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Atrial fibrillation inducibility during cavotricuspid isthmus-dependent atrial flutter ablation as a predictor of clinical atrial fibrillation. A meta-analysis

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Abstract

Background Atrial fibrillation (AF) and cavotricuspid isthmus (CTI)-dependent atrial flutter (AFL) are two separate entities that coexist in a significant percentage of patients. We sought to investigate whether AF inducibility during CTI AFL ablation predicted the occurrence of AF at follow-up after successful AFL ablation.

Methods A systemic review of Medline, Cochrane, and Embase was done for all the clinical studies in which assessment of AF inducibility in patients undergoing ablation for CTI AFL was performed. Given the low heterogeneity (i.e., I^2 <25), we used a fixed effect model for our analysis.

Results A total of 10 studies (4 prospective and 6 retrospective) with a total of 1299 patients (male, 73%; mean age 59 ± 11 years) fulfilled the inclusion criteria. During a mean follow-up period of 23 ± 7.6 months, 407 patients (31%) developed AF during AFL ablation. The overall incidence for new-onset AF during follow-up was 29% (47% in the group with inducible AF vs. 21% in the non-inducible group). The odds ratio (OR) for developing AF after AFL ablation in patients with AF inducibility for all studies combined was 3.72, 95% CI 2.83–4.89 [prospective studies (OR 5.52, 95% CI 3.23–9.41) vs. retrospective studies (OR 3.23, 95% CI 2.35–4.45)].

Conclusions Although ablation for CTI AFL is highly effective, AF continues to be a long-term risk for individuals undergoing this procedure. AF induced by pacing protocols in patients undergoing CTI AFL predicts for future AF. Inducible AF is a clinically relevant finding that may help guide decisions for long-term anticoagulation after successful typical AFL ablation especially in patients with elevated

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CHADS-VASc scores (≥2) and in considering prophylactic PVI during CTI AFL ablation.

Keywords Atrial flutter · Cavotricuspid isthmus atrial flutter · Atrial fibrillation · AF inducibility

Abbreviations

AF	Atrial fibrillation
AFL	Atrial flutter
CTI	Cavotricuspid isthmus
LAE	Left atrial enlargement
AAD	Antiarrhythmic drugs
CA	Catheter ablation
CI	Confidence interval
LV	Left ventricle
LVEF	Left ventricular ejection fraction
RFA	Radiofrequency ablation
OR	Odds ratio

1 Introduction

The prevalence of atrial fibrillation (AF) and atrial flutter (AFL) is rising to epidemic proportions with critical effect on health care costs, resource utilization, and economic burden. Typical cavotricuspid isthmus (CTI)-dependent AFL is characterized by successful cure by radiofrequency ablation (RFA) and low risk of recurrence. However, AF occurs in 15 to 82% of patients by 6 to 40 months after AFL ablation. Notably, despite having a 6% cumulative incidence of embolic stroke during mean follow-up of 30 months after ablation for CTI AFL, there are scant recommendations for anticoagulation for this population [1, 2]. The progressive occurrence of AF after AFL ablation has been associated with numerous factors including advanced age, female sex, BMI, prior history of AF, left atrial enlargement (LAE), reduced left ventricular ejection fraction (LVEF), treatment with antiarrhythmic drugs (AAD) before ablation, mitral regurgitation, and AF inducibility. The significance of AF inducibility has been controversial. In this meta-analysis, we assessed the prognostic value of AF inducibility for new development of AF following successful RFA of CTI AFL.

2 Methods

Search strategy We searched PubMed, Embase, and Cochrane Central Register of Clinical Trials (Cochrane Library, Issue 09, 2015) using the following terms: "(typical atrial flutter OR cavotricuspid atrial flutter OR CTI atrial flutter OR CTI AFL OR right sided atrial flutter OR common atrial flutter OR Type I atrial flutter) AND (atrial fibrillation inducibility OR AF inducibility OR Afib inducibility)." Our search was limited to humans in peer-reviewed journals from 1990 to January 2016. No language restriction was applied. The reference lists of identified articles were also reviewed.

