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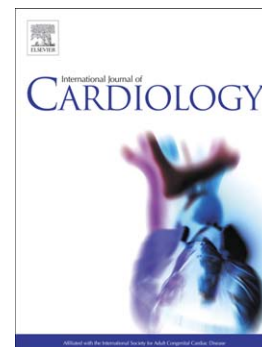
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Use of Statins and Adverse Outcomes in Patients with Atrial Fibrillation:**An Analysis from the EURObservational Research Programme Atrial Fibrillation (EORP-****AF) General Registry Pilot Phase**

Marco Proietti¹ MD, Cécile Laroche² MSc, Ole Nyvad³ MD, Maciej Haberka⁴ MD, Vassilios P. Vassilikos⁵ MD, Aldo P Maggioni^{2,6} MD PhD, Giuseppe Boriani^{7,8} MD PhD, Gregory YH Lip^{1,9} MD on behalf of the EORP-AF Pilot Investigators

¹Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom;

²EURObservational Research Programme Department, European Society of Cardiology, Sophia Antipolis, France; ³SVS Esbjerg, Esbjerg, Denmark; ⁴Upper Silesia Medical Center, Medical

University of Silesia, Department of Cardiology, Katowice, Poland; ⁵Ippokrateion University

Hospital of Thessaloniki, ^{3rd} Cardiology Department, Thessaloniki Greece; ⁶ANMCO Research

Center, Firenze, Italy; ⁷Institute of Cardiology, Department of Experimental, Diagnostic and

Specialty Medicine, University of Bologna, S. Orsola-Malpighi University Hospital, Bologna, Italy;

⁸Cardiology Department, University of Modena and Reggio Emilia, Policlinico di Modena,

Modena, Italy; ⁹Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

Prof. Gregory Lip takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Corresponding Author

Professor GYH Lip

University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Dudley Road, B18
7QH, Birmingham, United Kingdom

Tel: +44 121 507 5080; Fax: +44 121 554 4083; E-mail: g.y.h.lip@bham.ac.uk

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ABSTRACT

Background: Despite oral anticoagulation being highly effective in reducing stroke and thromboembolism, patients with atrial fibrillation (AF) still have a significant residual excess in mortality risk. Additional management strategies are needed to reduce the mortality risk seen in AF patients.

Methods: Ancillary analysis from the EURObservational Research Programme Atrial Fibrillation (EORP-AF) General Pilot Registry, to evaluate 1-year outcomes in AF patients according to statin use at baseline.

Results: Of 2636 patients, 1286 (48.8%) patients used statins at baseline. Patients prescribed statins had more comorbidities. At 1-year follow-up, logistic regression analysis adjusted for AF type, symptomatic status and CHA₂DS₂-VASc score demonstrated that statin use was inversely associated with CV death (odds ratio [OR]: 0.50, 95% confidence interval [CI]: 0.30-0.82, $p<0.0001$), all-cause death (OR: 0.52, 95% CI: 0.37-0.73, $p<0.0001$) and the composite outcome of CV death/any thromboembolic event/bleeding (OR: 0.71, 95% CI: 0.52-0.98, $p<0.0001$). Similar findings were observed for 'high risk' subgroups including the elderly, primary prevention and high thromboembolic risk AF patients.

Survival analysis showed that statins prescribed patients had a lower risk of all-cause death at follow-up ($p=0.0433$). Multivariate Cox regression analysis found that statin use remained independently associated with a lower risk for all-cause death (hazard ratio [HR]: 0.61, 95% CI: 0.42-0.88, $p=0.0077$).

Conclusions: Statin use in AF patients was associated with improved outcomes, with an independent association with a lower risk of all-cause death at 1-year follow-up.

Keywords: atrial fibrillation; statin therapy; cardiovascular events; all-cause death.

