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Statin use and mortality in atrial fibrillation: A systematic review and meta-analysis of 100,287 patients

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ABSTRACT

Statins are effective for reducing cardiovascular disease in patients at risk or with cardiovascular disease. The benefit of statin therapy on adverse cardiovascular outcomes in patients with non-valvular atrial fibrillation (AF) is not clear. We performed a systematic review and meta-analysis of studies retrieved from MEDLINE via PubMed and Cochrane (CENTRAL) database of studies investigating the efficacy of statins in AF patients. The principal endpoint was all-cause mortality. Other endpoints were cardiovascular mortality, ischemic stroke, composite endpoints and any bleeding. We included 14 studies (2 post-hoc analysis of randomized clinical trials, 8 prospective and 4 retrospective) with 100,287 AF patients, of whom 23,228 were on statins. The pooled hazard ratio (HR) for all-cause mortality was 0.59 (95 % Confidence Interval [CI] 0.54−0.65). This association was consistent by aging, sex and prevalent cardiovascular or cerebrovascular disease. and the beneficial effect was evident already after 12 months of therapy. The absolute risk reduction for all-cause mortality in patients treated with statins was 10 % (95 % CI 9–10). The pooled HR for statins against cardiovascular mortality was 0.75 (95 % CI 0.58−0.96). No association was found with other secondary endpoints. Regarding bleeding events, the pooled HR for statin use was 0.60 (95 % CI 0.48−0.76). Our meta-analysis shows that in AF patients, statin therapy was associated with a reduction in all-cause and cardiovascular mortality are reduced by 41 % and 25 %, respectively. Randomized clinical trials in AF patients are necessary, as well as clarity on AF-specific LDL cholesterol targets.

1. Introduction

Several large and well-conducted studies performed in the last decades have consistently shown that statin therapy is effective for the primary and secondary prevention of cardiovascular disease, such as myocardial infarction, ischemic stroke and peripheral artery disease [1–3]. It is estimated that statin therapy may reduce the 5-year incidence of major coronary events and stroke by about 20 % per mmol/L reduction in LDL-cholesterol [4]. A pooled analysis of randomized clinical trials including 27,548 patients with coronary disease showed that intensive lipid-lowering treatment is associated with 16 % reduction of cardiovascular death/MI (incidence rates 8.0 vs. 9.4 %/year, respectively) and 18 % reduction of ischemic stroke (2.3 vs. 2.8 %/year, respectively) compared to standard dose [5]. A recent meta-analysis also showed that statin therapy may reduce the rate of major adverse limb events and amputation by 30 % and 35 %, respectively [6], which is relevant for the atrial fibrillation (AF) patients given that the coexistence of peripheral artery disease increases cardiovascular risk in this patient population [7,8].

Statins have been also investigated in patients with ischemic and haemorrhagic stroke with positive results including a lower severity of stroke [9], better functional outcome [10] and reduced mortality at 90 days [11] and 1 year [12]. In particular, statin treatment was associated with improved survival and reduced risk for future cardiovascular

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events in AF-related stroke [13]. This evidence is clinically important, since AF-related ischemic stroke is more severe and disabling, compared to non-AF related strokes [14].

In addition to thromboembolism, increasing evidence shows that patients with AF may also suffer from complications related to coronary artery disease (CAD), such as myocardial infarction, and vascular death [15]. This risk is only partially lowered by anticoagulation treatment [16], suggesting that other factors, such as concomitant cardio-metabolic diseases, may account for this increased cardiovascular risk. Hence, proactive management of comorbidities may result in a lower rate of cardiovascular events and mortality in patients with AF, as part of a holistic or integrated approach to AF care [17,18].

Despite this evidence, a structured cardiovascular prevention strategy beyond anticoagulation in patients with AF is not well established, although mentioned in recent guidelines [19,20]. In other cardiovascular settings, such as hypertension and diabetes, there are clear therapeutic targets to goal and specific drugs to recommend (i.e. use of renin angiotensin aldosterone system blockers in diabetes) it is unclear if patients with AF should be managed using a primary or secondary prevention strategy, in absence of a previous ischemic event.