Selection criteria The studies had to fulfill the following criteria to be included in the analysis: (1) the study was prospectively or retrospectively designed; (2) the population was composed of patients undergoing RFA for typical CTI-dependent AFL; (3) AF inducibility was assessed during that procedure; (4) follow-up duration was at least 6 months to determine new development of AF; (5) the study provided enough data to calculate odds ratio (OR).

Data extraction and quality assessment Two authors (J.R. and J.D) searched the studies and extracted the data independently and in duplicate. Data was extracted using standardized protocol and reporting forms. Disagreements were resolved by consensus. We extracted characteristics of each study including AF inducibility methodology and baseline patient demographics for our analysis. If this information was not readily available, the principal investigator of the particular study was approached to supply pertinent information. The quality and reporting of the studies were assessed using the Newcastle-Ottawa Scale [3]. Three categories were included in the analysis, with some of them having subcategories for assessment (i.e., *Selection criteria*: 1—representativeness of the exposed cohort, 2—selection of non exposed cohort, 3—ascertainment of exposure, 4—demonstration that outcome of interest was not present at start of study. *Comparability criteria:* 1—study controls for the presence of previous AF, 2—study controls for additional factors. *Outcome*: 1—assessment of outcome, 2—was follow-up long enough for outcomes to occur, 3—adequacy of outcome of controls). Studies were subsequently classified into one of three categories: (1) high quality, 7–8 points; (2) satisfactory quality, 3–6 points; and (3) unsatisfactory quality, 0–2 points [3].

Statistical analysis Descriptive statistics are presented as means and standard deviations (SD) for continuous variables or number of cases (n) and as percentages (%) for dichotomous and categorical variables. Statistical analysis was performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, using Review Manager (RevMan), version 5.3, the Cochrane Collaboration, 2014. Heterogeneity was assessed using the I^2 statistics, which is the proportion of total variation observed among the studies attributable to differences between studies rather than sampling error (chance) [4]. Data were summarized across treatment arms using the Mantel-Haenszel or fixed effects model. We considered I^2 less than

25% as low and I^2 greater than 75% as high. The Random-Effects Model of DerSimonian and Laird was used if I^2 >25% [5]. All analyses were performed using the intention-to-treat principle. Likewise, we calculated the incidence of new onset of AF for all patients, with and without AF inducibility during RFA of CTI AFL, detected by ECG, Holter monitoring, or event monitor using relative risk (OR) ratios and 95% confidence intervals with the use of the Mantel-Haenszel method. Publication bias was estimated visually by funnel plots [5, 6].

Sensitivity analysis We further evaluated if the prognostic value of AF inducibility during AFL ablation for the development of AF depended on features of the study design (prospective vs. retrospective), pacing protocol, and duration of follow-up. One study excluded due to low sample size was also included in the sensitivity analysis of this meta-analysis to determine if it has any impact on our results. We estimated differences between subgroups according to the tests of interaction [7].

3 Results

Study selection We identified 720 abstracts, out of which 320 abstracts were screened after removing duplicates. A total of 48 abstracts were retrieved and carefully reviewed for possible inclusion (Fig. 1). Fourteen full-text manuscripts were assessed for eligibility. Ten studies (Tables 1 and 2) with a total of 1299 patients fulfilled the inclusion criteria and were included in the present meta-analysis [8–17]. Four studies were ultimately excluded from the final analysis since they did not meet the inclusion criteria: the studies by Chinitz et al. and by Chen et al. were excluded from the analysis because AF induction was not performed in all patients [18, 19]. Although the study published by Katritsis and colleagues met inclusion criteria, we excluded it due primarily to the fact that they reported outcomes with a very small sample size ($n = 6$) [20]. Finally, the study published by Schneider et al. was excluded due to incomplete data to calculate OR.

