**Prevalence and prognostic significance of device-detected subclinical atrial fibrillation in patients with heart failure and reduced ejection fraction**

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**Abstract**

**Background:** Cardiac implanted electronic devices (CIEDs) can detect short durations of previously unrecognised atrial fibrillation (AF). The prognostic significance of device-detected subclinical AF, in the context of contemporary heart failure (HF) therapy, is unclear.

**Methods:** Amongst patients enrolled in the Remote Monitoring in HF with implanted devices (REM-HF) trial, three categories were defined based on total AF duration in the first year of follow-up: no AF, subclinical AF (≥6 minutes to ≤24 hours), and AF >24 hours. All-cause mortality, stroke, and cardiovascular hospitalisation were assessed.

**Results:** 1,561 patients (94.6%) had rhythm data: 71 (4.6%) had subclinical AF (median of 4 episodes, total duration 3.1 hours) and 279 (17.9%) had AF >24h. During 2.8±0.8 years’ follow-up, 39 (2.5%) patients had a stroke. Stroke rate was highest among patients with subclinical AF (2.0 per 100-person years) versus no AF or AF >24h (0.8 and 1.0 per 100-person years, respectively). In the overall cohort, AF >24h was not an independent predictor of stroke. However, amongst patients with no history of AF (n=932), new-onset subclinical AF conferred a three-fold higher stroke risk (adjusted HR 3.35, 95%CI 1.15-9.77, p=0.027). AF >24h was associated with more frequent emergency cardiovascular hospitalisation (adjusted HR 1.46, 95%CI 1.19-1.79, p<0.0005). Neither AF classification was associated with mortality.

**Conclusions:** In patients with HF and a CIED, subclinical AF was infrequent but, as a new finding, was associated with an increased risk of stroke. Anticoagulation remains an important consideration in this population, particularly when the clinical profile indicates a high stroke risk.

**Keywords:** Atrial fibrillation, heart failure, cardiac implanted electronic device, stroke.**Introduction**

 In patients with heart failure (HF), clinically detected atrial fibrillation (AF) has been associated with reduced life-expectancy1, more frequent hospitalisation2, and possible attenuated benefits of proven HF therapies, including beta-blockers3 and cardiac resynchronisation therapy4. Importantly, with greater use and sophistication of cardiac implanted electronic devices (CIEDs) for HF treatment, it has now become possible to detect even short-lived episodes of previously unrecognised atrial arrhythmias in this population. Many of these ‘subclinical’ episodes, which are often less than 24 hours in duration, are verified to be AF but are either asymptomatic or confer few additional symptoms. Limited data exist regarding their association with clinical outcomes amongst patients with HF and, as yet, the optimal management of subclinical AF in the setting of HF remains unclear.

One expectation is that more sensitive detection and quantification of AF may improve the prevention of ischaemic stroke by enabling earlier initiation of oral anticoagulant therapy. To date, however, the minimum duration of AF that poses a stroke risk has not been reproducibly identified. Furthermore, among patients with HF, the incidence of stroke and the number of patients without pre-existing anticoagulation, in whom this may be initiated, may be low, thus limiting the benefits of this approach. Alternatively, recent data suggest that incident and worsening HF are more frequent adverse outcomes than stroke, amongst patients with AF5, and in the ASSERT trial, for example, even short durations of AF were associated with an increased risk of HF hospitalisation6. Only a minority of patients enrolled in ASSERT (13%) had previous HF, hence this association may be magnified in a HF population and have important implications for therapeutic decision making.

In order to determine the prevalence and prognostic significance of subclinical AF in a large contemporary cohort of patients with HF and reduced ejection fraction (HFrEF), we analysed CIED-detected rhythm data and adjudicated clinical outcomes for patients enrolled in the Remote Management of Heart Failure Using Implanted Electronic Devices (REM-HF) trial7. We hypothesised that subclinical AF, defined as CIED-detected AF lasting between 6 minutes and 24 hours, would not be associated with an increased risk of stroke, but would identify patients at increased risk of cardiovascular (CV) hospitalisation and death, and therefore provide relevant information for risk stratification in HF.

**Methods**

The design8 and results7 of the REM-HF trial have been reported previously. In summary, 1650 patients with stable HFrEF (NYHA class II-IV) and a CIED implanted within 6 months7, were randomized 1:1 to receive usual care or management informed by remote monitoring. The primary endpoint was a composite of death or unplanned CV hospitalisation, and was not different between treatment groups7. All patients participating in the trial provided written informed consent and the trial conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by independent ethics committees at each participating site.

