EuroIntervention 2016;12:e1047-e1056 ■ published online ahead of print November 2015 ■ published online e-edition October 2016

A meta-analysis of the impact of pre-existing and new-onset atrial fibrillation on clinical outcomes in patients undergoing transcatheter aortic valve implantation

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KEYWORDS

- mortality
- new-onset atrial fibrillation
- pre-existing atrial fibrillation
- severe aortic stenosis
- transcatheter aortic valve implantation

Abstract

Aims: Little is known about the prognostic role of pre-existing atrial fibrillation (AF) and new-onset AF (NOAF) in transcatheter aortic valve implantation (TAVI). Therefore, the aim of this meta-analysis was to compare the short- and long-term clinical outcomes of patients undergoing TAVI with and without pre-existing and new-onset AF.

Methods and results: Twenty-six studies, enrolling 14,078 patients undergoing TAVI, of whom 33.4% had pre-existing AF and 17.5% had NOAF, were analysed for early and long-term all-cause mortality, cardiovascular mortality and cerebrovascular events (CVE). In patients with pre-existing AF, 30-day all-cause mortality was similar to patients in sinus rhythm (SR). Conversely, long-term all-cause and cardiovascular mortality were significantly greater in pre-existing AF patients than in patients with SR (20 studies; 8,743 patients; HR: 1.68; p<0.00001, and three studies; 1,138 patients; HR: 2.07; p=0.01, respectively). Pre-existing AF was not a predictor of CVE at long-term follow-up. NOAF patients showed similar short- and long-term all-cause mortality when compared to patients in SR, whereas they experienced a significantly higher incidence of CVE at short-term follow-up (six studies; 2,025 patients; HR: 2.86; p<0.00001). A non-significant increase in the incidence of CVE was observed at long-term follow-up.

Conclusions: Pre-existing AF is a predictor of all-cause mortality in patients undergoing TAVI. NOAF is related to the occurrence of CVE at short-term follow-up. Similarly to surgical aortic valve replacement (SAVR), the optimal management and risk stratification of these patients should be further investigated.

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SUBMITTED ON 23/03/2015 - REVISION RECEIVED ON 01/07/2015 - ACCEPTED ON 22/09/2015

DOI: 10.4244/EIJY15M11_12

Abbreviations

AF	atrial fibrillation
AS	aortic stenosis
CI	confidence interval
CVE	cerebrovascular events
HR	hazard ratio
NOAF	new-onset atrial fibrillation
SAVR	surgical aortic valve replacement
SR	sinus rhythm
TAVI	transcatheter aortic valve implantation

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the general population, with a higher prevalence in the elderly as well as in patients with severe aortic stenosis (AS)[1]. AF and AS coexist in almost 30% of patients, with a prevalence that varies from 16% to 40%[2]. New-onset AF (NOAF) post transcatheter aortic valve implantation (TAVI), however, occurs in approximately 13% of patients, ranging from 0.7% to 31.9%[3].

Pre-existing AF and NOAF significantly affect cardiovascular physiology, due to loss of atrioventricular synchrony and irregularity of ventricular contraction resulting in reduced cardiac output and increased filling pressures, which may be further accentuated by the presence of severe AS and myocardial hypertrophy[4]. Additionally, the left ventricular outflow obstruction provoked by AS results in left ventricular hypertrophy and diastolic dysfunction, which may itself precipitate AF due to increased left atrial pressures[4].

AF has an important impact on cardiovascular morbidity and mortality[5]. Population-based studies have indicated an increased risk of stroke and systemic embolism as well as impaired long-term survival of individuals with AF compared to those with normal sinus rhythm (SR)[6]. In the general population, AF is estimated to increase the risk of death 1.5-fold among men and 1.9-fold among women[5]. Moreover, it has been shown previously that, after surgical aortic valve replacement (SAVR), AF represents an independent predictor of late adverse cardiac and cerebrovascular events (CVE), including congestive heart failure, stroke, and mortality[7,8]. Similarly, NOAF is associated with overall and late mortality after coronary artery bypass graft surgery and perioperative complications, and 30-day mortality and CVE in post-myocardial infarction patients[9].

In the last decade, TAVI has become the treatment of choice for inoperable or high-risk patients with severe, symptomatic AS, but the indication might be expanded in the near future. In the subset of patients with indications for TAVI, sparse and partly contrasting evidence exists regarding the impact of AF on morbidity and mortality. Some studies have indicated the absence of any significant impact of AF on prognosis[10-18], whilst others have shown increased mortality among patients with AF undergoing TAVI[19-30]. Moreover, a recent meta-analysis did not mention AF among predictors of all-cause mortality in patients undergoing TAVI[31].

Therefore, the aim of this meta-analysis was to compare the short- and long-term clinical outcomes of patients undergoing TAVI with and without pre-existing and new-onset AF.

Methods

The study was designed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) requirements[32,33]. MEDLINE, Cochrane, ISI Web of Science and SCOPUS databases were searched for articles published from April 2002[34] (first-in-human TAVI date) until January 2015. Studies were identified using the major medical subject heading "transcatheter aortic valve implantation OR transcatheter aortic valve replacement OR TAVI OR TAVR" combined with "clinical outcome or mortality" and "atrial fibrillation". Citations were screened at the title and abstract level by two independent reviewers and retrieved as a full report if they reported data on outcomes after TAVI, based on the presence/absence of AF and/or if AF was considered as a predictor of mortality in their regression models. No language limitations were applied. The full texts and bibliographies of all potential articles were also retrieved in detail to seek additional relevant studies.

Studies were included if: 1) TAVI was performed in high surgical risk or inoperable patients (as defined by a logistic EuroSCORE >20 or by the presence of contraindications to surgery such as porcelain aorta, severe respiratory failure, unfavourable anatomy for sternotomy) with symptomatic, severe AS (defined as an aortic valve area <1 cm^2, or an indexed aortic valve area <0.6 cm^2/m^2); 2) they reported data of mortality outcomes according to the presence of pre-existing AF or NOAF.

Studies were excluded if any of the following criteria applied: 1) duplicate publication; 2) lack of data on pre-existing AF before TAVI or NOAF after the procedure; 3) the outcome of interest was not clearly reported or was impossible to extract or calculate from the published results.

Two reviewers independently screened articles for fulfilment of inclusion criteria. Reviewers compared selected trials and discrepancies were resolved by consensus. Baseline characteristics, AF at baseline and outcomes, including mortality outcomes, were abstracted.

The primary endpoint evaluated was the incidence of early and long-term all-cause mortality in patients with baseline or new-onset AF undergoing TAVI. Secondary endpoints of interest were the cardiovascular mortality and the incidence of CVE in the same population. Long-term follow-up included a time frame ranging from six months to five years from the procedure. Short-term follow-up corresponded to 30-day follow-up.

Of 1,424 articles identified by the initial search, 45 were retrieved for more detailed evaluation and 26 trials were included in the study **(Appendix Figure 1)**.

The number of events, participants, hazard ratios (HR) and confidence intervals (CI) were abstracted. Pooled measures were calculated assuming a random effects model using inverse variance weighting, and used the adjusted HR. The results were also confirmed with a fixed effects model; however, the random effects model was prioritised in case of significant heterogeneity. Statistical significance was set at $p \leq 0.05$ (two-tailed). Heterogeneity was assessed by a Q-statistic and I^2 test. Significant heterogeneity was considered present for p-values <0.10 or an I^2 >50%.

Meta-regressions were performed to test the influence of baseline characteristics included in **Table 1** as potential effect modifiers (significance at p≤0.05).

Publication bias was assessed using funnel plots and Egger's test, consisting of a linear regression of the intervention effect estimates on their standard errors, weighting by 1/(variance of the intervention effect estimate)[35]. If there was some evidence of publication bias, the trim and fill method, which estimates the number and results of potential missing studies resulting from publication bias, was applied[36].

All data analyses were performed using Prometa Software, Version 2 (Internovi, Cesena, Italy), and Review Manager (RevMan), Version 5.2 (The Cochrane Collaboration, London, United Kingdom)[37-41].

Results

Of the 1,424 articles identified in the initial search, 45 were retrieved for more detailed evaluation. Nineteen studies were subsequently excluded. Therefore, 26 studies, enrolling 14,078 patients, were finally included in the analyses **(Table 1, Appendix Table 1, Appendix Figure 1)**[10-30,42-46].

Pre-existing AF is common among patients with symptomatic severe aortic stenosis undergoing TAVI, with an average prevalence of 33.4±9.6% in our meta-population (23 studies; 13,241 patients; 3,824 pre-existing AF). NOAF incidence after TAVI was, on the other hand, 17.5±8.7% (nine studies; 4,749 patients; 831 NOAF).