1. INTRODUCTION

Atrial fibrillation (AF) is a well-established risk factor for higher morbidity and mortality, particularly from stroke and thromboembolic events (TE).[1] Oral anticoagulation is highly effective in reducing stroke and thromboembolism, but patients with AF still have a significant residual excess in mortality risk.[2–4] This residual excess in mortality risk merits consideration of additional clinical management strategies.[5,6]

Use of statins for both primary and secondary prevention of cardiovascular (CV) and cerebrovascular disease is well established[7,8] and is recommended in guidelines.[9,10] Statins reduce all-cause death, both in primary and secondary prevention, in the general population.[11,12] The pharmacological actions of statin go beyond the lipid-lowering effects,[13] with putative antithrombotic[14] and cardioprotective[15] actions. Also, statin therapy seems to play an important role in preventing AF occurrences,[16] for example, in the post-operative[17] and post-ablation[18] clinical scenarios. Such AF preventive actions are mediated through antioxidant and anti-inflammatory properties.[19] Statin treatment in AF patients reduces the risk of incident dementia[20], as well as the risk for all-cause death after an AF-related stroke.[21] Limited data are available about the use of statin in observational AF cohorts and their influence on major adverse outcomes.

Thus, the aims to this ancillary analysis of the EURObservational Research Programme in Atrial Fibrillation (EORP-AF) General Registry Pilot Phase were to describe the use of statins in AF patients and the associated clinical profile, and second, to investigate the association of statin use with major adverse events and all-cause death over a 1-year follow-up observation period.

2. METHODS

The EORP-AF General Registry is a prospective, observational, multicentre European-wide registry on AF patients in current cardiology practice conducted by the European Society of Cardiology (ESC).[22] In brief, the EORP-AF Pilot Phase enrolled consecutive AF patients managed by cardiologists in nine ESC members' European countries (Belgium, Denmark, Netherlands, Norway, Poland, Romania, Greece, Italy, and Portugal) from February 2012 to March 2013. Patients eligible for the study were both AF inpatients and/or outpatients referred to cardiology services (either hospital or office-based centres). Across the entire enrolment period, all patients consecutively presenting at every site were considered for eligibility. AF had to be recorded as a primary or secondary cardiovascular disease. Qualifying events were recorded by any electrocardiographic documentation occurring within the 12 months before the enrolment. Institutional review board for every institution approved study protocol. All patients entered the study after signing a written informed consent. Study was performed according to the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

At the baseline, a full clinical and medication history was collected from any patient through clinical interview and/or access to clinical/hospital notes. Over 13 months of enrolment, a total of 3119 AF patients were collected. Follow-up procedures were performed according to the local procedures, via clinical interview, telephonic interview and hospital notes searching. During the pre-specified 1-year follow-up, ended in March 2014, the occurrence of major adverse events was recorded. All patients with available data on statin use at discharge/after consultation and follow-up observation were considered for this analysis. Thus, patients would have been already taking statins at the time of enrolment or prescribed statins during admission/consultation, according to physician's clinical judgement.

Thromboembolic risk was defined according to the CHA₂DS₂-VASc score. ‘Low risk’ patients were defined as a CHA₂DS₂-VASc 0 in males or 1 in females; ‘moderate risk’ was defined as male patients with a CHA₂DS₂-VASc score 1; and ‘high risk’ was defined as CHA₂DS₂-VASc score ≥ 2 . Bleeding risk was also assessed according to the HAS-BLED score. Symptomatic status at the baseline was defined according to European Heart Rhythm Association (EHRA) score. Accordingly, patients with EHRA I were considered as asymptomatic, while EHRA score from II to IV described patients progressively more symptomatic. Type of AF was defined as first detected, paroxysmal, persistent, long-standing persistent and permanent according to 2010 ESC guidelines on AF management.[23]

2.1 Statistical Analysis

Continuous variables were reported as mean \pm SD or as median and interquartile range (IQR). Among-group comparisons were made using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages. Among-group comparisons were made using a chi-square test or Fisher’s exact test (if any expected cell count was less than five). For qualitative variables with more than two possibilities, the Monte Carlo estimates of the exact p-values are used. A stepwise forward multiple logistic regression was used to determine the clinical factors associated with statin use in AF patients at discharge/after consultation. From the baseline characteristics, we selected a list of covariates based on biological plausibility. Next, to obtain an accurate multivariate model, a univariate analysis was performed to select covariates to be include in the final multivariate model (all variables with $p < 0.10$, see Supplemental Table 1). A significance level of 0.05 is required to allow a variable into the model (SLENTRY=0.05) and a significance level of 0.05 is required for a variable to stay in the model (SLSTAY=0.05). No interaction was tested. A Hosmer and Lemeshow Goodness-of-Fit test was used to verify that the model was optimal. A backward model was also performed to verify the results of the forward model.

