations**:** CABG, Coronary artery bypass grafting; MoCA, Montreal Cognitive Assessment; PAD, Peripheral artery disease; TIA, Transient Ischemic Attack; COPD, Chronic obstructive pulmonary disease; CHA2DS2-VASc, Congestive heart failure or left ventricular dysfunction Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category.

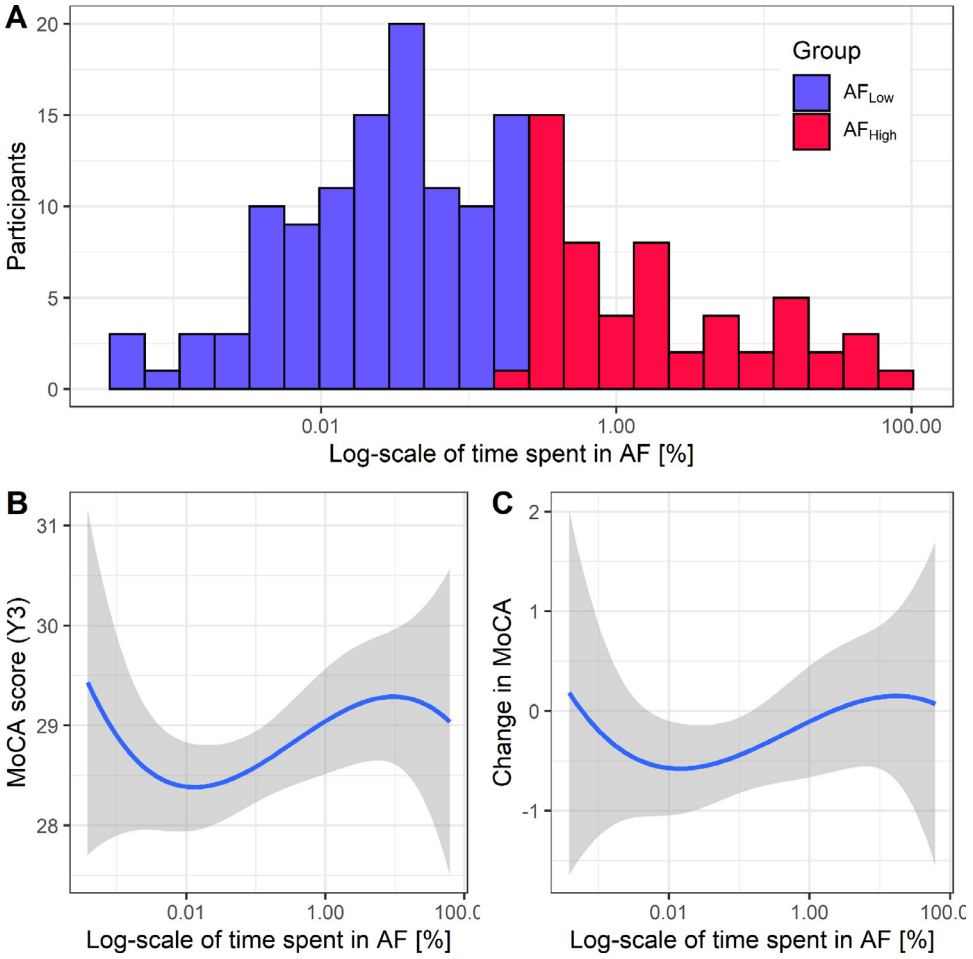
**Table II.** Table providing information about the participant after three years of follow-up.