For the present study, all device-detected atrial high rate episodes recorded within the first year of follow-up were captured and summated. For patients without an intra-atrial lead, where rhythm data were unavailable from remote transmission, rhythm data were obtained from routine (12-month) in-person CIED interrogation. Although individual episodes were not exhaustively adjudicated, such episodes have been shown to correlate well with electrocardiographic documentation of AF9, and will be referred to as AF in this manuscript. We initially defined four mutually exclusive rhythm categories based on the total duration of AF in the first year of follow-up: (1) no device-detected AF, (2) subclinical AF, lasting >6 minutes to ≤24 hours, (3) paroxysmal AF, lasting >24 hours to <7 days, and (4) persistent AF (≥7 days to <1 year) or longstanding persistent (LSPAF, continuously present for the duration of monitoring). The definition of subclinical AF was adopted from the European Heart Rhythm Association expert consensus statement on device-detected subclinical atrial tachyarrhythmias10. A minimum duration of 6 minutes was similarly used to define the lower-limit of subclinical AF in the ASSERT trials11, 12. As few patients were found to have paroxysmal AF by this classification, a combined category incorporating all patients with a total AF duration in the first year of greater than 24 hours (AF >24h), was defined for risk prediction modelling. The time of onset, duration, or symptoms associated with individual AF episodes were not available for this study. Similarly, additional rhythm data to chart the progression of subclinical AF to AF >24h, beyond the first year of monitoring, was not captured. Patients who died within the first year of follow-up (n=65) were categorised according to the rhythm data available (no AF=53, subclinical AF=0, paroxysmal AF=1, persistent AF=11). All hospitalisations and deaths occurring during the trial were recorded and adjudicated, and additional data was collected regarding non-hospitalisation clinical activity, such as clinic visits and telephone calls8.

*Statistical analysis*

Patient characteristics were compared between rhythm groups using the Chi-squared goodness of fit (categorical variables), one-way analysis of variance (continuous variables) or Wilcoxon rank-sum/Kruskal-Wallis tests (for non-normally distributed data). Categorical variables are reported as frequency (%), continuous variables as mean (SD) or median (LQ-UQ). Rates of stroke, hospitalisation, and death were calculated from the total number of events divided by the number of person-years at risk for each event.

Cox proportional hazard models were used to compare the risk of all-cause and CV mortality (as endpoints) between rhythm groups, adjusting for relevant baseline variables, using no AF as the reference. The proportional hazard assumption was checked using the scaled Schoenfeld residuals and found to be valid13. Competing risks regression, based on Fine and Gray’s proportional sub-hazards model, was used to compare the cumulative incidence functions of ischaemic stroke or CV hospitalisation between rhythm groups, with death assigned as a competing risk14. Regression models for ischaemic stroke were adjusted for age, sex, and baseline anticoagulation use. Due to the low number of stroke events, further multivariable adjustment was not performed to avoid statistical overfitting. A sensitivity analysis was performed in which patients with a history of AF or flutter ablation (n=108) were excluded. p-values are reported as two-sided with significance at p<0.05. Analyses were conducted with STATA version 14 (StataCorp LP, TX, USA).

**Results**

*Prevalence of subclinical atrial fibrillation*

During the first year of enrolment, CIED-detected rhythm data were available for 1561 patients (94.6% of the REM-HF cohort; mean age [±SD] 69.4±10.2, 14% female). Since REM-HF was designed to be a pragmatic trial, representative of real-world clinical practice, in the remaining 89 patients, the treating physician had judged that management of atrial rhythm status was of insufficient clinical priority to warrant implantation of an atrial lead, and therefore accurate rhythm assessment was not possible. Patients without rhythm data were marginally less likely to be treated with an ACEI or ARB, and more likely to have CRT-P (versus CRT-D), as compared to patients with rhythm data available. Other baseline characteristics were similar between groups (**Supplemental Table 1**).

Among patients with rhythm data available, 71 (4.6%) were classified as having subclinical AF (n=49 [69%] as a new diagnosis i.e. no history of AF documented at baseline), 279 (17.9%) had AF >24h (n=59 [21%] as a new diagnosis) based on the total duration of AF in the first year of follow-up (**Figure 1**). In patients with subclinical AF, the median number of AF episodes over one year was 4 (LQ-UQ 2-20) and the median total duration of AF was 3.1 hours (LQ-UQ 0.6-6.9 hours). The median duration of the longest AF episode was 1.7 hours (LQ-UQ 0.3-5.3 hours), which significantly correlated with total AF duration (Spearman’s rho 0.93, p<0.0001). There was no correlation between the number of AF episodes and total AF duration (p=NS).