A logistic regression analysis, adjusted for type of AF, symptomatic status (EHRA score) and thromboembolic risk (CHA₂DS₂-VASc score), was performed to establish the relationship with major adverse event occurrence according to statin use at baseline. Additional analyses were also performed according to the following specific subgroups: i) elderly patients (age \geq 75 years); ii) CV disease free patients (excluding those patients with previous coronary artery disease [CAD], previous coronary artery by-pass graft [CABG], previous myocardial infarction [MI], peripheral vascular disease, previous stroke/transient ischemic attack [TIA]); iii) patients with high thromboembolic risk (CHA₂DS₂-VASc score \geq 2). The subgroups analyses were performed exploring interactions with the complementary subgroups (younger patients (age $<$ 75 years), patients with CV disease history and patients with CHA₂DS₂-VASc score $<$ 2).

Plots of the Kaplan-Meier curves for time to all-cause death according to statin use were performed. The survival distributions have been compared using the Log-Rank test. A stepwise Cox model was used to determine the predictors of all-cause death during follow-up. From the baseline characteristics, we selected a list of covariates based on biological plausibility. Next, to obtain an accurate multivariate model, a univariate analysis was performed to select covariates to be included in the final model (all variables with $p<0.10$, see Supplemental Table 3). A significance level of 0.05 is required to allow a variable into the model (SLENTY=0.05) and a significance level of 0.05 is required for a variable to stay in the model (SLSTAY=0.05). No interaction was tested. A Hosmer and Lemeshow Goodness-of-Fit test was used to verify that the model was optimal. A backward model was then performed to verify the results of the forward one.

A two-sided $p<0.05$ was considered statistically significant. All analyses were performed using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA) in 2016.

3. RESULTS

Among the overall population of 3119 patients, 2636 (84.5%) were eligible for this analysis, while for the remaining 483 (15.5%) data about statin use were missing. Accordingly, 1286 (48.8%) were prescribed with a statin at discharge/after consultation. By-centre variability of prescription rate was wide, ranging from 0% to 84%, with a median [IQR] prescription of 50 [34-62] %. Prescription rates ranged from 33.3% in Norway to 62% in Romania [Supplemental Figure 1].

Baseline characteristics according to statin prescription are reported in Table 1. Patients prescribed statins were older ($p<0.0001$) and more frequently overweight and obese ($p<0.0001$). A difference in distribution of types of AF, with patients prescribed with statins more likely to have paroxysmal and long-standing persistent AF, while non-statin users were more likely to have first detected, persistent and permanent AF ($p=0.0155$). Among classical CV risk factors, patients prescribed statins had more prevalent hypertension, hypercholesterolemia and diabetes mellitus ($p<0.0001$), as well as CAD, previous MI and previous percutaneous transluminal coronary angioplasty (PTCA)/CABG (all $p<0.0001$). Patients using statins at discharge were also more likely found to have chronic kidney disease than those not using statins ($p=0.0080$). Also, previous stroke/TIA ($p=0.0002$), peripheral vascular disease ($p=0.0002$) and chronic heart failure (CHF) ($p<0.0001$) were more prevalent in patients prescribed with statins compared to non-users. Accordingly, patients prescribed with statins had both higher bleeding and thromboembolic risks (both $p<0.0001$), as well as higher proportions categorised as high bleeding or thromboembolic risk (both $p<0.0001$).

At discharge/after consultation (Table 1), statin users were more frequently treated with at least one antithrombotic drug ($p<0.0001$), as well as more use of aspirin ($p<0.0001$) compared to non-users.

At least one antiarrhythmic drug was more frequently used in patients prescribed statins ($p=0.0032$). While class III antiarrhythmic drugs were more commonly used in patients prescribed

statins ($p < 0.0001$), class I antiarrhythmic drugs were more used in non-users of statins ($p = 0.0020$). Statin users were more commonly treated with angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers, beta blockers, diuretics (all $p < 0.0001$), dihydropyridine (DHP) calcium-channel blockers ($p = 0.0001$), while non-DHP calcium-channel blockers were less likely used by statins users ($p = 0.0064$).