| Variable | No AF ($n = 855$) | $AF_{low}$ (burden <0.25%) ($n = 232$) | $AF_{high}$ (burden >0.25%) ($n = 107$) | All ($n = 1194$) | *P*-value |
|---|---|---|---|---|---|
| Age, years | 76.7 ± 3.7 | 78 ± 4.5 | 77.6 ± 3.9 | 77 ± 4 | < .01 |
| Male sex [%] | 450 (52.6) | 137 (59.1) | 72 (67.3) | 659 (55.2) | < .01 |
| MoCA score | 28 ± 2.5 | 27.5 ± 2.4 | 28.1 ± 2.3 | 27.9 ± 2.5 | .02 |
| ΔMoCA score | -0.8 ± 2.3 | -0.6 ± 2.3 | -0.8 ± 2.3 | -0.7 ± 2.3 | .4 |
| MoCA < 26 | 119 (13.9) | 39 (16.8) | 16 (15.0) | 174 (14.6) | .5 |
| Previous Stroke or TIA | 157 (18.4) | 42 (18.1) | 30 (28.0) | 229 (19.2) | .05 |
| Diabetes | 239 (28.0) | 71 (30.6) | 22 (20.6) | 332 (27.8) | .2 |
| Hypertension | 789 (92.3) | 211 (90.9) | 99 (92.5) | 1,099 (92.0) | .8 |
| Heart Failure | 30 (3.5) | 10 (4.3) | 7 (6.5) | 47 (3.9) | .3 |

Values are presented as *n* (%) or mean ±SD with p-value for test for difference across subgroups.

Abbreviations**:** MoCA, Montreal Cognitive Assessment; ΔMoCA, change in MoCA score from baseline to year 3; TIA, Transient Ischemic Attack.

**Figure 2**




AF burden and correlation with cognition in patients with AF Caption: Overview of the proportion of time during the study spent in AF (AF burden) in participants with AF events ($n = 339$) and how it related to their final MoCA score at year three. (A) Histogram of AF burden in the dataset on a logarithmic x-scale to get an idea of the skewedness towards low AF-burden in the dataset. (B) Fitted spline trendline based on a scatterplot consisting of AF-burden and year three MoCA score for all 339 participants with AF events. (C) Same as (B) but using the difference in MoCA from baseline to year three, to provide an overview of the progression. Abbreviations: AF, Atrial Fibrillation; MoCA, Montreal Cognitive Assessment.

group had a higher $MoCA_{y3}$ score compared to baseline. Figure 2(C) shows a general increasing trend in MoCA score from baseline to year 3. Figure 3 provides an overview of ΔMoCA, defined as MoCA score from baseline to year 3, using boxplots stratified by AF burden in which no difference between the burden groups were found ($P = .3$).

Table III shows the results from 2 different linear regression models: M1 and M2, analyzing the association between AF burden and $MoCA_{y3}$. Only in M1 was 1 of 2 AF burden groups, $AF_{low}$ associated with a drop in ΔMoCA ($P = .03$) of 0.33-points. In M2, both load groups: $AF_{low}$ ($P = .12$) and $AF_{high}$ (0.4) were not associated with $MoCA_{y3}$. $MoCA_{baseline}$ score, age, diabetes and TIA or stroke were all significant ($P < .01$). An analysis was conducted using $MoCA_{y3}$ instead of ΔMoCA showing similar results as seen in the Supplementary Table 2. Supplementary Figure 4 shows an overview of frequency of MoCA < 26 at study year3 , stratified by burden group.

## MoCA < 26 according to subclinical AF status

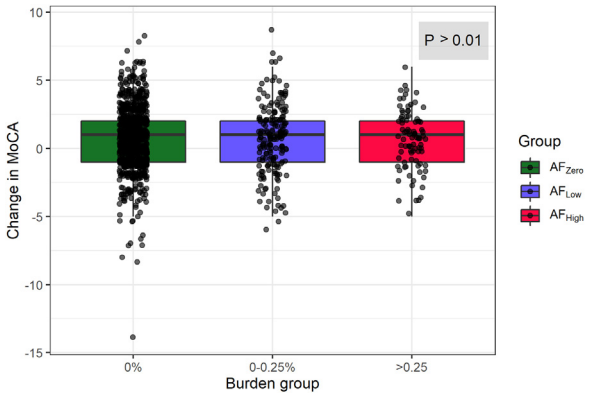
There was no association between frequency of MoCA < 26 at 3 years and AF burden group ($P = .6$) but both age and diabetes were associated ($P<.01$) with MoCA < 26 at 3 years. Figure 3 shows the barplot with informa-