In patients with pre-existing AF, the overall mortality risk post TAVI was not significantly increased at 30-day follow-up (eight studies, 3,329 patients, HR: 1.12, 95% confidence interval [CI]: 0.95 to 1.33; p=0.19, I^2=25%) **(Figure 1A, Appendix Table 2, Appendix Table 3)**. Conversely, it was significantly increased at long-term follow-up (20 studies, 8,743 patients, HR: 1.68, 95% CI: 1.45 to 1.96; p<0.00001, I^2=54%) **(Figure 1B, Appendix Table 2, Appendix Table 3)**.

Cardiovascular mortality at long-term follow-up was significantly increased in patients with pre-existing AF when compared to patients with baseline SR (three studies, 1,138 patients, HR: 2.07, 95% CI: 1.17 to 3.65; p=0.01, I^2=53%) **(Figure 2A, Appendix Table 2, Appendix Table 3)**.

Additionally, the presence of pre-existing AF in patients undergoing TAVI did not predict CVE at long-term follow-up (five studies, 4,604 patients, HR: 1.68, 95% CI: 0.86 to 3.30; p=0.13, I^2=75%) **(Figure 2B, Appendix Table 2-Appendix Table 4)**. All these results were confirmed with fixed effect models (**Appendix Figure 2** and **Appendix Figure 3**).

Table 1. Studies included in the meta-analysis.

	Publication year	Number of patients	FU (months)	Type of study
Alassar et al[29]	2013	119	16	Observational prospective, single-centre
Allende et al[24]	2014	619	12	Observational prospective, multicentre (9 centres)
Amat-Santos et al[44]	2012	138	12	Observational prospective, single-centre
Auffret et al[14]	2014	163	6	Observational prospective, single-centre
Barbash et al[30]	2015	371	1 12	Observational prospective, single-centre
Elhmidi et al[27]	2013	373	12	Observational prospective, single-centre
Gotzmann et al[26]	2013	202	18	Observational prospective, single-centre
Lange et al[12]	2012	420	1 6	Observational prospective, single-centre
LeVen et al[21]	2013	639	12	Observational retrospective, multicentre (2 centres)
Maan et al [46]	2014	137	12	Observational prospective, single-centre
Nombela-Franco et al[22]	2012	1,061	12	Observational prospective, multicentre (5 centres)
Nuis et al[28]	2012	995	1 12	Observational prospective, multicentre (7 centres)
Nuis et al[42]	2012	214	13	Observational prospective, single-centre
Ribeiro et al[13]	2014	333	20	Observational prospective, single-centre
Rodés-Cabau et al[20]	2010	339	1 42	Observational prospective, multicentre (6 centres)
Sabaté et al[25]	2014	1,416	12	Observational prospective, single-centre
Salinas et al[11]	2012	34	1 10.4	Observational prospective, single-centre
Seiffert et al[43]	2013	326	12	Observational prospective, single-centre
Stortecky et al[19]	2014	389	12	Observational prospective, single-centre
Tamburino et al[16]	2011	663	12	Observational prospective, multicentre (14 centres)
Tay et al [10]	2011	253	12	Observational prospective, single-centre
Tchetche et al[17]	2014	3,191	6	Observational prospective, multicentre (34 centres)
Toggweiler et al[15]	2013	88	60	Observational prospective, single-centre
Unbehaun et al[23]	2014	730	12	Observational prospective, single-centre
Urena et al[45]	2015	485	1	Observational prospective, multicentre (6 centres)
Yankelson et al[18]	2014	380	1 12	Observational retrospective, single-centre

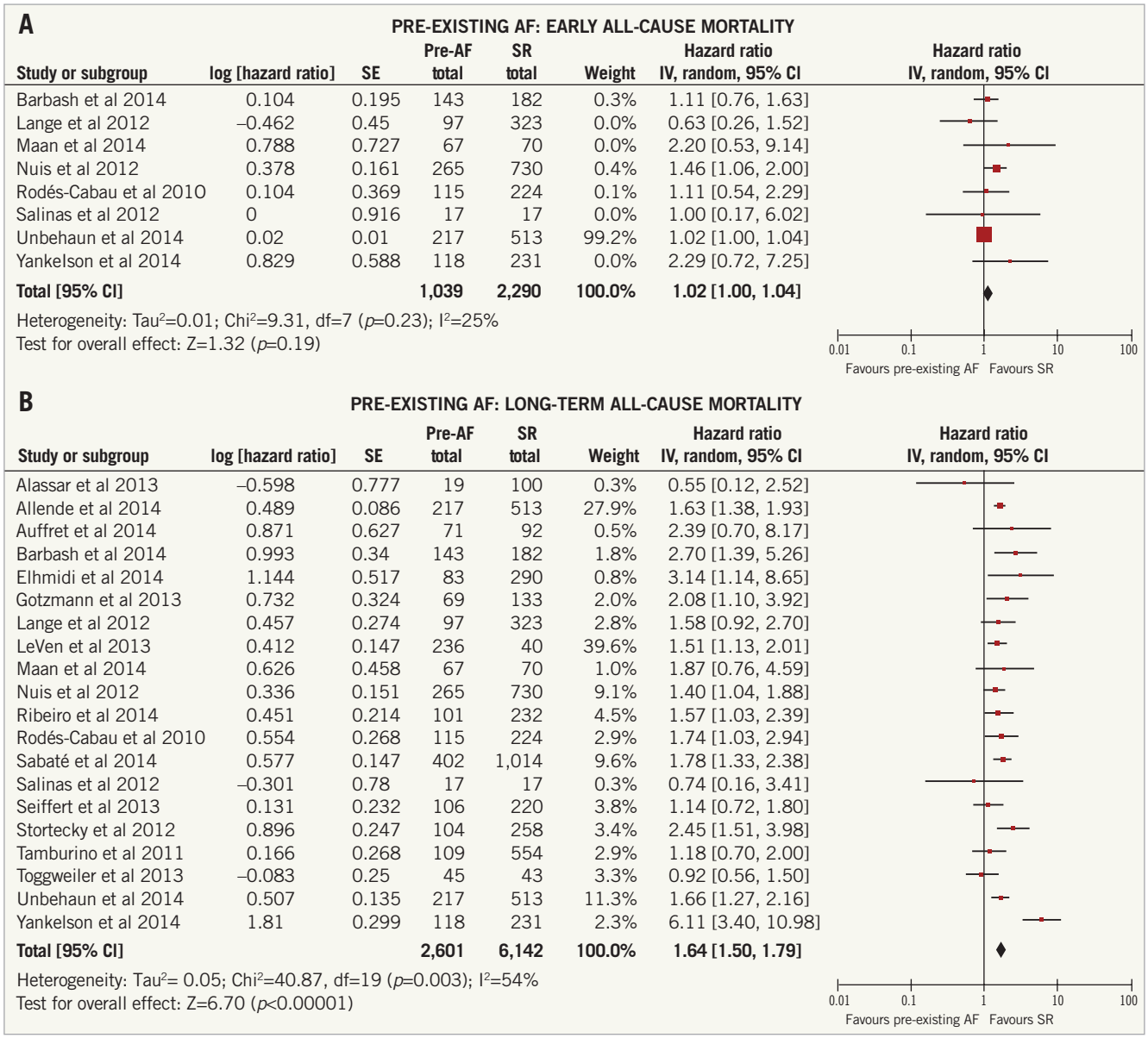

Figure 1. *Impact of pre-existing AF on early and long-term all-cause mortality. Random effects hazard ratio and 95% confidence interval for early (A) and long-term (B) all-cause mortality.*

Patients with and without NOAF did not show significant differences of 30-day (four studies, 971 patients, HR: 1.41, 95% CI: 0.85 to 2.34; p=0.18, I^2=0%) **(Figure 3A, Appendix Table 2, Appendix Table 3)** or long-term all-cause mortality (four studies, 971 patients, HR: 1.43, 95% CI: 0.96 to 2.14; p=0.08, I^2=0%) **(Figure 3B, Appendix Table 2, Appendix Table 3)**.

On the other hand, NOAF proved to be a significant predictor of CVE at short-term follow-up (six studies, 2,025 patients, HR: 2.86, 95% CI: 1.88 to 4.34; p<0.00001, I^2=0%) **(Figure 4A, Appendix Table 2-Appendix Table 4)**, while there was a non-significant increase in the incidence of CVE at long-term follow-up (five studies, 3,997 patients, HR: 1.44, 95% CI: 0.50 to 4.10; p=0.50, I^2=79%) **(Figure 4B, Appendix Table 2-Appendix Table 4)**.