After a univariate analysis (Supplemental Table 1), a logistic regression model was compiled to describe the clinical factors associated with prescription of statin. The final multivariate forward model (Table 2) found prescription of statin at discharge/after consultation in AF patients was independently associated with the presence of hypercholesterolemia ($p < 0.0001$), overweight ($p = 0.0034$) and obese ($p = 0.0002$) weight classes, as well as a clinical history of CAD ($p < 0.0001$) and previous stroke/TIA ($p = 0.0279$). Being underweight ($p = 0.0231$) was inversely associated with statin prescription. Repeating the analysis with a backward model found no difference in association between covariates considered and statin prescription (data not shown).

3.1 Follow-up and Survival Analysis

Data on AF progression were available for 659 (95.2%) out of 692 patients with paroxysmal AF at baseline. Patients with paroxysmal AF at baseline that became persistent, long-standing persistent or permanent AF were considered ‘progressors’ with regard to arrhythmia progression, while those remaining in paroxysmal AF were considered as ‘non-progressors’. There was no significant difference for statin use at baseline between progressors and non-progressors (52.6% vs. 49.8%, $p = 0.6162$).

During the pre-specified 1-year follow-up (Supplemental Table 2), patients prescribed with statin had a lower rate of all-cause death ($p = 0.0545$), while no other significant differences were noted for the other outcomes. Logistic regression analysis (Table 3), adjusted for type of AF, EHRA score

and CHA₂DS₂-VASc score, found that statin prescription was inversely associated with CV death ($p<0.0001$), all-cause death ($p<0.0001$) and the composite outcome of CV death, any TE or bleeding ($p<0.0001$). Only a trend for significance was found for the occurrence of bleeding alone ($p=0.0673$), while no reduction in any TE occurrence was reported for statin treatment ($p=0.0494$).

Kaplan-Meier curves [Supplemental Figure 2] showed, according to Log-Rank test, that patients prescribed with statins had a lower risk for all-cause death at 1-year follow-up ($p=0.043$). A multivariate Cox regression analysis was performed based on variables identified on univariate analysis (Supplemental Table 3). The final model (Table 4) found that statin prescription was associated with a lower risk of all-cause death ($p=0.0077$), independent of age ($p<0.0001$), permanent AF ($p=0.0011$), diabetes mellitus ($p=0.0001$), previous MI ($p=0.0001$), CHF ($p<0.0001$), symptomatic status ($p=0.0231$), occasional ($p=0.0001$) or regular ($p=0.0001$) physical activity and concomitant treatment with angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers ($p<0.0001$). The inverse association between statin use and all-cause death was independent of both antithrombotic and antiplatelet drugs. Repeating the analysis with a backward model found no difference in association between covariates considered and all-cause death (data not shown).

3.2 Additional Subgroup Analyses

The following ‘high risk’ specific subgroups were considered: i) elderly patients (age \geq 75 years); ii) CV disease free patients (excluding those patients with previous coronary artery disease [CAD], previous coronary artery by-pass graft [CABG], previous myocardial infarction [MI], peripheral vascular disease, previous stroke/TIA); iii) patients with high thromboembolic risk (CHA₂DS₂-VASc score \geq 2).

In elderly patients, as well as for the high thromboembolic ones, those prescribed with statins had a lower rate for both CV death ($p=0.0396$ and $p=0.0426$, respectively) and all-cause death ($p=0.0278$

and $p=0.0029$, respectively) (Supplemental Table 4). In the CV disease free subgroup, a significant lower rate of events was found for all-cause death ($p=0.0017$) and the composite outcome of all-cause death or any TE ($p=0.0084$); only a trend for significance was found for the CV death outcome ($p=0.0618$) (Supplemental Table 4).

A logistic analysis (Supplemental Table 5), adjusted for type of AF, EHRA score and CHA₂DS₂-VASc score, found that similar to the overall cohort, statin prescription was inversely associated with risk of CV death and all-cause death in elderly patients and also, the composite outcome of CV death, any TE or bleeding in CV disease free and high thromboembolic risk patients. Interaction analyses within the considered subgroups and the complementary subgroups did not show any significant differences, except for a trend for a lower risk for all-cause death in CV disease free patients of borderline statistical significance.