*Patient characteristics*

Compared to patients with either no AF or AF >24h, those with subclinical AF were more frequently female, NYHA class 3 (versus 2), had CRT-D (versus CRT-P or ICD alone), and had a higher systolic blood pressure (**Table 1; Supplemental Table 2**). Baseline heart rate was incrementally higher with increasing AF burden (i.e. lowest values in patients with no AF, highest values in patients with AF >24h). Eleven (15.4%) patients with subclinical AF and 31 (11.2%) patients with AF >24h reported a previous ablation procedure for AF or atrial flutter. Comorbid diseases were equally distributed and mean CHA2DS2VASc scores similar across rhythm groups. Loop diuretic and cardiac glycoside (digoxin) therapy were more frequently used, and anti-arrhythmic therapy (typically amiodarone) less frequently used in patients with any AF versus no AF (**Table 1**). In total, 26% of patients with subclinical AF and 73% of patients with AF >24h were prescribed oral anticoagulation at enrolment.

*Risk of ischaemic stroke and systemic embolism*

During a mean (SD) follow up of 2.8±0.8 years, 41 adjudicated systemic thromboembolic events occurred in 39 (2.5%) patients (30 ischaemic strokes, 11 transient ischaemic attacks). In 1 patient, ischaemic stroke was attributed as the cause of death. The crude incidence of ischaemic stroke or systemic embolism was highest among patients with subclinical AF (2.0 events per 100 person-years) versus no AF (0.8 events per 100 person-years) or AF >24h (1.0 event per 100 person-years; **Supplemental Figure 1A-B**). After adjustment for baseline anticoagulation use and death as a competing risk, there was no significant association between AF >24h (adjusted HR 1.35, 95%CI 0.58-3.14, p=0.488) and ischaemic stroke but there was a possible trend towards an association between subclinical AF and stroke (adjusted HR 2.56, 95%CI 0.90-7.29, p=0.079). When the analysis was restricted to patients with no prior history of AF or flutter (n=923), the association between newly detected subclinical AF and stroke risk was significant (adjusted HR 3.35, 95%CI 1.15-9.77, p=0.027). There were no stroke events amongst patients with newly detected AF >24h.

The median duration of AF, the duration of the longest episode, and the median number of AF episodes in the first year of follow-up, were not significantly different between patients with and without a stroke event (data not shown). Additionally, amongst patients with a stroke event, 9/27 patients with no AF, 1/4 patients with subclinical AF, and 5/8 patients with AF >24h were already prescribed anticoagulation at baseline (**Supplemental Figure 1B**). One further patient with subclinical AF was commenced on anticoagulation during the trial, prior to their stroke event. Thus, 18 (1.5%) patients with no AF, 2 (2.8%) patients with subclinical AF and 3 (1.1%) patients with AF >24h had a stroke event while not receiving anticoagulation. Assuming AF >24h could be detected without monitoring, in total, 3511 patient-years of RM for individuals with no clinically detected AF, was required to identify 2 additional patients in whom anticoagulation might have prevented a stroke.

*Risk of hospitalisation and death*

In total, 567 patients (36.3%) had a CV hospitalisation: 410 (33.9%) patients with no AF, 25 (35.0%) patients with subclinical AF, and 132 (47.3%) patients with AF >24h (p<0.0005 across groups). Decompensated HF was the most common reason for CV hospitalisation for all rhythm groups (**Supplemental figure 2**). Patients with subclinical AF had the highest rate of hospitalisation for device-related complications. After adjustment for differences in baseline characteristics, only AF >24h, and not subclinical AF, was independently associated with an increased risk of CV hospitalisation, as compared to patients with no AF (**Table 2, Figure 2**). When the analysis was restricted to patients with no prior history of AF or flutter (n=923), there was a possible trend towards increased CV hospitalisation amongst patients with newly detected subclinical AF, but this did not achieve statistical significance (adjusted HR 1.60, 95% CI 0.97-2.62, p=0.065, **Supplemental Table 3**).