Meta-regression analysis showed no relationship between all the analysed effect modifiers and the outcomes of interest (all p-values >0.05) **(Appendix Table 5, Appendix Table 6)**.

The funnel plots **(Appendix Figure 4-Appendix Figure 7)**, Egger's test **(Appendix Table 2)** and the trim and fill method did not show any publication bias, in all the analyses performed.

Discussion

The present meta-analysis demonstrated that AF is common among high-risk elderly patients undergoing TAVI, with a prevalence of 33.4% in this patient population, and that AF is associated with a significantly increased risk of all-cause mortality at long-term follow-up. However, the presence of AF at baseline does not

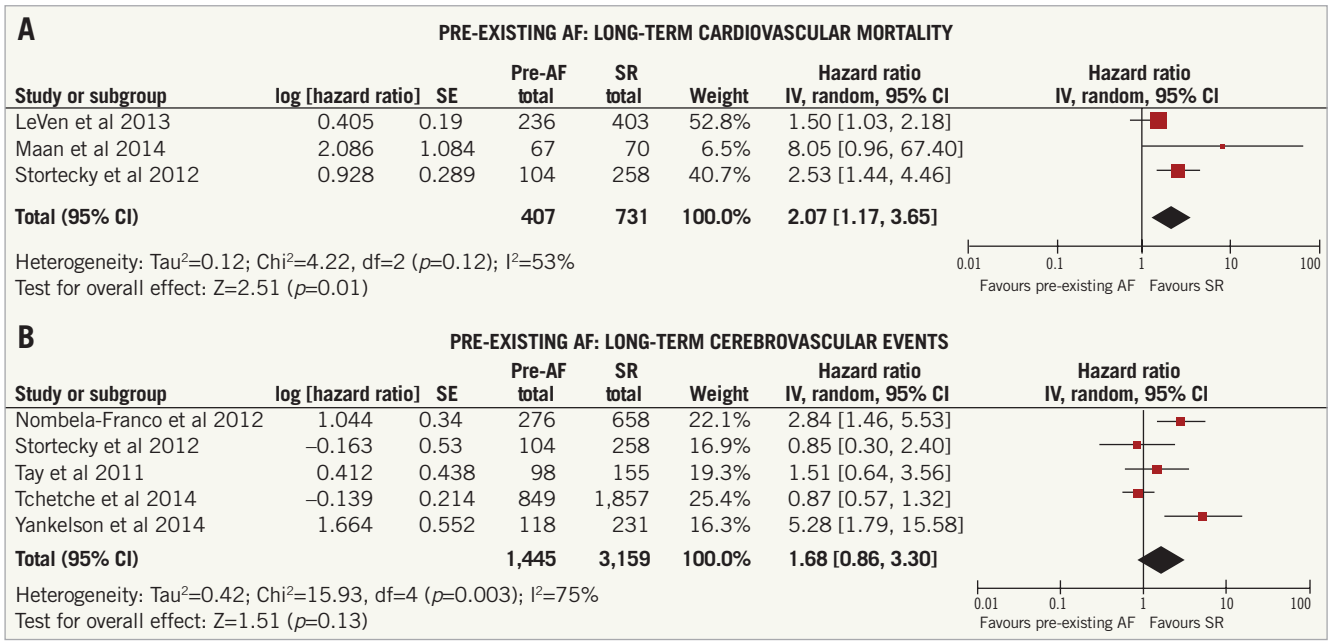

Figure 2. *Impact of pre-existing AF on long-term cardiovascular mortality and cerebrovascular events. Random effects hazard ratio and 95% confidence interval for long-term cardiovascular mortality (A) and long-term cerebrovascular events (B).*

seem to represent a risk factor for 30-day all-cause mortality or for CVE in the long term following TAVI. On the other hand, NOAF occurred in 17.5% of patients after TAVI and was not associated with increased mortality, but with an increased risk of CVE.

AF is the most common cardiac arrhythmia, and is associated with structural heart disease, in particular hypertensive heart disease, coronary artery disease and valvular heart disease. Due to the high prevalence of AF in the elderly population and to the similarity of risk factors for both AF and severe degenerative AS, both conditions coexist in almost 50% of patients. Similar to the general population, in whom AF is estimated to carry a 1.5-fold increased risk of death among men and 1.9-fold among women[5],

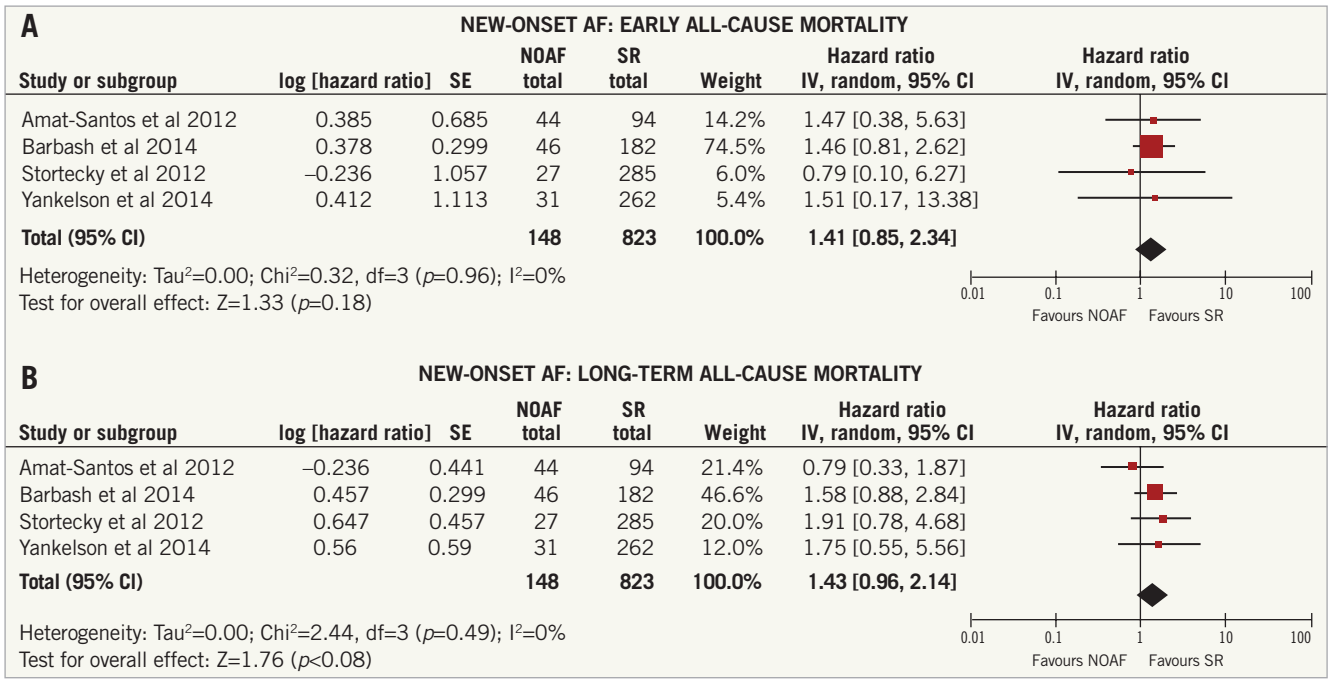

Figure 3. *Impact of NOAF on early and long-term all-cause mortality. Figure showing random effects hazard ratio and 95% confidence interval for early (A) and long-term (B) all-cause mortality. Note: fixed effects estimates for early (four studies, 971 patients, HR: 1.41, 95% CI: 0.85 to 2.34; p=0.18, I^2=0%) and long-term all-cause mortality (four studies, 971 patients, HR: 1.43, 95% CI: 0.96 to 2.14; p=0.08, I^2=0%).*