This lack of evidence is particularly evident for the treatment of dyslipidaemia and statin treatment. While in many cardiac diseases, the LDL-target became more and more ambitious, the optimal LDL target for AF patients remains unclear, and no randomized clinical trial have investigated the potential beneficial effect of statins in AF.

Given the lack of solid and pooled data, nor specific clinical trials, on this issue, our aim was to perform a systematic review and meta-analysis of observational studies on the association between statin use and different cardiovascular endpoints.

2. Methods

We conducted a systematic review of literature searching MEDLINE via PubMed and Cochrane (CENTRAL) database using a combination of the following keywords: “atrial fibrillation” and “statin” or “lipid lowering therapy” with the following terms: “cardiovascular events”, “mortality” “stroke”, “myocardial infarction”, “bleeding”, “haemorrhage”. There was no time restriction for articles inclusion. The last search was run on March 15, 2020.

We included only journal articles in English language with full text available. We included 14 cohort studies (2 post-hoc analysis of randomized clinical trials, 8 prospective and 4 retrospective). We excluded cross-sectional and case-control studies, case reports, editorials/comments, letters, review and meta-analysis, and experimental studies. **Supplementary** Fig. 1 reported the search strategy which was performed according to the PRISMA guidelines.

2.1. Study selection and quality assessment

Two physicians (FB, DP) independently screened the titles and abstracts of manuscripts identified through the database searches to identify studies potentially eligible for further assessment. A third physician (MDB) reviewed eligible studies for appropriateness and completeness. The study selection was performed in multiple phases. In the first phase, potentially relevant studies were obtained by combined searches of electronic databases using the selected above-mentioned keywords. Then, studies not in English language, not involving humans, or not addressing study question were excluded. In the second phase, studies were reviewed and selected according to the inclusion and exclusion criteria. The quality of observational studies was assessed by the Assessment Tool for Observational Cohort and Cross-Sectional Studies” developed by the National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). According to the answers obtained from a specific list of 14 questions, the studies were divided into high, medium and low quality. Specifically, three (+++) defined high quality and are assigned to the studies that positively answered all the 14 questions of the questionnaire. Two (++) defined medium-quality studies, assigned to studies that present one negative answer and one (+) defined low-quality studies that had more than one negative answer to the questionnaire. Quality assessment was reported in Table 1.

2.2. Endpoints

The principal endpoint was all-cause mortality. Other endpoints were cardiovascular mortality, CAD, ischemic stroke and composite endpoints. The type of endpoint reported in each study is given in Table 1. Definitions of CAD, bleeding and composite cardiovascular endpoints are reported in Supplementary Table 1.

Ethical approval was not required given the study type.

2.3. Statistical analysis

When available, hazard ratios (HRs) were recorded from each study. When other measures of association in place of HR were reported (ie. OR), HR was then approximated using the cumulative incidence stratified by treatment group, according to the methods described by Tierney and colleagues [21]. A continuity correction was used to incorporate zero-event studies with a correction factor of 0.5. For further details see also reference [22].

Overall, 12 out of 14 studies used multivariable-adjusted or propensity-adjusted HRs from Cox proportional hazard regression analysis; a detailed list of confounders for each study is reported in the Supplementary Table 2.

We then performed several separate meta-analyses for each outcome. After stratifying, as the number of studies to be included was low, we decided to use a Bayesian approach, according to the guidelines [23]. We assumed each log-HR was Gaussian distributed centred on a study-specific effect and the extracted standard error. The latter was increased by 25 % to obtain a conservative statement. The study-specific effect was assumed to be Gaussian, centred on a pooled effect.

We also calculated the absolute risk reduction for all-cause mortality between patients taking or not statins. The absolute risk reduction has been computed as the difference of incidence between the two groups.

We subsequently carried out a hierarchical Bayesian meta-regression with heterogeneity and informative priors. A linear model was used for describing the pooled effect as a function of moderators, such as age, gender, diabetes, previous MI, and duration of treatment. An informative prior (inverse Gamma centred on an estimator obtained with a moment-based approach, increased by 25 % to obtain a conservative statement) was used for the variance of the regression coefficients. Results of meta-regression were summarized by means of bubble plots, with bubbles proportional to the inverse variance of each study and trends estimated through non-parametric local polynomial regression.