**Table III.** Association between AF load and ΔMoCA ($n = 339$).

| Coeffcient | M1 | | | M2 | | |
|---|---|---|---|---|---|---|
| | Est | CI (95%) | *P* | Est | CI (95%) | *P* |
| $AF_{Low}$ | -0.33 | -0.63 – -0.03 | .03 | -0.24 | -0.53 – 0.06 | .1 |
| $AF_{High}$ | 0.09 | -0.32 – 0.51 | .6 | 00.17 | -0.24 – 0.58 | .4 |
| MoCA Baseline | 0.57 | 0.52 – 0.62 | <.01 | 00.56 | 0.51 – 0.60 | <.01 |
| Age [Years] | | | | -0.07 | -0.10 – -0.04 | <.01 |
| Gender [Male] | | | | -0.01 | -0.24 – 0.22 | .9 |
| Hypertension | | | | -0.17 | -0.61 – 0.27 | .4 |
| Diabetes | | | | -0.59 | -0.86 – -0.33 | <.01 |
| TIA or Stroke | | | | -0.63 | -0.93 – -0.33 | <.01 |

Caption**:** Results from the two linear regression models; M1 and M2, both with ΔMoCA (defined by $MoCA_{y3} - MoCA_{baseline}$) as the outcome parameter. The dependable variable is the categorical AF burden parameter (No AF, $AF_{low}$ and $AF_{high}$), where No AF is used as reference. M1 is a raw model where the only independent variable is baseline MoCA score. In M2, the model is further adjusted by known risk factors for cognitive decline and dementia.
Abbreviations**:** Est, Estimate; CI, Confidence Interval; P, P-value; AF, Atrial Fibrillation; MoCA, Montreal Cognitive Assessment; TIA, Transient Ischemic Attack.

**Figure 3**




Change in cognition stratified by AF burden or AF diagnosis for all patients Caption: Information about change of MoCA score (MoCA at year three compared to MoCA at baseline), stratified by burden group; No AF ($n = 855$), $AF_{low}$ ($n = 232$) and $AF_{high}$ ($n = 107$). A Kruskal Wallis test showed no statistical difference between the groups. Abbreviations: AF, Atrial Fibrillation; MoCA, Montreal Cognitive Assessment; TIA, Transient Ischemic Attack.

tion about each group as well as the baseline group. The logistic regression model also found no association between MoCA < 26 and AF burden.

## Discussion

The present study provides new knowledge about the relationship between cognitive decline and AF. Using ≈1.3 million days of continuous heart rhythm data along with MoCA scoring at baseline and at year 3 follow-up in 1194 participants without known AF but with risk factors, we were able to determine AF burden and relate it to cognitive changes. The key findings were: (1) There was no association between new-onset subclinical AF and cognitive decline. (2) There was no association between AF burden and cognitive decline in those with AF. (3) There was no association between AF burden and frequency of MoCA < 26.

### Theoretical link between AF and cognitive decline

Multiple mechanisms leading to cognitive decline and dementia in patients with AF have been investigated in previous studies.[14–16] One finding was that AF-induced ischemia does not only occur as a result of clinical strokes, but also due to subclinical vascular lesions with "silent" brain damage; macrovascular as well as microvascular. Furthermore, a study including 187 heart failure patients found that there was a reduced cardiac output and cerebral hypoperfusion associated with AF.[5] Hypothetically, the irregular cardiac contractions during AF causes beat-to-beat variability in flow which may worsen this hypoperfusion. Also, both AF and cognitive decline are linked to inflammation, and the inflammatory proteins found in either state could contribute to worsening of the other.[5] Finally, investigations into comorbidity-links between AF and cognitive dysfunction have been conducted, looking at issues such as (pre)diabetic metabolic disturbances and hypertension-induced strain on the blood vessels causing damage to the brain.[15,17]