Two hundred and fifty-two patients (16.1%) died during follow-up. Progressive HF (i.e. pump failure) was the most common cause of death in patients with either AF >24h or no detected AF; progressive HF and other causes for CV death, besides HF and sudden arrhythmia, were equally prevalent in patients with subclinical AF (**Supplemental Figure 2**). In multivariable adjusted Cox models, neither subclinical AF nor AF >24h were significantly associated with all-cause mortality in the overall cohort (**Table 2, Figure 2**) or in the subset of patients with newly detected AF (**Supplemental Table 3**).

**Discussion**

In this large contemporary HF cohort from the REM-HF trial, less than 5% of patients exhibited CIED-detected subclinical AF lasting between 6 minutes and 24 hours (and 18% of patients exhibited AF >24h). Most cases of subclinical AF were new diagnoses. The absolute number of ischaemic stroke or systemic embolism events was low (2.5% of the total cohort). In the overall analysis there was no association between AF >24h and stroke risk. However, amongst the subset of patients with newly detected subclinical AF (i.e. no history of AF or atrial flutter at enrolment), there was a three-fold elevated risk of stroke, and the increased risk of stroke appeared similar (albeit not statistically significant at a nominal p value of 0.05) in those with a history of this at enrolment. By contrast, only an AF duration >24h, but not subclinical AF, was associated with an increased risk of CV hospitalisation, and neither AF classification was independently associated with all-cause mortality. Taken together, these findings suggest that CIED-detected subclinical AF, as a new diagnosis, may be a clinically relevant risk factor for stroke, however it does not appear to increase mortality or CV hospitalisation in the context of contemporary medical therapy for HF.

*Prevalence of subclinical AF*

The advent of modern CIEDs that enable continuous, long-term monitoring has led to the detection of previously unrecognised atrial arrhythmias of short duration. Although different studies have used different cut-offs to define subclinical AF, a lower limit of 6 minutes has been suggested to minimise false positives9, and was used to identify subclinical AF in patients with a CIED in the ASSERT trial11. By this definition, and using an upper limit of 24 hours to define clinically relevant device-detected AF (based on expert consensus10and the threshold of AF associated with adverse outcomes in the ASSERT trial15), only 5% of the REM-HF population were identified to have subclinical AF (3.1% as a new diagnosis).

This is seven times lower than the prevalence of subclinical AF, using a similar definition, among comparatively aged older persons, with no known history of AF, in ASSERT II (mean age 73.9 years, 8.6% patients with HF)12. One potential explanation could be the shorter duration of rhythm monitoring in the REM-HF trial (1 year) versus ASSERT II (16±4 months), giving rise to a lower rate of detection among patients with HF. Alternatively, and perhaps more likely, a higher rate of progression from subclinical AF to persistent forms of AF may occur in patients with HF, and within a short(er) timeframe, as compared to individuals without HF. This is supported by the low prevalence of paroxysmal (versus persistent) AF in our cohort. The rate of progression of subclinical AF to AF>24h in the general population is reported as 15-16% 6, 16; a comparative figure for patients exclusively with HF has not been reported. Given that HF is a strong risk factor for AF, as are HF-associated characteristics, such as left atrial dilatation, our data suggest that the population prevalence of subclinical AF, which does not progress to longer (>24h) durations of AF, in patients with established HF is low.

*Subclinical AF and ischaemic stroke*

In previous studies, the minimum AF duration reported to confer an increased risk of stroke has varied between 6 minutes11, 3.8 hours17, 5.5 hours18, and 24 hours19. In the most recent analysis of data from the ASSERT trial, only subclinical AF or AT >24 hours was associated with an increased the risk of stroke or systemic embolism within a general population of patients with a CIED and no prior history of AF (mean follow-up 2.5 years)15. In the present study, we extend these observations to a large real-world population of patients exclusively with HFrEF and demonstrate that subclinical AF of less than or equal to 24 hours’ duration was associated with a significantly increased risk of ischaemic stroke, only when this was a new finding. It is relevant to note that in the REM-HF trial, few stroke events occurred over the trial duration (mean follow-up 2.8 years), and stroke events were not a stated primary or secondary endpoint. Therefore, these data must be considered hypothesis-generating only. Nevertheless, 2 out of 4 stroke events in patients with subclinical device-detected AF occurred in patients who were not prescribed anticoagulation at the time of their event, hence the potential for prevention may exist, although the overall scope for a CIED-rhythm monitoring strategy to significantly improve upon stroke prevention in HF at a population level may be limited.