Potential publication bias was evaluated through funnel plots and Egger’s linear regression test.

All analyses were conducted with R version 3.6.3, using the ‘metafor and‘adaptMCMC’ packages. Several methods were not directly available in any package and appropriate functions to conduct the meta-analyses were written by the authors.

3. Results

3.1. Study characteristics and results of individual studies

The final analysis included 14 studies: 2 post-hoc analysis of randomized clinical trial, 8 were prospective and 4 retrospective observational cohort studies. A total of 100287 patients with AF were included, of whom 23228 were on treatment with statins and 77059 were not (Table 2). The proportion of patients treated with statins ranged from 14.8 %–80.1 %. The mean age of patients was 70.6 years and 43.3 % were women. The median follow-up ranged from 12 to 50 months.

Table 1
Type of endpoint reported in each study.

	All-cause Mortality	Coronary artery disease	Stroke	Bleeding	Composite endpoint	Cardiovascular Death
ATHERO-AF (2020)					X	
K-ATTENTION (2020)	X	X	X	X		
Ho (2019)				X		
START registry (2019)	X					
Taiwan National Health Insurance Database (2019)	X	X	X	X		
Taiwan National Health Insurance Database (2016)					X	X
EORP-AF (2017)	X					
J-RHYTHM (2017)	X		X	X		X
Korean National Health Insurance Service database (2017)		X				
Athens Stroke Registry (2014)	X		X		X	
Wändell (2013)	X					
Girerd (2012)	X					
AFFIRM (2010)	X		X		X	X
SPORTIF III/IV (2008)					X	

Table 2
Study design, number of participants and quality assessment of each study included in the meta-analysis.

Study/Author (year)	Study design	Total cohort	Patients on statin	Mean age	Women (%)	FU (months)	Q.A.
ATHERO-AF (2020)	P	1735	777	74.8	43.9	18.7	++
K-ATTENTION (2020)	P	2727	1579	73.1	47.1	17.3	++
Ho et al. (2019)	P	652	336	71.5	38.9	12.0	++
START registry (2019)	P	5215	1803	75.0	45.4	19.2	++
Taiwan National Health Insurance Database (2019)	R	50740	7498	69.2	43.8	12.0	+
EORP-AF (2017)	P	2636	1286	69.5	44.2	12.0	++
J-RHYTHM (2017)	P	6404	1605	71.0	39.0	24.0	++
Korean National Health Insurance Service database (2017)	R	3295	1259	62.8	50.1	50.4	++
Taiwan National Health Insurance Database (2016)	R	4638	1546	75.6	50.9	12.0	++
Athens Stroke Registry (2014)	P	404	102	67.2	31.8	22.0	++
Wändell et al. (2013)	P	12302	3398	74.4	45.9	42.0	++
Girerd et al. (2012)	R	1868	1496	64.2	22.2	33.6	++
AFFIRM (2010)	RCT[c]	4060	913	69.5	39.2	42.0	++
SPORTIF III/IV (2008)	RCT[c]	3665	1432	70.8	30.4	19.0	++
	2 RCT						
Total	8 P	100287	23228	70.6[a]	43.3	24.0[b]	
	4 R						

FU = follow-up; P = prospective; Q.A.= quality assessment; R = retrospective; RCT = randomized clinical trial.
[a] Weighted mean.
[b] Mean value.
[c] Post-hoc analysis.

3.2. All-cause mortality

Nine studies reported data on all-cause mortality according to statin treatment. A total of 86365 patients were included, with 12488 deaths (Table 3). The pooled HR for statin treatment in preventing all-cause mortality was 0.59 (95 % CI 0.54−0.65) (Fig. 1 - Panel A).