### AF diagnosis and Cognitive Impairment

A recent epidemiologic review by Ding *et al.* listed 14 studies investigating the association between AF and cognitive impairment by including between $n = 553$ and $n = 31.500$ participants followed between 2 and 25 years.[18] 9 out of these 14 studies found a statistical association between AF diagnosis and cognitive impairment mainly based on the Mini Mental State Examination (MMSE). This is not in line with the results of this paper (Figure 1) where no association between AF diagnosis and cognitive impairment based on MoCA score was found. One explanation for this could be that all 14 studies included patients with clinically diagnosed AF, while the LOOP study investigated individuals without a

history of AF, who often had subclinical AF when thoroughly investigated. Patients with clinical AF will likely have received the diagnosis due to illness, high AF burden or symptoms that trigger a clinical investigation and will have a far longer history of AF than those with new-onset subclinical AF.

### AF burden and Cognitive Impairment

One of the main strengths of this study distinguishing it from previous studies is the high diagnostic accuracy of subclinical AF in the participants, and the measurement of AF burden over a 3-year period. This provides the opportunity to investigate if the theoretical links are dependent on the severity of AF and not just the presence of the diagnosis. As seen by the AF burden boxplot in Figure 2(A) of participants with new-onset subclinical AF, the median AF burden of 0.072% (0.02,0.39) indicates that it is unlikely that routine investigation for AF, would result in a diagnosis in the majority of the participants. Furthermore, as indicated by the U-shape of the spline trendline in **Figure 2**(B), the participants with high AF burden in the current study could comprise a healthier subgroup of AF patients. Additionally, the learning bias introduced by the annual tests, can be seen in Figure 2(C). While this provides an unnatural picture of progression in MoCA score throughout the study, it does not influence the within-individual regression analysis, since all participants in the current study were exposed to the MoCA test an equal number of times. In M1, $AF_{low}$ was significantly associated ($P$=.03) with a negative ΔMoCA (point estimate = -0.33), but the significance disappeared after adjustment for risk factors (see Table III). The previously mentioned risk factors linking AF with cognitive decline was in line with the findings in M2: age, diabetes and TIA or stroke. However, a supplementary analysis (see Supplementary Table 4) showed that all risk factors but diabetes became insignificant when patients with prior stroke or a $MoCA_{baseline}$ < 26 were excluded. While the 207 participants excluded in order to ensure equal test exposure differed from the study population in terms of higher age, lower $MoCA_{baseline}$ and more comorbidity (Table I) as well as AF load, no significant association to prevalence of AF diagnosis was found.

No association between subclinical AF and MoCA < 26 at 3 years was found. A drop from a score of 30 (or 31 if uneducated) to < 26 is substantial. Even if AF has an influence on the pace at which a MoCA < 26 is reached, other risk factors such as stroke or family history of dementia are likely more dominant during a limited time span of 3 years. This is further empathized by the fact that the AF burden in the dataset was low, partly due to the high diagnostic accuracy of the ILR, capable of detecting subclinical AF episodes. The previously mentioned studies using traditional methods for diagnosing AF, were more likely to find patients with high AF burden, where AF-induced ischemia and other complications occur at a much higher pace. Also, the threshold MoCA < 26 was based on a report by the Danish Health Authority in 2018,[11] however, the threshold has been widely argued to be placed as low as a MoCA score < 22.[11] A supplementary test of MoCA < 22 and AF burden showed similar findings, and can be found in the Supplementary Figure 2.

### Treatment for AF

A possible explanation why no associations were found between AF diagnosis or AF burden and cognitive decline, could be the rigorous monitoring for unknown AF and concomitant OAC treatment in the vast majority of patients. As OAC reduce the risk of clinical thromboembolic events, it is also supposed to mitigate small-vessel and larger vascular changes leading to cognitive decline.[14] There is still no prospective studies of the effect of OAC on AF-induced cognitive decline, although multiple studies are ongoing.[5] However, a population-based cohort study using the U.K. Clinical Practice Research Datalink (2008–2016) showed that only patients with clinical AF and without OAC were at increased risk of dementia compared to patients without AF or with AF and receiving OAC, suggesting that OAC may give a protective effect on cognitive decline in relation to AF (Field *et al.* 2019). However, future randomized clinical trials are needed before definite conclusions can be made.[19] AF is frequently observed in remote monitoring of device patients and since the documentation of an protective effect of OAC to prevent strokes have been incomplete the general guidelines are conservative recommending that device-detected AF (subclinical AF) should have a duration of > 24 hours before OAC is indicated (Gorenek *et al.* 2017).[20] These recommendations are being investigated in the ongoing randomized controlled ARTESIA and NOAH AFnet trials (Lopes *et al.* 2017, Kirchhof *et al.* 2017), where patients with AF episodes < 24 hours are included.[21,22]