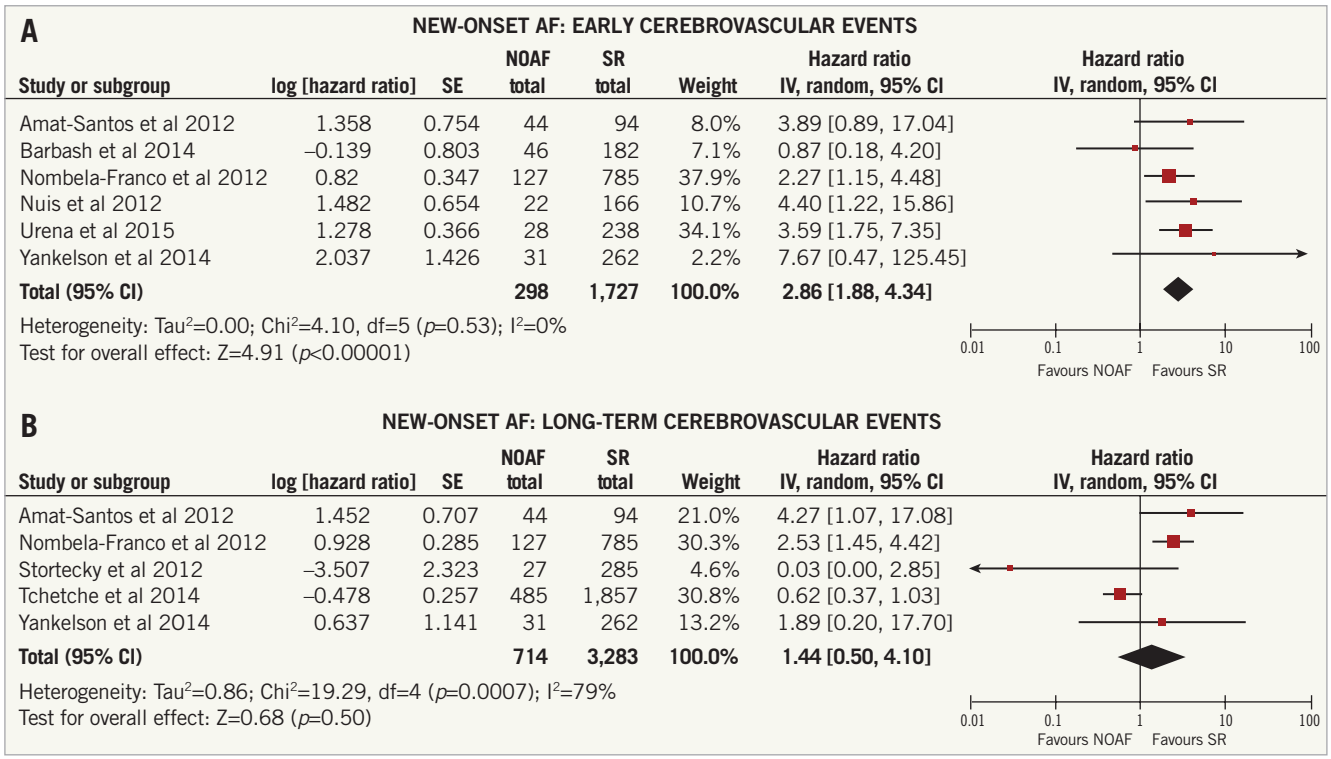

Figure 4. *Impact of NOAF on early and long-term cerebrovascular events. Figure showing random effects hazard ratio and 95% confidence interval for early (A) and long-term cerebrovascular events (B). Note: fixed effects estimates for early (six studies, 2,025 patients, HR: 2.86, 95% CI: 1.88 to 4.34, p<0.00001, I^2=0%) and long-term cerebrovascular events (five studies; 971 patients, HR: 0.26, 95% CI: 0.88 to 1.79; p=0.21, I^2=79%).*

our meta-regression analysis confirms these data also for patients undergoing TAVI, with a higher HR for all-cause mortality.

The observed differences in outcome among patients in SR and patients with baseline AF are not surprising and may be attributable to a worsening in heart failure from decreased ventricular filling secondary to loss of atrial systolic contraction, tachycardia-induced cardiomyopathy and/or complications associated with systemic embolisation, all conditions also contributing to all-cause mortality[37,47]. Indeed, heart failure might be precipitated in hypertrophied left ventricles with a lower ejection fraction because of the sudden loss of the Frank-Starling mechanism in cardiac reserve compensating in part for the reduced left ventricle contractility. This is particularly relevant in pressure-overload left ventricular hypertrophy, when geometry is often concentric and myocardial mechanics are substantially depressed due to structural modifications. As far as NOAF is concerned, although inflammatory components have been shown to be responsible for its occurrence after cardiac surgery[48], the mechanisms leading to the arrhythmia after TAVI have still to be clarified. No hypothetical differences between different types of valve or procedure have emerged up to now. Indeed, the results of our meta-regression analysis did not evidence any significant difference between the CoreValve® (Medtronic, Minneapolis, MN, USA) and the Edwards SAPIEN (Edwards Lifesciences, Irvine, CA, USA) valve, or between transfemoral and transapical implantation in terms of the incidence of NOAF.

The results of this meta-analysis demonstrate that pre-existing AF is a predictor of all-cause mortality in the long term following TAVI. This provides clarification to the current literature, since, even in recent publications, AF was not identified as a predictor of all-cause mortality[31].

It is important to underline that patients undergoing TAVI exhibit an incidence of stroke which is not negligible[49]: this is principally due to manipulation of large catheters in atherosclerotic and calcified aortas and to embolisation after valvuloplasty or valve implantation. On the other hand, AF itself represents a risk factor for stroke. Interestingly, the result of this meta-analysis, although coming from a pooled analysis of only five studies with a limited number of patients (4,604), clarifies that patients with pre-existing AF did not experience a higher incidence of new CVE when compared to patients in SR. These data, probably corroborating what has been previously shown, might support the concept that the main causes of stroke following TAVI are technical. However, in the subset analysed in this meta-analysis, we were not able to reach a statistical significance on this outcome. This might be due to a variety of issues. First, the total number of CVE is generally low and the number of studies/patients for this analysis is relatively low to draw consistent and final conclusions. Second, it has to be taken into account that, both in patients with pre-existing AF and in those with NOAF, drug therapy was administered. Unfortunately, we were not able to consider the effects of drugs on CVE because often these data were not reported in the primary studies. Conversely, the occurrence of

NOAF seemed to be linked to a higher incidence of CVE, particularly at short-term follow-up.

However, while pre-existing AF analysis demonstrating increased mortality was obtained in up to 8,000 patients, the results in NOAF were observed in fewer than 1,000 patients. Therefore, we cannot exclude an impact of NOAF on mortality, and future studies in larger populations of NOAF are needed.

Certainly, these results might have been induced by the different therapeutic strategies adopted in AF patients when compared to patients in SR. Unfortunately, the absence of the use of a standardised therapy in the available trials made it impossible to analyse, in this meta-analysis, the effect of different antithrombotic regimens on outcome after TAVI, in particular in AF patients. Therefore, future randomised studies are needed to determine the most appropriate antithrombotic therapy in arrhythmic TAVI patients. In addition, this meta-analysis is limited by the inclusion of observational studies not directly comparing AF and non-AF patients, except in one case. The limitations of this study are mainly related to differences in the studies included, as is the case for all meta-analyses. All the studies were observational and the data reported were not sufficient to analyse the role of AF subtypes or AF clinical management. Due to incomplete/unequal reporting of data, not all studies were analysed for all outcomes.

Long-term CVE for both pre-existing AF and NOAF showed a high heterogeneity (>70%) not explained by analysis of potential modifiers or publication bias. Therefore, the results should be considered with caution. However, this heterogeneity reflects the contrasting results among the studies included on this issue, supporting the need for a meta-analysis and future larger studies.

Finally, among the studies included there were no overlapping populations (duplicates were excluded in the eligibility screening). However, given that many studies are multicentre, a small number of overlapping patients cannot be excluded.

Conclusions

In conclusion, pre-existing AF, but not NOAF, is a predictor of long-term mortality. NOAF, on the contrary, predicts new CVE in the short term after TAVI. Screening patients' rhythm may help to identify a subgroup at higher risk of future major events, while preventing NOAF may help to reduce CVE in patients undergoing TAVI. Thus, similar to the results with SAVR, AF should be taken into account when referring a patient for a TAVI procedure.

Impact on daily practice

Despite the clinical safety of TAVI, mortality and cerebral events still occur. New prognostic predictors could be useful for future risk scores and for decision making in daily practice for patients with moderate-to-severe aortic stenosis. These findings should be taken into account not only when selecting patients for TAVI, but also after treatment in order to reach an appropriate diagnosis, to decide on clinical management and to reduce clinical events, optimising prognosis after TAVI.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Appendix Table 1. Baseline characteristics of the studies included in the meta-analysis.

Appendix Table 2. Outcome summary information in pre-existing AF and NOAF.

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Appendix Table 5. Meta-regression analysis in pre-existing AF.

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Appendix Figure 1. Meta-analysis flow chart.

Appendix Figure 2. Early and long-term all-cause mortality in pre-existing AF. Fixed effects model.