The meta-regression analysis showed that the inverse association between statin use and mortality was consistent by aging (Supplementary Figure 2). Furthermore, this beneficial effect started to be evident already after 12 months of statins therapy and persisted also in studies with longer follow-up (up to 4 years) (Supplementary Figure 2). This effect did not vary with the number of women included in the study, nor with patients having diabetes, previous cardiovascular or cerebrovascular disease (Supplementary Figure 2). The absolute risk reduction for all-cause mortality in patients treated with statins was 10 % (95 %CI 9–10). (Supplementary figure 3). The studies from Girerd (2012) and Wändell (2013) were not used in this analysis as they did not report the number of events in each study group.

Table 3
Number of studies, patients and events according to each endpoint.

	Number of studies	Number of patients	Patients on statin	Patients not on statin	Number of events	Events on statin	Events not on statin
All-cause mortality	9	86356	19680	66676	13373	896[b]	10870[b]
Stroke	5	64355	11697	52638	25295[a]	3784[a]	21511[a]
Coronary artery disease	3	56762	10336	46426	7868	1117	6691
Cardiovascular death	3	15102	4064	11038	470	101	369
Composite	5	14502	4470	9732	1105[c]	366[c]	739[c]
Bleeding	4	60523	11018	49505	2258	299	1959

[a] Data missing in 1 study.
[b] Data missing in 2 studies.
[c] Data missing in 3 studies.