Quality assessment All the studies included in this meta-analysis had good methodological quality indicating "low risk of bias" (Table 3). Nine studies were classified as high quality and only one study was classified as satisfactory quality based on the Newcastle-Ottawa Assessment scale using eight different parameters. Most studies scored poorly on the demonstration that outcome of interest was not present at the start of study. Moreover, a significant amount of patients in each study already had previous documentation of AF. Fifty percent of the studies had a relatively limited follow-up period of less than 2 years, which might underestimate the real incidence of AF (Table 3).

Baseline characteristics and data analysis The prognostic yield of AF inducibility during CTI AFL ablation for the new onset of AF was assessed from 10 studies (4 prospective and 6 retrospective) that enrolled a total of 1299 patients [mean age 59 ± 11 years; male, 73%]. The specific pacing protocols used in each study are described in Table 2. All studies included patients who underwent RFA for typical, CTI-dependent AFL. Mean LVEF and LA size were 51 ± 7% and 38 ± 1 mm, respectively. A history of documented AF prior to the procedure was present on average in 24% of patients (range 0 to 47%). These studies had a mean follow-up of 24 ± 8 months (range 13–35 months). Most of the studies used Holter monitor as the main strategy for post-procedural AF monitoring (Table 1).

The overall incidence for new-onset AF during follow-up was 29% (47% in the group with inducible AF vs. 21% in the non-inducible group). The odds ratio (OR) for developing AF after AFL ablation in patients with AF inducibility for all studies combined was 3.72, 95% CI 2.83–4.89,