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Appendix Figure 4. Pre-existing AF: funnel plots of outcome.

Appendix Figure 5. Pre-existing AF: funnel plots of outcome.

Appendix Figure 6. New-onset AF: funnel plots of outcome.

Appendix Figure 7. New-onset AF: funnel plots of outcome.

Supplementary data

Appendix Table 1. Baseline characteristics of selected studies included in the meta-analysis.

Author (Ref. #)	Male (%)	Age (yrs)	AF (%)	NOAF (%)	CAD (%)	CKD (%)	COPD (%)	CVs (%)	Diabetes (%)	ESv (%)	HP (%)	LAS (%)	Logistic Euro SCORE (%)	LVEF (%)	NYHA III/IV (%)	Prior MI (%)	Prior PCI (%)	Prior stroke (%)	STS score (%)
Alassar et al[29]	58.7	81.0	15.9	N/A	N/A	N/A	31.4	91.0	23.1	9.0	N/A	N/A	22.0	N/A	62.0	24.8	19.0	14.0	N/A
Allende et al[24]	49.9	80.0	35.1	N/A	58.2	54.2	29.8	48.1	30.0	51.9	78.8	N/A	20.0	54.2	82.4	N/A	N/A	12.6	9.2
Amat-Santos et al[44]	39.1	79.0	N/A	31.9	65.2	64.5	28.3	0	37.7	100	91.3	44.7	21.7	55.0	83.3	34.8	39.9	22.5	7.4
Auffret et al[14]	55.2	79.9	43.5	N/A	52.1	44.2	38.9	39.2	16.6	60.7	66.3	28.0*	18.4	50.7	72.4	N/A	14.7	14.7	5.8
Barbash et al[30]	48.8	85.0	44.0	20.2	55.2	55.5	30.7	7.5	30.1	92.5	92.0	48.0	28.7	52.5	N/A	14.3	26.7	21.0	10.5
Elhmidi et al[27]	37.2	81.0	22.2	N/A	55.1	N/A	19.3	69.8	N/A	31.2	N/A	N/A	20.4	N/A	96.3	N/A	26.2	14.2	6.17
Gotzmann et al[26]	47.0	79.0	34.0	N/A	52.0	N/A	30.0	100	35.0	0	86.0	43.0	22.0	53.0	94.0	21.0	29.0	9.0	N/A
Lange et al[12]	37.0	83.0	23.3	N/A	55.0	N/A	N/A	68.7	N/A	30.6	N/A	N/A	23.0	52.1	96.7	21.6	28.5	13.2	N/A
LeVen et al[21]	48.7	81.0	36.9	N/A	63.1	N/A	29.9	N/A	29.7	N/A	79.0	N/A	21.7	54.0	84.5	40.2	26.4	16.9	7.0
Maan et al[46]	64	84.2	49.9	30.0#	72.0	N/A	28.0	0	34.0	100	80.0	43.7	14.3	55.3	N/A	N/A	37.0	N/A	6.9
Nombela-Franco et al[22]	50.7	81.0	29.6	13.9	64.7	N/A	29.2	33.4	29.4	64.1	74.5	N/A	N/A	N/A	83.5	35.6	N/A	18.1	6.5
Nuis et al[28]	50.0	82.0	26.6	N/A	N/A	73.0	28.0	N/A	28.0	N/A	78.0	N/A	17.0	N/A	81.0	26.0	31.0	20.0	N/A
Nuis et al[42]	50.0	80.0	N/A	11.7	N/A	N/A	28.0	N/A	N/A	N/A	N/A	N/A	13.8	N/A	82.0	24.0	26.0	23.0	5.0
Ribeiro et al[13]	53.2	79.6	30.3	N/A	63.1	N/A	29.7	0	33.9	97.9	88.0	N/A	N/A	53.8	78.7	N/A	N/A	19.5	7.3
Rodés-Cabau et al[20]	44.8	81.0	33.9	N/A	69.0	56.3	29.5	0	23.3	100	74.3	N/A	N/A	55.0	90.9	51.0	29.2	22.7	9.8
Sabaté et al[25]	46.0	81.0	29.0	N/A	53.0	N/A	21.3	43.0	34.0	67.0	78.0	N/A	17.0**	N/A	74.0	14.0	26.0	10.0	N/A
Salinas et al[11]	76.5	82.6	50.0	N/A	94.1	17.7	35.3	0	82.4	100	N/A	N/A	23.3	56.7	93.8	24.4	N/A	N/A	N/A
Seiffert et al[43]	44.4	80.5	32.5	N/A	N/A	N/A	26.7	13.8	N/A	86.2	N/A	N/A	22.7	N/A	73.4	19.9	35.3	19.3	8.3
Stortecky et al[19]	42.0	82.5	28.7	8.7	61.0	69.0	N/A	58.0	27.0	42.0	78.0	N/A	24.3	51.9	66.0	16.0	24.0	8.0	6.8
Tamburino et al[16]	44.0	81.0	16.4	N/A	48.3	23.2	21.3	100	26.4	0	75.1	N/A	23.0	52.1	71.5	21.6	28.5	7.2	N/A
Tay et al[10]	51.0	85.0	39.0	N/A	76.0	N/A	N/A	N/A	25.0	N/A	70.0	N/A	28.0	54.8	84.0	20.0	N/A	17.0	8.1
Tchetche et al[17]	51.0	84.1	26.6	20.7	N/A	N/A	N/A	33.1	N/A	66.9	69.4	N/A	18.9	55.0	75.8	N/A	N/A	10.0	10.0
Toggweiler et al[15]	63.0	83.0	51.1	N/A	72.0	53.0	26.0	0.0	25.0	100	69.0	N/A	N/A	60.0	N/A	78.0	N/A	16.0	9.0
Unbehaun et al[23]	39.8	80.1	29.7	N/A	61.2	N/A	N/A	0.0	29.3	100	N/A	N/A	28.8	55.0	97.1	N/A	20.9	22.2	10.4
Urena et al[45]	50.1	81.0	38.8	10.5	70.0	55.7	22.9	N/A	34.7	N/A	85.7	N/A	25.0	50.05	N/A	N/A	N/A	N/A	7.6
Yankelson et al[18]	40.5	83.0	33.8	10.6	56.3	N/A	70.0	N/A	32.6	N/A	87.1	N/A	24.3	N/A	N/A	16.6	42.4	N/A	N/A

#: this refers to 21 of 70 patients, excluding those with pre-existing AF. AF: atrial fibrillation; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVs: CoreValve System; ESv: Edwards SAPIEN valve; HP: hypertension; LAS: left atrial size (mm or cm^2 when *); LVEF: left ventricular ejection fraction; MI: myocardial infarction; N/A: not applicable (data not shown in the primary study or not obtainable; otherwise, the analysis was conducted only in a subgroup of the entire study population); NYHA: New York Heart Association; PCI: percutaneous coronary interventions; STS: Society of Thoracic Surgeons; TIA: transient ischaemic attack

Appendix Table 2. Outcome summary information in pre-existing AF and NOAF.

		Studies	Patients	Mean FU	RE HR	95% CI	*p*-value	FE HR	95% CI	*p*-value	Q	I^2%	Egger's test
Pre-existing AF	30-day all-cause mortality	8	3,329	30 d	1.12	0.95-1.33	0.19	1.02	1.00-1.04	0.030	9.31	25	0.193
	Long-term all-cause mortality	20	8,743	*17.0±12.6 12 [12-18]	1.68	1.45-1.96	<0.00001	1.64	1.50-1.79	<0.00001	40.87	54	0.645
	Long-term cardiovascular mortality	3	1,138	12 mo	2.07	1.17-3.65	0.01	1.81	1.33-2.47	<0.0002	4.22	53	0.305
	Long-term CVE	5	4,604	*12.4±4.7 12 [8.6-16.4]	1.68	0.86-3.30	0.13	1.36	1.01-1.83	0.05	15.93	75	0.296
NOAF	30-day all-cause mortality	4	971	30 d	1.41	0.85-2.34	0.18	1.41	0.85-2.34	0.18	0.32	0	0.456
	Long-term all-cause mortality	4	971	*13.4±2.8 12 [12-16.2]	1.43	0.96-2.14	0.08	1.43	0.96-2.14	0.08	2.44	0	0.936
	30-day CVE	6	2,025	30 d	2.86	1.88-4.34	<0.00001	2.86	1.88-4.34	<0.00001	4.10	0	0.820
	Long-term CVE	5	3,997	*11.8±4.4 12 [8.6-14.8]	1.44	0.50-4.10	0.50	1.26	0.88-1.79	0.21	19.29	79	0.956

* The values expressed in months indicate mean±standard deviation and median with interquartile range, respectively. CI: confidence interval; CVE: cerebrovascular events; FE: fixed effects; FU: follow-up; HR: hazard ratio; NOAF: new-onset atrial fibrillation; RE: random effects

Appendix Table 3. Adjustment of data included in the meta-analysis according to each outcome analysed.