## Limitations

The findings are limited by the fact that the algorithm used in the ILR has a sensitivity of ≈95% to detect AF, while the specificity is lower.[23] However, a rigorous adjudication regimen was applied, and the unrecognized or falsely detected AF episodes would mostly have been short, and thus not a huge problem when investigating the AF burden.

Another limitation is that the dataset contained no information regarding stroke making its association to cognitive decline unknown.

Furthermore, the fact that most AF positive participants had a low AF burden could also be a limitation to the study, in the case that cognitive change requires a larger burden to occur.

Another limitation is the exploratory method used to group participants into AF burden groups. The arbitrary cutoffs were based on the distribution of AF burden since no clinical cutoffs exist for association with cognitive impact. However, the categorization of AF burden was considered optimal, as no signal was found in a model with AF burden as a continuous variable, see Figure 2. Results from the regression model with a continuous AF burden parameter, can be found in the Supplementary Table 3.

Importantly, the multiple cognitive assessments introduce a learning bias which was accounted for by exclusion of participants with missing MoCA scores during the 3 years of follow-up to ensure that all included participants underwent an equal number of assessments. This led to the exclusion of more comorbid participants with lower baseline MoCA scores (Table I). In this way, the study was limited by the fact that MoCA was performed at year 1 and 2. However, the models were statistically adjusted for baseline MoCA score, and there were no differences in AF diagnosis or AF burden between those included or excluded from the analyses. Yet, pre-existing subclinical AF could not be excluded at baseline which is a limitation of the study. The study could also be underpowered for the association between AF and cognitive decline either due to short follow-up, population size, population selection, or the performance of the cognitive test. Finally, we cannot rule out that cognitive decline associated with AF burden may occur at a later stage and therefore will remain undetected due to our relative short follow-up. We are planning to perform an extended follow-up of the LOOP study participants.

## Conclusion

Using data from >3 years of continuous heart rhythm monitoring in 1196 participants with stroke risk factors, of whom 397 (33%) were found to have AF and 324 (96 %) of these received concomitant OAC, we found no association between AF diagnosis or AF burden and change in MoCA score. A possible explanation could be that the early detection and treatment might mitigate the accelerated cognitive decline attributed to AF in other studies. Other possible explanations include the relatively short follow-up and the exclusion of subjects in whom one or more annual MoCA scores were missing. Future studies should test the effect of early AF detection and treatment on cognitive decline in a randomized setting.

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## Conflicts of interest

S.Z.D. reports to be a part-time employee of Vital Beats not related to this work. K.J.H. reports travel and educational grants from Medtronic, Abbott, and Biotronik and speaker honoraria from Boehringer-Ingelheim not related to this work. A.B. reports a research grant from Gilead and speaker honoraria from Bayer, Boehringer Ingelheim, Merck Sharp & Dohme, and Bristol-Myers Squibb not related to this work. D.W.K reports to be a member of a Medtronic advisory board on stroke and has received speaker honoraria and travel grants from Medtronic, St Jude Medical, and Boehringer Ingelheim, outside the submitted work.. AGH is an employee of Acesion Pharma, outside the submitted work L.K. reports speaker honoraria from, Bayer, Astra-Zeneca, Orion Pharma, Novartis, and Sanofi, not related to this work. J.H.S. reports to be a member of Medtronic advisory boards and to have received speaker honoraria and research grants from Medtronic in relation to this work.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.08.006.