For individual patients with HF and subclinical AF, current management guidelines recommend anticoagulation based on stroke risk (i.e. CHA2DS2-VASc score) for CIED-detected episodes of atrial high rate >180bpm lasting greater than 5-6 minutes, with additional electrocardiographic documentation of AF to support the initiation of anticoagulation20. As most patients do not exhibit a temporal association between CIED-detected AF episodes and their stroke event17, 21, and the daily burden of AF does not appear to be reliable marker of stroke risk, based on our data and others22, these guideline recommendations might be open to challenge. Additionally, in randomised studies to date, early anticoagulation for subclinical AF lasting greater than 24 or 48 hours in duration has not consistently been shown to reduce stroke risk23, 24. Thus, for all patients with subclinical AF careful consideration of the risks and benefits of long-term anticoagulation is essential until further evidence is obtained from ongoing trials (SILENT-NCT02004509; ARTESiA-NCT01938248; NOAH-NCT02618577; LOOP-NCT02036450).

The lack of an independent association between AF >24h and stroke risk in this study is also interesting. Currently, it remains unclear whether patients with ‘asymptomatic’ AF >24h have a similar stroke risk to patients with symptomatic AF that is clinically detected and confirmed. Although, the present study was not designed to evaluate stroke risk as a primary outcome, factors such as the low rate of stroke events, as well as the high competing risk of death, in patients with HFrEF and AF, are likely to be relevant for contemporary stroke risk. A recent systematic review of 13 studies (n=54,587) examining patients with HF and AF, which included post-hoc analyses of randomised trials and observational studies, reported that only 55% of patients with HFrEF and AF were prescribed oral anticoagulation on pooled analysis25. Our data supports this observation and suggests that the use of oral anticoagulation in this population remains substantially below guideline-recommended levels.

*Subclinical AF, HF hospitalisation, and mortality*

New-onset of AF after CIED implantation (mostly persistent AF)26, 27, clinically-detected paroxysmal AF2, and CIED-detected AF episodes longer than 24hours6, have all been linked to higher rates CV hospitalisation. However, few studies have examined whether subclinical AF confers a similar risk in patients with HF. In a registry study of 1193 patients with HF and CRT, Santini et al. extended their examination to a lower AF duration cut-off (≥10 minutes), but found no increase in HF hospitalisation rate until AF was continuously present for more than 7 days28 (11.4% of patients hospitalised, median follow-up 13 months). In the present study, with a higher hospitalisation rate (36% patients hospitalised) and longer follow-up (mean 2.8 years), subclinical AF was not associated with an increased risk of emergency CV hospitalisation. Importantly, however, AF durations >24 hours were an independent risk factor, suggesting that close surveillance for progression to persistent AF may be the most valuable aspect of continuous CIED-rhythm monitoring with respect to identifying patients at risk of decompensation.

The lack of a positive association between subclinical AF or AF >24h and all-cause mortality in this study mirrors findings in other HF trial cohorts2. In part, this may be a reflection of high rates of use of medical therapy, but overall, it also suggests that AF is more a marker of advanced HF rather than an independent prognostic factor in patients with HFrEF and a CIED. Thus, in addition to rhythm-targeted treatment strategies, which have been shown to be beneficial in selected patients with HFrEF29, 30, our data highlight a concurrent need to identify rhythm-independent treatment strategies in order to further improve life-expectancy for patients with HFrEF and AF.

*Limitations*

This study represents a post hoc analysis of the REM-HF trial, and therefore our findings with respect to rhythm groups should be considered exploratory. We did not routinely adjudicate individual episodes of device-detected atrial tachyarrhythmia, therefore a proportion of episodes may reflect atrial flutter, atrial tachycardia or artefact, although published data suggest that exclusion of episodes of less than 6 minutes eliminates most over-sensing9. Because all participants in this study were symptomatic (NYHA class II or above) and there may be significant overlap in symptoms relating to AF and HF, our classification of subclinical AF was based on the duration of AF alone, rather than the absence of AF-related symptoms (i.e. ‘silent’ AF), which has been included as a diagnostic criterion in some non-HF studies. Surface ECG-verification of AF was not systematically recorded and information regarding the timing of individual AF episodes or AF duration beyond the first year of follow-up were not available. Therefore, we were unable to delineate the temporal relationship between AF episodes and clinical outcomes, or the rate of progression from subclinical AF to more persistent AF forms. The overall number of stroke events was low leading to reduced power to detect associations. Additional events are likely to have occurred with longer follow-up. Finally, compared to men, women with HF were underrepresented in the REM-HF trial cohort, therefore evaluation of sex-specific prevalence of subclinical AF or outcomes were not possible.