4. DISCUSSION

In this study, we found that 48.8% of European AF patients enrolled in the EORP-AF registry were prescribed with statins at discharge/after consultation. As expected, AF patients prescribed with statins had more major CV risk factors (hypercholesterolemia, obesity) and CV and cerebrovascular comorbidities. Importantly, statin prescription was inversely associated with the occurrence of CV death, all-cause death and a composite outcome of all-cause death, any TE or bleeding. These results were also found in the elderly ($\text{age} \geq 75$ years), CV disease free and high thromboembolic risk patients' subgroups. Indeed, use of statins was independently associated with a lower risk of all-cause death at 1-year follow-up (39% of relative risk reduction [RRR]).

The clinical profile of AF patients prescribed with statin resembles the recommendations of current guidelines, especially for secondary prevention whether for CAD,[9,24] stroke/TIA[25] or major

CV risk factors, as well as for hypercholesterolemia and obesity.[9,10] In AF management guidelines, use of statins as “upstream therapy” is mainly considered for AF primary prevention, even if stated that patients without any previous CV disease should not be treated.[26,27] The ESC guidelines also suggest that we consider use of statins in AF secondary prevention, even if with a very low quality of evidence.[26]

Our results suggest an association of statin use with a lower rate of major adverse events (*i.e.* CV death, all-cause death and the composite outcome of CV death, any TE or bleeding), even amongst elderly patients and in those without previous CV disease and at high thromboembolic risk. Opinions about statin use in elderly patients have been conflicting.[28–30] In particular, a large meta-analysis of elderly patients found that despite a reduction in major adverse events (MI relative risk [RR]: 0.606, 95% CI: 0.434-0.847; stroke RR: 0.762, 95% CI: 0.626-0.926), no beneficial effect was noted in terms of CV and all-cause death (RR: 0.907, 95% CI: 0.686-1.199 and RR: 0.941, 95% CI: 0.856-1.035, respectively).[29] Moreover, caution was advised in balancing risks and benefits when deciding to treat or not to treat an elderly patient with a statin, especially with the potential for altered metabolism, drug-drug interactions, etc. amongst the elderly.[9,30] Our data seem to show that in elderly AF patients, treatment with statins seems to be beneficial in reducing major adverse outcomes, for both CV and all-cause death. Interestingly, we did not find any significant difference according to statin use on stroke or any TE occurrence. Notwithstanding that our study was not powered to detect differences in events occurrence, these data could suggest how despite a relevant CV risk can be identified in AF patients, stroke risk is mostly due to embolic risk rather than vascular disease, *per se*.

As previously stated, the beneficial effect of statins in reducing major adverse events in the general population, both in primary and secondary prevention have been shown.[7,12] A comprehensive network meta-analysis including data from 199721 patients, reported strong evidence for statins in

reducing major adverse events (OR: 0.69, 95% CI: 0.64-0.75) and all-cause death (OR: 0.87, 95% CI: 0.82-0.92).[11] This effect was consistent both in primary (OR: 0.69, 95% CI: 0.61-0.79 and OR: 0.91, 95% CI: 0.83-0.99, respectively for major adverse events and all-cause death) and secondary prevention (OR: 0.69, 95% CI: 0.62-0.77 and OR: 0.82, 95% CI: 0.75-0.90, respectively for major adverse events and all-cause death).[11]

Results from our study confirm that, even in AF patients, a possible benefit related to statin use in reducing major adverse events seems to be consistent across the various clinical scenarios. Indeed, both CV disease free patients and high thromboembolic ones had a RRR ranging from 30% to 70% according to the various outcomes. Also, the non-significant differences found in the interaction analysis seems to reinforce the suggestion that use of statin could be associated with a lower risk of major outcomes regardless of clinical characteristics. Moreover, Cox regression analysis confirmed the favourable association of statin use with improved clinical outcomes, independent of various clinical factors related to all-cause death in AF patients.

Accumulating evidence has shown that statins have beneficial effects beyond their mere lipid-lowering effects.[15] For example, statins may beneficially alter the thrombotic/ inflammatory/ oxidative state seen in cardiovascular disease.[13,14] Furthermore, statins may provide myocardial protection[15] and the anti-inflammatory effect could play a pivotal role in modulating an AF-related inflammatory state.[31] Also, statins also modulate the detrimental effect of stroke occurrence in AF patients; for example, in a large cohort of AF patients presenting with an ischemic stroke, use of statins was inversely associated with risk of severe strokes, based on functional evaluation[32].