	Pre-existing AF				NOAF			
	30-day all-cause mortality	Long-term all-cause mortality	Long-term cardiovascular mortality	Long-term CVE	30-day all-cause mortality	Long-term all-cause mortality	30-day CVE	Long-term CVE
Alassar et al [29]	N/A	Unadjusted	N/A	N/A	N/A	N/A	N/A	N/A
Allende et al[24]	N/A	Unadjusted	N/A	N/A	N/A	N/A	N/A	N/A
Amat-Santos et al[44]	N/A	N/A	N/A	N/A	Unadjusted	Unadjusted	Unadjusted	Unadjusted
Auffret et al[14]	N/A	Unadjusted	N/A	N/A	N/A	N/A	N/A	N/A
Barbash et al[30]	Unadjusted	Unadjusted	N/A	N/A	Unadjusted	Unadjusted	Unadjusted	Unadjusted
Elhmidi et al[27]	N/A	Unadjusted	N/A	N/A	N/A	N/A	N/A	N/A
Gotzmann et al[26]	N/A	Unadjusted	N/A	N/A	N/A	N/A	N/A	N/A
Lange et al[12]	Adj. multivariate	Adj. multivariate	N/A	N/A	N/A	N/A	N/A	N/A
LeVen et al[21]	N/A	Adj. multivariate	Adj. multivariate	N/A	N/A	N/A	N/A	N/A
Maan et al[46]	Unadjusted	Unadjusted	Unadjusted	N/A	N/A	N/A	N/A	N/A
Nombela-Franco et al[22]	N/A	N/A	N/A	Adj. multivariate	N/A	N/A	Adj. multivariate	Adj. multivariate
Nuis et al[28]	Adj. multivariate	Unadjusted	N/A	N/A	N/A	N/A	N/A	N/A
Nuis et al[42]	N/A	N/A	N/A	N/A	N/A	N/A	Adj. multivariate	N/A
Ribeiro et al[13]	N/A	Unadjusted	N/A	N/A	N/A	N/A	N/A	N/A
Rodés-Cabau et al[20]	Adj. multivariate	Adj. multivariate	N/A	N/A	N/A	N/A	N/A	N/A
Sabaté et al[25]	N/A	Adj. multivariate	N/A	N/A	N/A	N/A	N/A	N/A
Salinas et al[11]	Unadjusted	Unadjusted	N/A	N/A	N/A	N/A	N/A	N/A
Seiffert et al[43]	N/A	Unadjusted	N/A	N/A	N/A	N/A	N/A	N/A
Stortecky et al[19]	N/A	Adj. multivariate	Adj. multivariate	Adj. multivariate	Adj. multivariate	Adj. multivariate	N/A	N/A
Tamburino et al[16]	N/A	Unadjusted	N/A	N/A	N/A	N/A	N/A	N/A
Tay et al[10]	N/A	N/A	N/A	Unadjusted	N/A	N/A	N/A	N/A
Tchetche et al[17]	N/A	N/A	N/A	Unadjusted	N/A	N/A	N/A	Unadjusted
Toggweiler et al[15]	N/A	Unadjusted	N/A	N/A	N/A	N/A	N/A	N/A
Unbehaun et al[23]	Adj. multivariate	Adj. multivariate	N/A	N/A	N/A	N/A	N/A	N/A
Urena et al[45]	N/A	N/A	N/A	N/A	N/A	N/A	Unadjusted	N/A
Yankelson et al[18]	Adj. multivariate	Adj. multivariate	N/A	Adj. multivariate	Adj. multivariate	Adj. multivariate	Adj. multivariate	Adj. multivariate

Appendix Table 4. Cerebrovascular event definitions in the included studies.

Study	Pre-existing AF CVE long-term	NOAF CVE 30-day	NOAF CVE long-term	Definition of CVE
Amat-Santos et al 2012	–	3.89 (0.89-17.08)	4.27 (1.07-17.09)	TIA or stroke, categorised in accordance with the MRS as major stroke if MRS ≥2 at 30 days, or minor stroke if MRS <2 at 30 days.
Barbash et al 2014	–	0.87 (0.18-4.19)	–	Ischaemic stroke defined according to the VARC endpoint definitions.
Nombela-Franco et al 2012	2.84 (1.46-5.53)	2.27 (1.15-4.48)	2.53 (1.45-4.43)	TIA or stroke defined according to the VARC endpoint definitions.
Nuis et al 2012	–	4.40 (1.20-15.60)	–	Ischaemic stroke defined according to the VARC endpoint definitions.
Stortecky et al 2012	0.85 (0.30-2.40)	–	0.03 (0.01-90.00)	Ischaemic stroke defined according to the VARC endpoint definitions.
Tay et al 2011	1.51 (0.64-3.56)	–	–	TIA or stroke, defined according to the VARC endpoint definitions.
Tchetche et al 2014	0.87 (0.57-1.32)	–	0.62 (0.38-1.04)	TIA or stroke, defined according to the VARC endpoint definitions.
Urena et al 2015	–	3.59 (1.75-7.36)	–	Ischaemic stroke defined according to the VARC endpoint definitions.
Yankelson et al 2014	5.28 (1.79-15.57)	7.67 (0.47-125.80)	1.89 (0.20-17.49)	Ischaemic stroke defined according to the VARC endpoint definitions.

AF: atrial fibrillation; CVE: cerebrovascular events; MRS: modified Rankin scale; NOAF: new-onset atrial fibrillation; TIA: transient ischaemic attack; VARC: Valve Academic Research Consortium

Appendix Table 5. Meta-regression analysis in pre-existing AF.

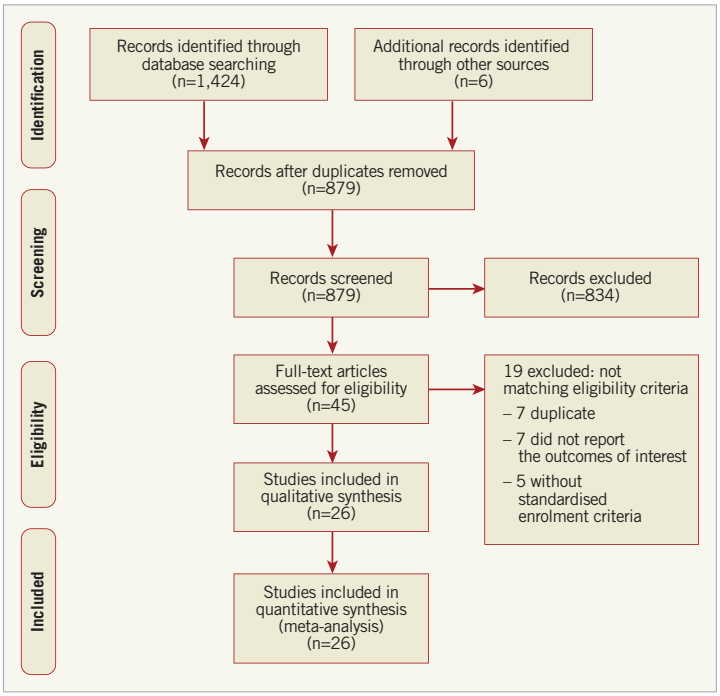
Pre-existing AF	30-day all-cause mortality		Long-term all-cause mortality		Long-term cardiovascular mortality		Long-term CVE	
	p-value	Intercept	*p*-value	Intercept	*p*-value	Intercept	*p*-value	Intercept
Age	0.413	–3.87	0.409	–4.23	0.154	–35.61	0.487	17.24
CAD	0.862	–0.16	0.250	0.68	0.641	–4.87	0.593	3.13
CKD	0.072	–0.54	0.321	–0.01	–	–	–	–
COPD	0.407	–0.03	0.052	–0.36	–	–	–	–
CoreValve	0.185	0.02	0.436	0.41	–	–	0.781	1.00
Diabetes	0.950	0.17	0.982	0.55	0.877	–0.57	0.160	–4.88
Edwards SAPIEN	0.185	–0.67	0.477	0.57	–	–	0.781	–0.83
EuroSCORE	0.146	0.87	0.473	0.13	–	–	0.616	–1.44
Hypertension	0.446	1.30	0.064	–2.52	0.986	–0.58	0.200	–5.16
LVEF	0.903	–0.43	0.204	4.38	0.926	3.08	0.603	–11.65
Male	0.141	–0.78	0.056	1.79	0.786	–0.50	0.612	2.73
NYHA III/IV	0.075	2.37	0.718	0.30	–	–	0.228	–4.25
Prior CVE	0.764	–0.29	0.527	0.59	–	–	0.074	–1.17
Prior MI	0.895	0.18	0.120	0.85	–	–	0.707	0.23
Prior PCI	0.069	–0.69	0.242	–0.06	0.633	–1.29	–	–
STS score	0.221	2.44	0.754	0.34	0.589	19.63	0.998	0.51
Transapical	0.166	0.26	0.748	0.42	0.914	0.89	–	–
Transfemoral	0.133	0.00	0.535	0.36	0.921	0.43	0.125	–6.35
Year of publication	0.579	–109.43	0.274	–181.73	0.986	–32.68	0.907	–83.04

AF: atrial fibrillation; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVE: cerebrovascular events; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons

Appendix Table 6. Meta-regression analysis in NOAF.