**Conclusions**

In a contemporary cohort of patients with HFrEF and a CIED, detection of subclinical AF lasting less than or equal to 24 hours, which did not progress to longer AF durations, was infrequent (<5% population), and was not associated with an overall increased risk of stroke, CV hospitalisation or mortality. However, for the subset of patients in whom subclinical AF was a new finding, the stroke rate was increased, emphasising the importance of considering anticoagulation when a patient’s clinical profile indicates a risk of stroke. Conversely, when AF was present for greater than 24 hours’ duration, there was a greater risk of CV hospitalisation, including hospitalisation for worsening HF. Thus, CIED-surveillance that identifies progression from sinus rhythm to persistent AF forms, may contribute relevant information for risk stratification in HF and allow better targeting of hospitalisation avoidance measures.

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**Declaration of interest**

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**Figure legends**

**Figure 1.** Prevalence and duration of device-detected atrial fibrillation (AF) during the first year of follow-up. *LSPAF, longstanding persistent AF*.

**Figure 2.** Cumulative incidence of A) all-cause mortality, B) cardiovascular hospitalisation (with death as a competing risk) by AF burden.

**Table 1. Baseline characteristics**

|  |  |  |
| --- | --- | --- |
| Characteristic | AF burden at 1-year follow-up | p value |
|  | **No AF** **(n=1211)** | **Sub-clinical AF (n=71)** | **AF >24h****(n=279)** |  |
| Randomisation groupRemote monitoring, n (%)Usual care, n (%) | 616 (50.9)595 (49.1) | 41 (57.8)30 (42.3) | 140 (50.2)139 (49.8) | 0.503 |
| Age (y) | 68.9 ±10.3 | 68.3±9.9 | 72.1±9.1 | <0.00005 |
| Male, n (%) | 1029 (85.0) | 58 (81.7) | 253 (90.7) | 0.028 |
| Systolic BP (mmHg) | 119.9±17.9 | 120.8±21.4 | 114.6±16.2 | <0.00005 |
| Diastolic BP (mmHg) | 70.0±11.2 | 70.4±11.5 | 70.0±11.0 | 0.865 |
| Heart rate (bpm) | 67.7±10.0 | 69.8±10.6 | 70.7±9.8 | 0.0002 |
| BMI (kg/m2) | 28.9±5.7 | 29.1±5.1 | 29.0±5.3 | 0.177 |
| NYHA, n (%)IIIIIIV | 862 (71.2)347 (28.7)2 (0.2) | 41 (57.8)29 (40.9)1 (1.4) | 186 (66.7)93 (33.3)0  | 0.012 |
| Type of CIEDICDCRT-DCRT-P | 446 (36.8)622 (51.4)143 (11.8) | 15 (21.1)46 (64.8)10 (14.1) | 68 (24.4)169 (60.6)42 (15.1) | <0.0005 |
| Previous AF/flutter | 400 (33.0) | 22 (31.0) | 216 (77.4) | <0.0005 |
| Prior AF ablation, n (%) | 42 (3.5) | 7 (9.9) | 22 (7.9) | 0.001 |
| Prior A flutter ablation, n (%) | 22 (1.8) | 5 (7.0) | 10 (3.6) | 0.006 |
| Prior AF or flutter ablation, n (%) | 62 (5.1) | 11 (15.5) | 31 (11.1) | <0.0005 |
| Prior VT ablation, n (%) | 36 (3.0) | 7 (9.9) | 9 (3.3) | 0.007 |
| Hypertension, n (%) | 388 (32.2) | 29 (40.9) | 92 (33.5) | 0.311 |
| Prior MI, n (%) | 715 (59.4) | 44 (62.0) | 164 (59.6) | 0.911 |
| Prior CABG surgery, n (%) | 367 (30.5) | 26 (36.6) | 95 (34.6) | 0.265 |
| Prior PCI, n (%) | 306 (25.4) | 20 (28.2) | 61 (22.2) | 0.439 |
| Documented CAD, n (%) | 812 (67.4) | 49 (69.0) | 192 (69.8) | 0.722 |