Our results could be interpreted as reinforcing the concept that AF would be considered as a vascular disease/risk factor itself. Recently, there have been an increasing body of evidence

suggesting a strong association between AF and cardiac or vascular disease.[33–35] One comprehensive systematic review and meta-analysis recently investigated the relationship between AF and several cardiovascular events and outcomes.[4] The latter found that AF was significantly associated with all major cardiovascular events, including peripheral arterial disease (RR: 1.31, 95% CI: 1.19-1.45), ischemic heart disease (RR: 1.61, 95% CI: 1.38-1.87), cardiovascular mortality (RR: 2.03, 95% CI: 1.79-2.30) and heart failure (RR: 4.99, 95% CI: 3.04-8.22), as well as vascular-related events such as chronic kidney disease (RR: 1.64, 95% CI: 1.41-1.91).[4] A recent meta-analysis reported how >50% of deaths in AF were related to cardio-vascular reasons that were different than thromboembolic or bleeding events.[36] Thus, we could hypothesize that the supposed benefit of statin use in AF patients could be related to their ability in modulating vascular disease burden. Thus, the use of statins for treatment of AF patients could help reduce the excess mortality risk that remains despite anticoagulation.[5,6] Additional studies investigating the possible mechanistic pathways, are still needed to clarify the precise mechanisms by which statins show their benefits in the AF population. Interestingly, our data are consistent with previous evidence from patients post-coronary artery by-pass graft surgery with AF whereby statins resulted in reductions of both short- and long-term mortality.[37]

Our data showed a reduction in risk of major adverse events associated to the use of statin, perhaps even stronger than most of the interventional trials testing statins. Also, considering that patients using statins reported a higher prevalence of most comorbidities, we could hypothesize that the strong reduction in risk could be partially explained by a stronger treatment intensity and/or more intensive risk factors management, even though the multivariate analysis did consider the most relevant risk factors and the main cardioprotective pharmacological treatments.

4.1 Limitations

The observational nature of our study is the main limitation to generalizability of our results. Moreover, EORP-AF has not been powered to detect differences in the specified subgroups and the relatively small number of patients, as well as the non-randomised nature of statin allocation are major limitations to our study. Furthermore, the relatively short follow-up and the missing data on statin use for around 15% of patients originally enrolled, have to be considered as limitations of this analysis. Enrolling procedures in EORP-AF were based on management by cardiologists, so it could not fully represent the entire AF population. Furthermore, we have no specific data about use of the different statins and doses or adherence to prescriptions, which would have allowed a deeper and more detailed analysis of their effects. Also, we do not have any data to see if there was any difference in terms of other medical management (e.g. number/frequency of clinical reviews) during the 1-year follow-up. Residual confounders for factors which we cannot fully account for, are additional limitations. Finally, given the lack of specific laboratory data, our study cannot establish any direct causal pathophysiological link between use of statins and outcomes in AF, but associations that would-be hypothesis generating.

5. CONCLUSIONS

Use of statins among AF patients was found to be associated with improved outcomes, with an independent association with a lower risk for all-cause death occurrence at 1-year follow-up.

Table 1: Baseline characteristics according to statin use at discharge/after consultation