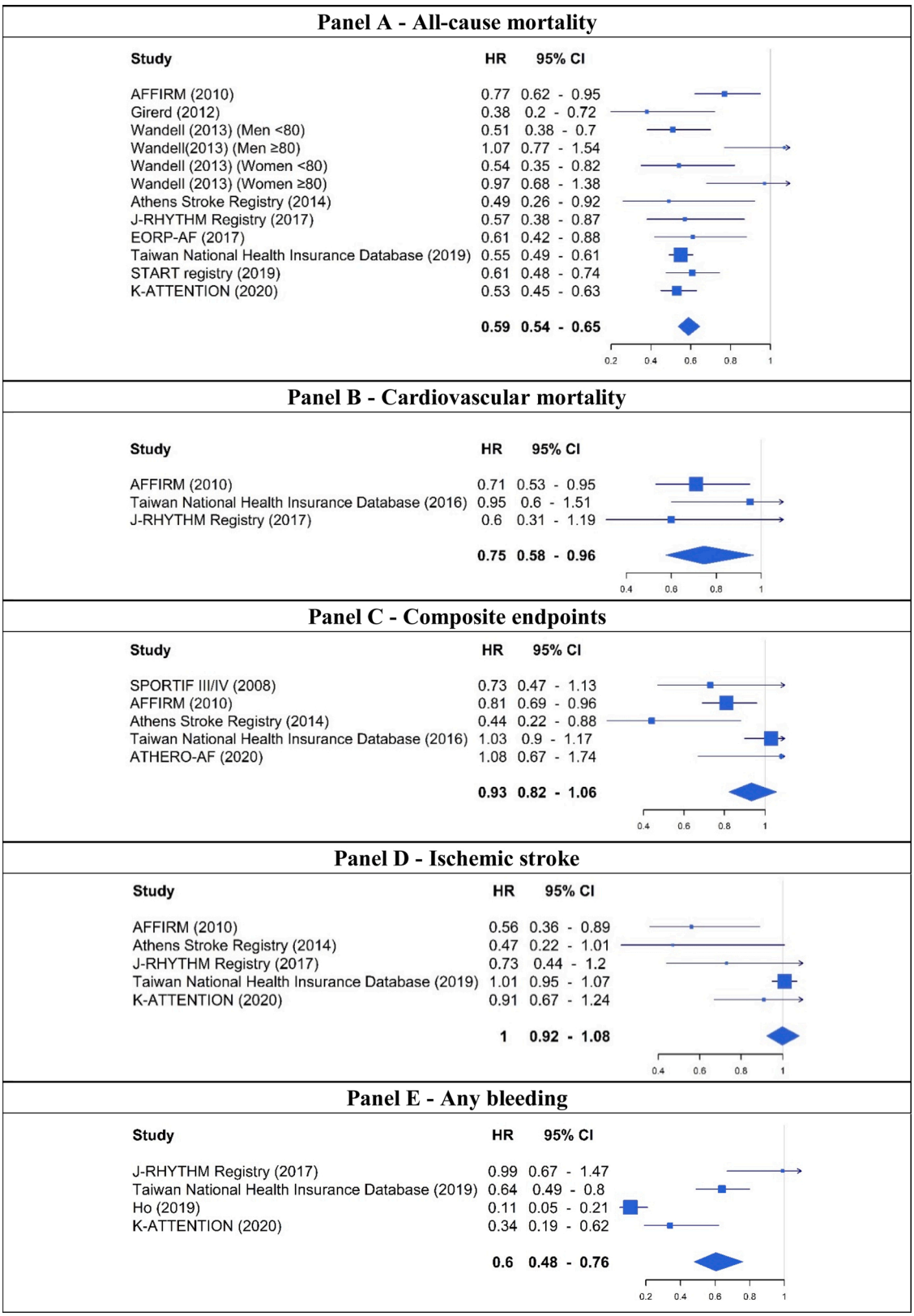

Fig. 1. Forest plots for statin use for each endpoint. (Panel A - All-cause mortality; Panel B - Cardiovascular mortality; Panel C - Composite endpoints; Panel D - Ischemic stroke; Panel E - Any bleeding).

3.3. Other endpoints

Three studies reported data on cardiovascular mortality according to statin treatment. A total of 15102 patients were included with 4064 deaths. The pooled HR for statin use was 0.75 (95 % CI 0.58−0.96) (Fig. 1 - Panel B).

No association was found between statin and composite endpoints [HR 0.93 (95 % CI 0.82–1.06); 5 studies, 14502 patients] (Fig. 1 - Panel

C) and ischemic stroke [HR 1.00 (95 % CI 0.92–1.08); 5 studies, 64335 patients] (Fig. 1 - Panel D).

We decided to not perform a formal analysis on CAD events given the very heterogeneous definition used in the three studies reporting this outcome (Supplementary Table 1).

When we analysed the incidence of any bleeding in 60523 patients with 2258 events, there was a lower risk associated with statin use, pooled HR 0.60 (95 %CI 0.48−0.76) (Fig. 1 - Panel E).

Funnel plots are reported in the Supplementary Figure 4.

4. Discussion

This is the first meta-analysis investigating the efficacy of statin therapy in patients with AF showing that the use of statins is associated with a reduction in total mortality rate by 40 % and cardiovascular mortality by 25 %. These data are suggestive of statin use to reduce adverse cardiovascular events in patients with AF, as part of a holistic or integrated care approach to AF care.

A recent Evidence Report and Systematic Review for the US Preventive Services Task Force showed that in adults at increased CVD risk but without prior CVD events, statin therapy was associated with reduced risk of all-cause (risk ratio [RR], 0.86 95 %CI, 0.80−0.93), and cardiovascular mortality (RR, 0.69 95 %CI, 0.54−0.88) [24]. This evidence is particularly important for the AF population. Thus, while after a first ischemic event patients are eligible for secondary prevention strategies, patients with AF but without a history of cardiovascular or cerebrovascular events are not still clearly classified as high-risk patients by current guidelines. In the evaluation of cardiovascular risk, the presence of AF is not considered as a risk modifier for therapeutic targets, such as blood pressure and LDL cholesterol level, and thus, statins are not perceived as a key component of the medical therapy of these patients. Indeed, in AF patients, the evaluation of cardiovascular risk and of corresponding LDL targets is currently based only on the presence of comorbidities and not of AF by itself.

Our results highlight the need for an appropriate cardiovascular prevention strategy in most patients with AF. Such patients are high risk, with high 1-year mortality (5.7 %), with most deaths were cardiovascular (70 %), despite anticoagulation rates [25].

In particular, the consistent effect of statin against mortality in elderly patients, who represent the majority of AF population, is in line with recent evidence showing that interruption of statin may lead to a 33 % increased risk of admission for cardiovascular event in 75-year-old primary prevention patients [26]. Another finding of interest is that the beneficial effect of statin therapy is evident even in studies with 12-month follow-up and persisted thereafter, independently from the length of observation.