| COPD, n (%) | 143 (11.9) | 6 (8.5) | 23 (8.4) | 0.189 |
| Prior stroke or TIA, n (%) | 161 (13.4) | 9 (12.7) | 45 (16.4) | 0.411 |
| Diabetes mellitusI, n (%)II, n (%)II on medication | 13 (1.1)293 (24.2)205 (17.2) | 021 (29.6)14 (20.0) | 1 (0.4)82 (29.4)53 (19.2) | 0.2290.649 |
| Valve disease, n (%) | 50 (5.4) | 0  | 13 (6.0) | 0.207 |
| Valve replacement (%) | 84 (7.0) | 2 (2.8) | 24 (8.7) | 0.215 |
| LVEF (%) | 30.0±10.2 | 29.8±8.4 | 29.9±9.6 | 0.135 |
| LA diameter (mm) | 46.9±8.5 | 47.3±9.0 | 49.7±7.0 | 0.134 |
| LVEDD (mm) | 61.1±9.4 | 66.0±8.1 | 61.2±8.6 | 0.444 |
| LVESD (mm) | 51.0±11.1 | 55.7±7.3 | 50.5±10.0 | 0.100 |
| Haemoglobin (g/L) | 133.8±16.0 | 137.1±14.1 | 134.0±16.0 | 0.583 |
| Creatinine (umol/L) | 114.5±51.5 | 107.3±28.5 | 116.9±38.5 | 0.0005 |
| Smoking history (%) | 810 (67.2) | 48 (67.6) | 191 (69.2) | 0.817 |
| CHA2DS2VASc score | 3.70±1.43 | 3.76±1.47 | 4.03±1.51 | 0.475 |
| *Medication at baseline* |  |  |  |  |
| Oral anticoagulant, n (%) | 432 (36.3) | 18 (25.7) | 200 (72.5) | <0.0005 |
| Antiplatelet agent, n (%) | 728 (61.2) | 48 (68.6) | 105 (38.0) | <0.0005 |
| ACEI, n (%) | 787 (66.1) | 42 (60.0) | 179 (64.9) | 0.551 |
| ARB, n (%) | 315 (26.5) | 23 (32.9) | 79 (28.6) | 0.420 |
| ACEI or ARB, n (%) | 1085 (89.6) | 64 (90.1) | 253 (90.7) | 0.860 |
| Beta-blockers, n (%) | 1064 (89.4) | 60 (85.7) | 254 (92.0) | 0.231 |
| Aldosterone antagonist, n (%) | 530 (44.5) | 33 (47.1) | 130 (47.1) | 0.699 |
| Loop diuretic, n (%) | 739 (62.1) | 46 (65.7) | 198 (71.7) | 0.010 |
| Other diuretic, n (%) | 155 (13.0) | 5 (7.1) | 46 (16.7) | 0.080 |
| Cardiac glycoside, n (%) | 152 (12.8) | 11 (15.7) | 86 (31.2) | <0.0005 |
| Anti-arrhythmic, n (%) | 234 (19.7) | 13 (18.6) | 34 (12.3) | 0.018 |

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CIED, cardiac implanted electronic device; COPD, chronic obstructive pulmonary disease; CRF, case record form; CRT-D, cardiac resynchronisation therapy – with defibrillator; CRT-P, cardiac resynchronisation therapy – with pacing only; LA, left atrial; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; MI, myocardial infarction; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; VT, ventricular tachycardia.

**Table 2. Risk of death and hospitalisation**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Event rate****% per year** | **Unadjusted risk** | **Multivariable adjusted risk\*** |
| **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **All-cause mortality** |
| No AF | 5.9 | Reference | - | Reference | - |
| Subclinical AF | 2.9 | 0.49 (0.22-1.11) | 0.088 | 0.44 (0.18-1.06) | 0.068 |
| AF >24h | 6.1 | 1.02 (0.75-1.40) | 0.887 | 0.83 (0.60-1.15) | 0.272 |
| **Cardiovascular hospitalisation** |
| No AF | 14.8 | Reference | - | Reference | - |
| Subclinical AF | 15.5 | 1.08 (0.72-1.64) | 0.699 | 1.17 (0.77-1.80) | 0.459 |
| AF >24h | 22.5 | 1.51 (1.24-1.83) | <0.0005 | 1.46 (1.19-1.79) | <0.0005 |

\*Adjusted for age, sex, systolic blood pressure and device type.

**Figure 1**

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**Figure 2**