NOAF	30-day all-cause mortality		Long-term all-cause mortality		30-day CVE		Long-term CVE	
	p-value	Intercept	*p*-value	Intercept	*p*-value	Intercept	*p*-value	Intercept
Age	0.903	–0.53	0.412	–8.71	0.067	23.45	0.525	59.04
CAD	0.818	0.90	0.544	3.03	0.068	–4.73	0.058	–75.64
CKD	–	–	–	–	0.682	–3.05	–	–
COPD	–	–	–	–	0.575	2.35	–	–
CoreValve	0.124	0.45	0.552	0.15	0.979	0.75	0.523	1.83
Diabetes	0.636	–0.67	0.179	3.07	0.379	–1.80	0.650	–3.91
Edwards SAPIEN	0.124	–0.69	0.552	1.11	0.973	0.86	0.548	–2.25
EuroSCORE	0.802	–0.09	0.569	–1.32	0.373	2.62	–	–
Hypertension	0.097	–4.08	0.569	3.80	0.797	–0.06	0.808	–2.70
LVEF	0.703	–4.14	0.114	16.14	0.841	4.57	–	–
Male	0.971	0.14	0.306	–7.45	0.932	0.54	0.986	1.04
Moderate/severe MR	–	–	–	–	0.688	1.67	–	–
NYHA III/IV	–	–	–	–	0.366	35.95	0.150	–20–94
OAT	–	–	–	–	0.891	0.92	0.559	1.85
PAD	–	–	–	–	0.878	1.19	–	–
Prior CABG	0.217	–0.84	0.492	1.39	0.796	1.82	0.371	–5.50
Prior CVE	0.150	–0.49	0.732	0.72	0.960	1.03	0.260	–4.89
Prior MI	0.975	0.33	0.224	1.00	0.602	0.15	0.186	–7.16
Prior PCI	0.878	0.19	0.090	1.80	0.733	–0.36	–	–
STS score	0.624	–0.26	0.823	–0.16	0.371	2.36	0.849	–3.59
Transapical	0.875	0.29	0.085	0.89	0.510	0.12	0.664	–0.43
Transfemoral	0.871	0.46	0.800	–0.68	0.508	1.96	0.659	2.43
Year of publication	0.068	–242.5	0.549	725.08	0.607	–169.43	0.795	400.92

AF: atrial fibrillation; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVE: cerebrovascular events; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; OAT: oral anticoagulation therapy; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons



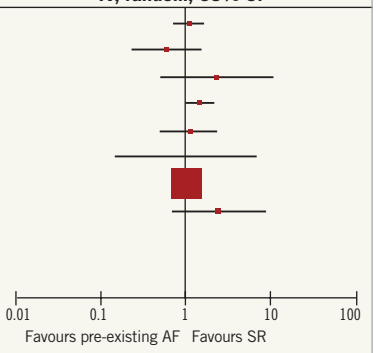
Appendix Figure 1. *Meta-analysis flow chart.*

A

PRE-EXISTING AF: EARLY ALL-CAUSE MORTALITY

Study or subgroup	log [hazard ratio]	SE	Pre-AF total	SR total	Weight	Hazard ratio IV, random, 95% CI
Barbash et al 2014	0.104	0.195	143	182	0.3%	1.11 [0.76, 1.63]
Lange et al 2012	–0.462	0.45	97	323	0.0%	0.63 [0.26, 1.52]
Maan et al 2014	0.788	0.727	67	70	0.0%	2.20 [0.53, 9.14]
Nuis et al 2012	0.378	0.161	265	730	0.4%	1.46 [1.06, 2.00]
Rodés-Cabau et al 2010	0.104	0.369	115	224	0.1%	1.11 [0.54, 2.29]
Salinas et al 2012	0	0.916	17	17	0.0%	1.00 [0.17, 6.02]
Unbehaun et al 2014	0.02	0.01	217	513	99.2%	1.02 [1.00, 1.04]
Yankelson et al 2014	0.829	0.588	118	231	0.0%	2.29 [0.72, 7.25]
Total [95% CI]			**1,039**	**2,290**	**100.0%**	**1.02 [1.00, 1.04]**

Heterogeneity: Chi²=9.31, df=7 (*p*=0.23); I²=25%
Test for overall effect: Z=2.19 (*p*=0.03)

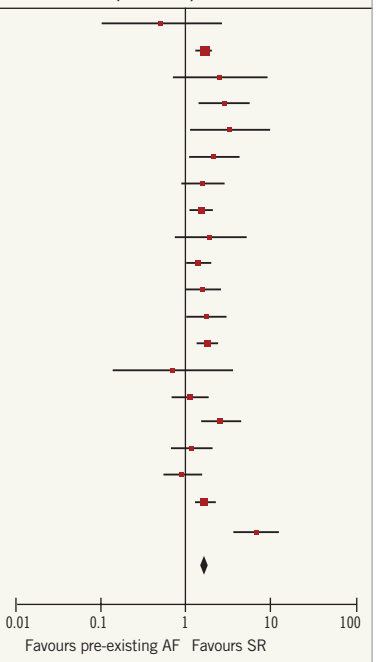


B

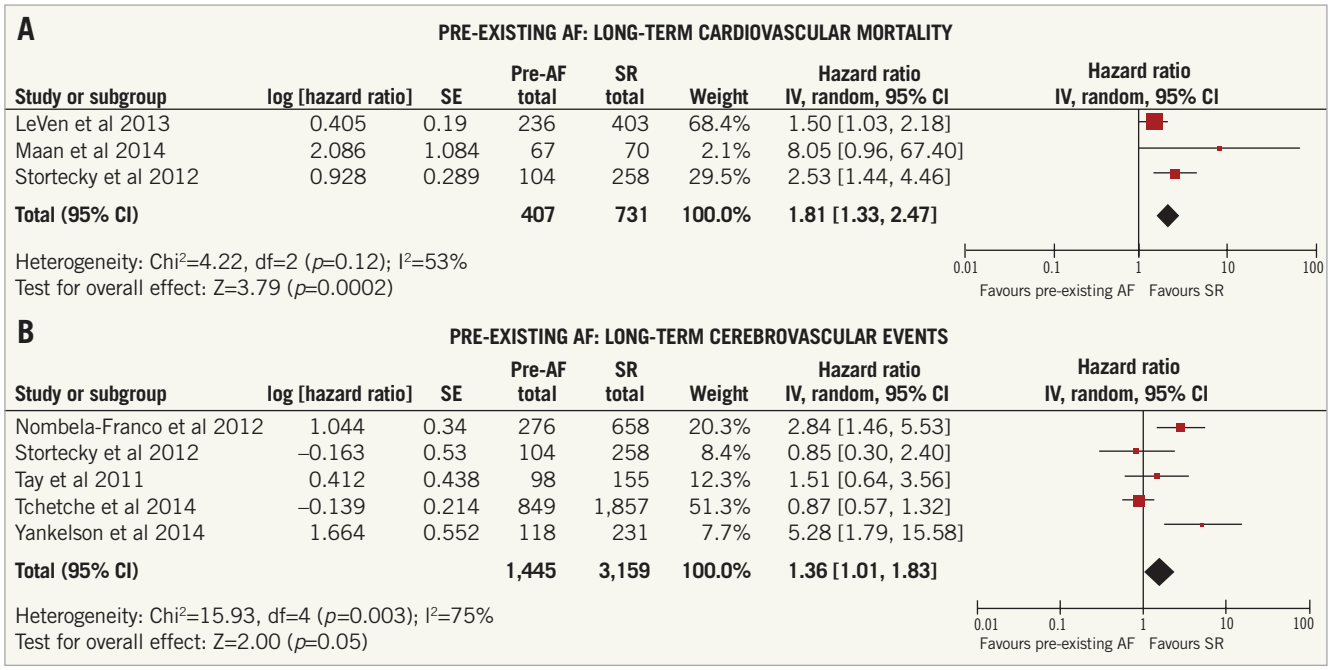
PRE-EXISTING AF: LONG-TERM ALL-CAUSE MORTALITY