## References

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed

in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42(5):373–498.
2. Marzona I, O'Donnell M, Teo K, Gao P, Anderson C, Bosch J, Yusuf S. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. Can Med Assoc J 2012;184:E329–36.
3. Nishtala A, Piers RJ, Himali JJ, et al. Atrial fibrillation and cognitive decline in the Framingham Heart Study. Heart Rhythm 2018;15:166–72.
4. Cao L, Pokorney SD, Hayden K, et al. Cognitive function: is there more to anticoagulation in atrial fibrillation than stroke? *J Am Heart Assoc* [Internet]. 2015. [cited 2020 Nov 23];4. Available from: https://www.ahajournals.org/doi/10.1161/JAHA.114.001573.
5. Dietzel J, Haeusler KG. Endres M. does atrial fibrillation cause cognitive decline and dementia? EP Eur 2018;20:408–19.
6. Rydén L, Zettergren A, Seidu NM, et al. Atrial fibrillation increases the risk of dementia amongst older adults even in the absence of stroke. J Intern Med 2019;286:101–10.
7. Sepehri Shamloo A, Dagres N, Müssigbrodt A, et al. Atrial fibrillation and cognitive impairment: new insights and future directions. Heart Lung Circ 2020;29:69–85.
8. 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.
9. Mast BT, Gerstenecker A. Chapter 19 - screening instruments and brief batteries for dementia [Internet]. Handbook of Assessment in Clinical Gerontology (Second Edition) Lichtenberg PA, editor. San Diego: Academic Press; 2010 [cited 2020 Oct 16]. p. 503–530.Available from: http://www.sciencedirect.com/science/article/pii/B9780123749611100193.
10. Davis KK, Allen JK. Identifying cognitive impairment in heart failure: A review of screening measures. Heart Lung 2013;42:92–7.
11. . Danish national health authority. diagnostics of mild cognitive impairment and dementia. National clinical guidelines 2018.
12. Herm J, Schirdewan A, Koch L, et al. Impact of atrial fibrillation burden on cognitive function after left atrial ablation – Results of the MACPAF study. J Clin Neurosci 2020;73:168–72.
13. Wickham H, Averick M, Bryan J, et al. Welcome to the Tidyverse. J Open Source Softw 2019;4:1686.
14. Diener H-C, Hart RG, Koudstaal PJ, et al. Atrial fibrillation and cognitive function. J Am Coll Cardiol 2019;73:612–19.
15. Staerk L, Sherer JA, Ko D, et al. Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes. Circ Res 2017;120:1501–17.
16. Kirchhof P, Bax J, Blomstrom-Lundquist C, et al. Early and comprehensive management of atrial fibrillation: Proceedings from the 2nd AFNET/EHRA consensus conference on atrial fibrillation entitled "research perspectives in atrial fibrillation. Europace 2009;11:860–85.
17. Iadecola C, Gottesman RF. Neurovascular and Cognitive Dysfunction in Hypertension: Epidemiology, Pathobiology, and Treatment. Circ Res 2019;124:1025–44.
18. Ding M, Qiu C. Atrial Fibrillation, Cognitive Decline, and Dementia: an Epidemiologic Review. Curr Epidemiol Rep 2018;5:252–61.
19. Field TS, Weijs B, Curcio A, et al. Incident atrial fibrillation, dementia and the role of anticoagulation: a population-based cohort study. Thromb Haemost 2019;119:981–91.
20. Gorenek B, Bax J, Boriani G, et al. Device-detected subclinical atrial tachyarrhythmias: definition, implications and management—an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). EP Eur 2017;19:1556–78.
21. Kirchhof P, Blank BF, Calvert M, et al. Probing oral anticoagulation in patients with atrial high rate episodes: Rationale and design of the Non–vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes (NOAH–AFNET 6) trial. Am Heart J 2017;190:12–18.
22. Lopes RD, Alings M, Connolly SJ, et al. Rationale and design of the apixaban for the reduction of thrombo-embolism in patients with device-detected sub-clinical atrial fibrillation (ARTESiA) trial. Am Heart J 2017;189:137–45.
23. 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.