	Statins	No Statins	p
	n= 1286	n= 1350	
Age years , median [IQR]	70.0 [64.0-77.0]	69.0 [60.0-77.0]	<0.0001
Female , n (%)	488 / 1286 (37.9)	556 / 1350 (41.2)	0.0893
BMI , n (%)			
<i>Underweight</i>	4 / 1258 (0.3)	24 / 1304 (1.8)	<0.0001
<i>Normal weight</i>	302 / 1258 (24.0)	417 / 1304 (32.0)	
<i>Overweight</i>	544 / 1258 (43.2)	537 / 1304 (41.2)	
<i>Obese</i>	408 / 1258 (32.4)	326 / 1304 (25.0)	
Type of AF , n (%)			
<i>First detected</i>	362 / 1262 (28.7)	410 / 1322 (31.0)	0.0155
<i>Paroxysmal</i>	352 / 1262 (27.9)	340 / 1322 (25.7)	
<i>LS Persistent</i>	75 / 1262 (5.9)	45 / 1322 (3.4)	
<i>Persistent</i>	260 / 1262 (20.6)	289 / 1322 (21.9)	
<i>Permanent</i>	213 / 1262 (16.9)	238 / 1322 (18.0)	
Hypertension , n (%)	1007 / 1276 (78.9)	845 / 1345 (62.8)	<0.0001
Hypercholesterolemia , n (%)	976 / 1261 (77.4)	260 / 1313 (19.8)	<0.0001
Diabetes mellitus , n (%)	336 / 1278 (26.3)	200 / 1343 (14.9)	<0.0001
Current smoker , n (%)	140 / 1247 (11.2)	147 / 1307 (11.2)	0.9871
Alcohol \geq2-3 units/day , n (%)	91 / 1198 (7.6)	116 / 1258 (9.2)	0.1474
Coronary artery disease , n (%)	622 / 1154 (53.9)	201 / 1134 (17.7)	<0.0001
Previous Myocardial infarction , n (%)	278 / 1154 (24.1)	85 / 1134 (7.5)	<0.0001
Previous PTCA/CABG , n (%)	306 / 1154 (26.5)	82 / 1134 (7.2)	<0.0001
Previous stroke/TIA , n (%)	148 / 1268 (11.7)	100 / 1345 (7.4)	0.0002

Peripheral vascular disease, n (%)	174 / 1231 (14.1)	118 / 1265 (9.3)	0.0002
Chronic heart failure, n (%)	654 / 1267 (51.6)	501 / 1246 (40.2)	<0.0001
Chronic Kidney Disease, n (%)	191 / 1283 (14.9)	153 / 1343 (11.4)	0.0080
Symptomatic status, n (%)	1286	1350	
<i>EHRA I</i>	539 / 1286 (41.9)	544 / 1350 (40.3)	0.3991
<i>EHRA II-IV</i>	747 / 1286 (58.1)	806 / 1350 (59.7)	
Physical activity, n (%)			
<i>None</i>	443 / 1184 (37.4)	506 / 1253 (40.4)	0.0017
<i>Occasional</i>	453 / 1184 (38.3)	393 / 1253 (31.4)	
<i>Regular</i>	243 / 1184 (20.5)	284 / 1253 (22.7)	
<i>Intense</i>	45 / 1184 (3.8)	70 / 1253 (5.6)	
HAS-BLED, median [IQR]	1.0 [1.0-2.0]	1.0 [0.0-2.0]	<0.0001
0-2	1077 / 1286 (83.7)	1197 / 1350 (88.7)	
≥3	209 / 1286 (16.3)	153 / 1350 (11.3)	
CHA₂DS₂-VASc, median [IQR]	4.0 [2.0-5.0]	3.0 [1.0-4.0]	<0.0001
<i>Low TE Risk</i>	32 / 1286 (2.5)	187 / 1350 (13.9)	
<i>Medium TE Risk</i>	103 / 1286 (8.0)	175 / 1350 (13.0)	
<i>High TE Risk</i>	1151 / 1286 (89.5)	988 / 1350 (73.2)	
<u>Therapy at discharge/after consultation</u>			
Antithrombotic therapy, n (%)			
<i>At least one</i>	1262 / 1285 (98.2)	1263 / 1348 (93.7)	<0.0001
<i>Antiplatelet</i>	601 / 1284 (46.8)	278 / 1349 (20.6)	<0.0001
<i>Any OAC</i>	1054 / 1283 (82.2)	1087 / 1348 (80.6)	0.3190
<i>VKA</i>	959 / 1283 (74.7)	979 / 1349 (72.6)	0.2057
<i>NOACs</i>	95 / 1285 (7.4)	109 / 1349 (8.1)	0.5096

Antiarrhythmic drugs, n (%)

<i>At least one</i>	488 / 1286 (37.9)	438 / 1349 (32.5)	0.0032
<i>Antiarrhythmic class I</i>	105 / 1286 (8.2)	159 / 1350 (11.8)	0.0020
<i>Antiarrhythmic class III</i>	388 / 1286 (30.2)	278 / 1349 (20.6)	<0.0001
ACEi/ARBs, n (%)	956 / 1286 (74.3)	738 / 1347 (54.8)	<0.0001
Beta Blockers, n (%)	959 / 1285 (74.6)	878 / 1347 (65.2)	<0.0001
Diuretics, n (%)	727 / 1286 (56.5)	621 / 1348 (46.1)	<0.0001
DHP calcium-channel blockers, n (%)	204 / 1285 (15.9)	146 / 1349 (10.8)	0.0001
Non-DHP calcium-channel blockers, n (%)	64 / 1285 (5.0)	102 / 1349 (7.6)	0.0064
Digoxin, n (%)	237 / 1286 (18.4)	282 / 1349 (20.9)	0.1103