Study or subgroup	log [hazard ratio]	SE	Pre-AF total	SR total	Weight	Hazard ratio IV, random, 95% CI
Alassar et al 2013	–0.598	0.777	19	100	0.3%	0.55 [0.12, 2.52]
Allende et al 2014	0.489	0.086	217	513	27.9%	1.63 [1.38, 1.93]
Auffret et al 2014	0.871	0.627	71	92	0.5%	2.39 [0.70, 8.17]
Barbash et al 2014	0.993	0.34	143	182	1.8%	2.70 [1.39, 5.26]
Elhmidi et al 2014	1.144	0.517	83	290	0.8%	3.14 [1.14, 8.65]
Gotzmann et al 2013	0.732	0.324	69	133	2.0%	2.08 [1.10, 3.92]
Lange et al 2012	0.457	0.274	97	323	2.8%	1.58 [0.92, 2.70]
LeVen et al 2013	0.412	0.147	236	40	39.6%	1.51 [1.13, 2.01]
Maan et al 2014	0.626	0.458	67	70	1.0%	1.87 [0.76, 4.59]
Nuis et al 2012	0.336	0.151	265	730	9.1%	1.40 [1.04, 1.88]
Ribeiro et al 2014	0.451	0.214	101	232	4.5%	1.57 [1.03, 2.39]
Rodés-Cabau et al 2010	0.554	0.268	115	224	2.9%	1.74 [1.03, 2.94]
Sabaté et al 2014	0.577	0.147	402	1,014	9.6%	1.78 [1.33, 2.38]
Salinas et al 2012	–0.301	0.78	17	17	0.3%	0.74 [0.16, 3.41]
Seiffert et al 2013	0.131	0.232	106	220	3.8%	1.14 [0.72, 1.80]
Stortecky et al 2012	0.896	0.247	104	258	3.4%	2.45 [1.51, 3.98]
Tamburino et al 2011	0.166	0.268	109	554	2.9%	1.18 [0.70, 2.00]
Toggweiler et al 2013	–0.083	0.25	45	43	3.3%	0.92 [0.56, 1.50]
Unbehaun et al 2014	0.507	0.135	217	513	11.3%	1.66 [1.27, 2.16]
Yankelson et al 2014	1.81	0.299	118	231	2.3%	6.11 [3.40, 10.98]
Total [95% CI]			**2,601**	**6,142**	**100.0%**	**1.64 [1.50, 1.79]**

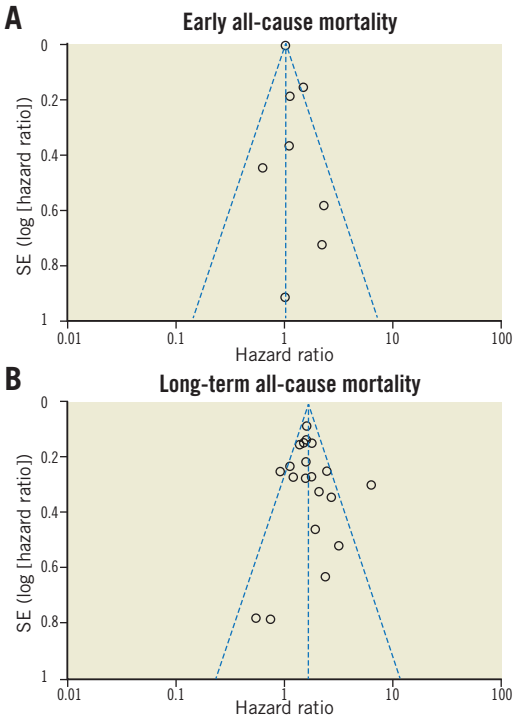
Heterogeneity: Chi²=40.87, df=19 (*p*=0.003); I²=54%
Test for overall effect: Z=10.91 (*p*<0.00001)



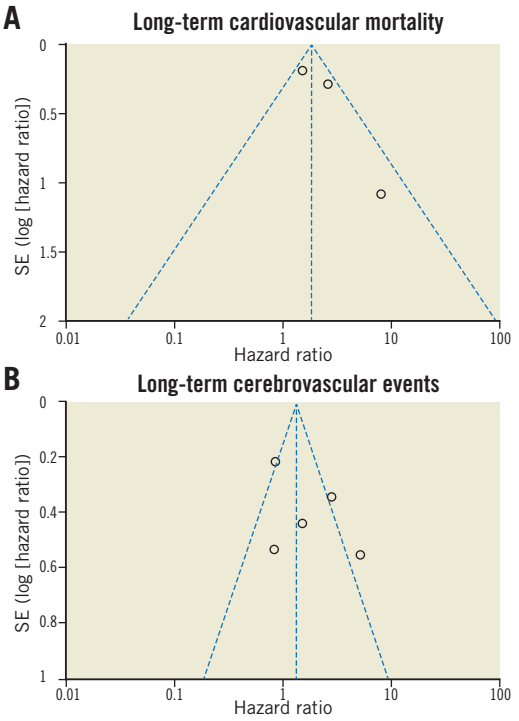
Appendix Figure 2. *Early and long-term all-cause mortality in pre-existing AF. Fixed effects model.*



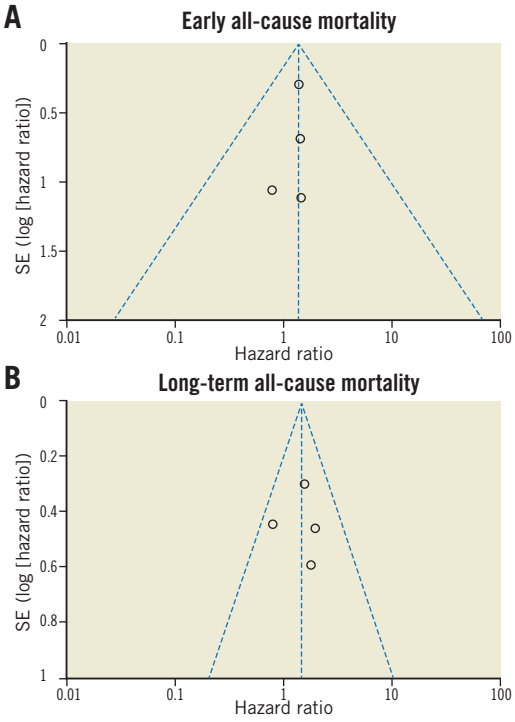
Appendix Figure 3. *Long-term cardiovascular mortality and cerebrovascular events in pre-existing AF. Fixed effects model.*



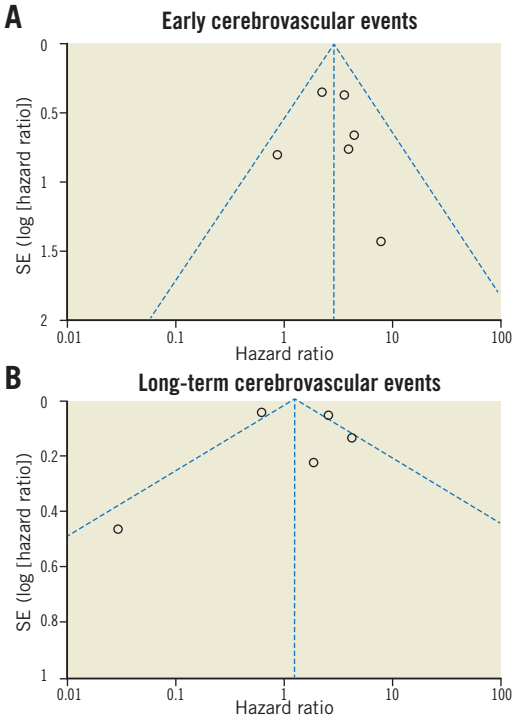
Appendix Figure 4. *Pre-existing AF: funnel plots of outcome.*



Appendix Figure 5. *Pre-existing AF: funnel plots of outcome.*



Appendix Figure 6. *New-onset AF: funnel plots of outcome.*



Appendix Figure 7. *New-onset AF: funnel plots of outcome.*