The beneficial effect of statins observed in patients with AF may have several explanations. Statins may have a peculiar beneficial effect for AF patients by interfering with some pathogenetic pathways specific of this arrhythmia, but they can lower mortality also reducing the atherosclerotic burden by acting on cardiovascular comorbidities that are frequently associated with this arrhythmia.

Regarding the AF-specific effect, AF is triggered and sustained by oxidative stress, as shown by studies showing that the activation of the NADPH oxidase (Nox2) within myocardial tissue promotes myocardial hypertrophy and cardiac/atrial remodelling so favouring susceptibility to AF [27–30]. Previous evidence showed that statins, and in particular atorvastatin, have the potential of inhibiting this enzyme [31], so counteracting the process of atrial remodelling and fibrosis development. Furthermore, in patients with paroxysmal AF or in those undergoing cardioversion, statins have been shown to reduce AF recurrences [32].

Secondly, patients with AF are characterized by an increased platelet function [33], probably as the consequence of the associated atherosclerotic cardiovascular risk factors. In this context, statins can inhibit platelet function both with an early/immediate effect not related to their lipid lowering effect [34] and also with a long-term mechanism related to LDL cholesterol reduction [35].

In addition to the reduction of LDL cholesterol, other general pleiotropic beneficial effects of statins not necessarily related to the presence of AF include the ability of statins of stabilizing atherosclerotic plaques by depleting the lipid core of the atheroma, favouring transition to a non-vulnerable phenotype of plaque [36,37]. Long-term treatment with statins may also cause a regression of atherosclerotic plaques, such as at carotid level [38].

Furthermore, patients with multiple cardiovascular risk factors show a persistent low-grade inflammation that may contribute to a residual cardiovascular “inflammatory” risk despite best medical treatment [39]. Statins may break the progression of systemic atherosclerosis also inhibiting the inflammatory process. Thus, the statin-induced reduction of C-reactive protein, a commonly used inflammatory biomarker may be of clinical relevant for the inhibition of the atherosclerotic disease [40].

The lack of association between statin use and stroke incidence may depend on several disease- and drug-related factors. On one hand, ischemic stroke secondary to AF is mainly due to thromboembolism rather than to an atherosclerotic complication, even if these conditions may also coexist. Thus, oral anticoagulation may have the most favourable impact on this outcome in comparison to other treatments. Furthermore, no study reported data on the adherence or quality of anticoagulation, which are determinants of the occurrence of thromboembolic stroke (and mortality) in AF [41].

We also included a safety endpoint in our analysis as previous studies reported a marginally increase of haemorrhagic stroke in lipid lowering drugs users in secondary prevention (OR, 1.18; 95 % CI, 1.00–1.38), but not in primary prevention trials (OR, 1.01; 95 % CI, .78–1.30) [42]. However, as acknowledged by the Authors, the benefit in terms of ischemic stroke reduction greatly exceed the risk of intracranial bleeding. In the present analysis, we found a significant reduction of bleeding events in patients treated with statins; however, the very heterogenous definitions for haemorrhages used warrants caution in the interpretation of this finding and should be regarded to as a positive safety endpoint that will deserve further study.

4.1. Limitations

A major limitation of this analysis is the lack of data from randomized clinical trials. However, most studies (12/14) used a fully adjusted model of Cox proportional hazard regression analysis adjusting for many covariates to calculate the relative HR of the use of statins against each outcome, and one study used the propensity score method. This is partially reassuring that the analysis considered at least the most common clinical features of patients with AF. Furthermore, almost all studies did not report data on statin type and dose and on the proportion of patients at target for LDL-C according to current guidelines, so that only an overall analysis has been possible. This aspect should be implemented by the analysis of the association between LDL-C levels and events, as despite being on statin therapy patients may still have raised blood levels of LDL-C, which are associated with an increased cardiovascular risk [43].

In conclusion, our meta-analysis shows that in AF patients, statin therapy was associated with a reduction in all-cause and cardiovascular mortality by 40 % and 25 %, respectively. Underuse of statins in the AF population may account for a significant proportion of preventable deaths. Randomized clinical trials in AF patients are necessary, as well as clarity on AF-specific LDL cholesterol targets.

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Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

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