Legend: AF= atrial fibrillation; ARB= angiotensin receptor blocker; BMI= body mass index;

CABG= coronary artery by-pass graft; DHP= dihydropyridine; EHRA= European Heart Rhythm

Association; IQR= interquartile range; LS= long standing; NOACs= non-vitamin K antagonist oral

anticoagulants; OAC= oral anticoagulant; PTCA= percutaneous transluminal coronary angioplasty;

TIA= transient ischemic attack; VKA= vitamin K antagonist.

Table 2: Multivariate logistic regression analysis for clinical factors associated with statin use at discharge/after consultation

	Odds Ratio	95% CI	P
BMI			
<i>Underweight</i>	0.19	0.05-0.80	0.0231
<i>Normal weight (reference)</i>	-	-	-
<i>Obese</i>	1.75	1.31-2.35	0.0002
<i>Overweight</i>	1.50	1.14-1.96	0.0034
Hypercholesterolemia	12.77	10.26-15.89	<0.0001
Coronary artery disease	4.22	3.32-5.36	<0.0001
Previous stroke/TIA	1.52	1.05-2.22	0.0279

Legend: BMI= body mass index; CI= confidence interval; TIA= transient ischemic attack.

ACCEPTED

Table 3: Logistic regression analysis for statin effect on adverse outcomes at 1-year follow-up^a

	Odds Ratio	95% CI	P
Stroke/TIA	0.74	0.31-1.80	0.2021
Any TE^b	1.10	0.71-1.72	0.0494
Bleeding	0.51	0.22-1.18	0.0673
CV death	0.50	0.30-0.82	<0.0001
All-cause death	0.52	0.37-0.73	<0.0001
CV death - any TE or Bleeding	0.71	0.52-0.98	<0.0001

Legend: ^aadjusted for type of AF, EHRA score and CHAD₂DS₂-VASc score; ^bStroke, TIA, ACS, coronary intervention, cardiac arrest, peripheral embolism and pulmonary embolism; AF= atrial fibrillation; CI= confidence interval; CV= cardiovascular; TE= thromboembolism; TIA= transient ischemic attack.

Table 4: Cox multivariate regression analysis for all-cause death at 1-year follow-up

	Hazard Ratio	95% CI	P
Statins	0.61	0.42-0.88	0.0077
Age (per year)	1.05	1.03-1.08	<0.0001
Type of AF			
<i>First Reported (reference)</i>	-	-	-
<i>Paroxysmal</i>	0.63	0.37-1.06	0.0823
<i>Persistent</i>	0.83	0.50-1.36	0.4504
<i>LS Persistent</i>	0.69	0.27-1.77	0.4419
<i>Permanent</i>	0.46	0.29-0.73	0.0011
Diabetes mellitus	2.02	1.41-2.89	0.0001
Myocardial infarction	2.11	1.44-3.10	0.0001
Chronic heart failure	2.97	1.99-4.45	<0.0001
EHRA II-IV (vs EHRA I)	0.65	0.45-0.94	0.0231
Physical activity			
<i>None</i>	-	-	-
<i>Occasional</i>	0.43	0.28-0.66	0.0001
<i>Regular</i>	0.19	0.07-0.46	0.0003
<i>Intense</i>	0.69	0.21-2.22	0.5309
ACEi/ARBs	0.49	0.34-0.69	<0.0001

Legend: ACEi= angiotensin converting enzyme inhibitor; AF= atrial fibrillation; ARB= angiotensin receptor blocker; CI= confidence interval; EHRA= European Heart Rhythm Association.

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AUTHORS' CONTRIBUTIONS

MP and GYHL conceived the study, interpreted results and drafted the manuscript. CL analysed data and provided critical revision of the manuscript. ON, MH, VPS collected data and provided critical revision of the manuscript. APM and GB supervised data collection, collected data and

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