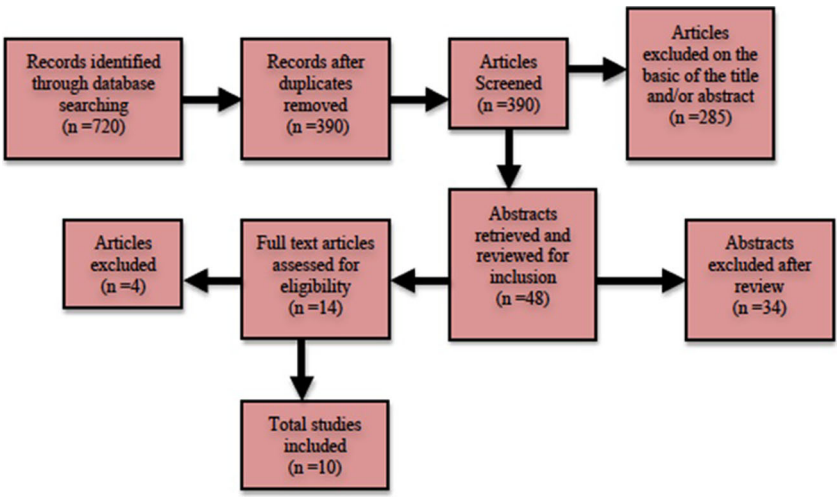

Fig. 1 Selection of studies included in this meta-analysis

Table 1 Baseline characteristics

Study	Year	Design	# Patients	% Male	Age	Previous AF	LVEF	LA size	Monitoring	Follow-up
Anselme et al.	1999	Retrospective	83	80	60 ± 11	29 (35%)	62 ± 12	37 ± 6	ECG 24-h Holter monitor	27 ± 9
Baszko et al.	2003	Prospective	61	44	48 ± 15	18 (29%)	54 ± 12	NR	24-h ECG monitoring 8-day event recording	16 ± 12
Haghjoo et al.	2013	Retrospective	84	75	49 ± 17	11 (13%)	44 ± 12	38 ± 8	12-lead ECG Holter monitor	26 ± 22
Hsieh et al.	2002	Retrospective	333	77	63 ± 16	121 (36%)	NR	NR	ECG 24-h Holter monitor Cardiac event recorder	29 ± 2
Joza et al.	2014	Retrospective	175	71	63 ± 14.0	82 (47%)	NR	39 (36–45)	48-h Holter monitor Device interrogations	34 ± 24
Laurent et al.	2009	Retrospective	148	82	65 ± 11	47 (32%)	NR	NR	ECG Holter monitor Event monitor	21 ± 8
Paydak et al.	1998	Prospective	110	78	62 ± 14	44 (40%)	50 ± 14	NR	ECG Holter monitor	20 ± 9
Philippon et al.	1995	Prospective	59	81	62 ± 12	12 (20)	46 ± 0.1	39 ± 6	Standard 12-lead ECG	13 ± 7
Romero et al.	2016	Retrospective	154	70	70 ± 13	0	48 ± 16	NR	ECG Event monitor Holter monitor	34 ± 24
Tai et al.	1998	Prospective	144	74	56 ± 18	33 (23%)	NR	NR	Standard 12-lead ECG 24-hour Holter monitor	17 ± 1

$P < 0.00001$. Prospective studies and retrospective studies were analyzed separately. Although there was a trend favoring prospective studies with a stronger OR of 5.52, 95% CI 3.23–9.41, $P > 0.00001$ when compared with retrospective studies (OR 3.23, 95% CI 2.35–4.45, $P < 0.00001$), no statistical difference was noted ($P = 0.09$). The overall heterogeneity among studies was low and hence a fixed effect model was used (Figs. 2 and 3).

Table 2 AF definition and pacing protocols

Study	Year	AF inducibility definition	Pacing protocol
Anselme et al.	1999	Irregular QRS complexes with totally disorganized atrial activity	Not defined
Baszko et al.	2003	Not defined	Baseline pacing with 8 beat drive at a pacing CL of 500 ms, with 1 extrastimulus introduced at decreasing intervals (10 ms decrease) until atrial refractoriness was achieved
Haghjoo et al.	2013	Not defined	Not defined
Hsieh et al.	2002	Not defined	Baseline pacing with 8 beat drive at 500 and 400 ms, with 1 or 2 extrastimuli; burst pacing for more than 20 beats at progressively shorter cycle lengths until 2:1 atrial capture occurred. Pacing was carried out from the high right atrium, low right atrium, and CS
Joza et al.	2014	Atrial fibrillation lasting >30 s	Burst pacing from the anterolateral right atrium and coronary sinus with decremental pacing from 290 to 200 ms or refractoriness over 5 s
Laurent et al.	2009	Atrial fibrillation lasting >30 s	Bust pacing (30 s) from the high right atrium at a frequency of 200 to 300 bpm by steps of 10 bpm
Paydak et al.	1998	Atrial fibrillation lasting >30 s	Burst pacing from 2 atrial sites (proximal CS and inferolateral tricuspid annulus) at pacing CL of 600, 500, and 400 ms, with progressive 10 ms decreases until 2:1 atrial capture
Philippon et al.	1995	Atrial fibrillation lasting >30 s	PAS from the HRA or the CS at a pacing CL of 500 ms with 1 or 2 extrastimuli + incremental atrial pacing
Romero et al.	2016	Atrial fibrillation lasting >30 s	Atrial burst pacing was carried out to induce AFL before and after ablation. Formal decremental pacing (atrial burst) and atrial pacing at two cycle lengths with single and double extrastimuli to intentionally try to induce AFL
Tai et al.	1998	Atrial fibrillation lasting >30 s	Baseline pacing with 8 beat drive at 600, 500, and 400 ms, with 1 or 2 extrastimuli; burst pacing for more than 20 beats at progressively shorter cycle lengths until 2:1 atrial capture occurred. Pacing was carried out from the high right atrium, low right atrium, and CS

Table 3 Methodology assessment

Author	Year	Selection				Comparability		Outcome			Total
		1	2	3	4	1	2	1	2	3	
Paydak et al.	1998	*	*	*	–	*	*	*	*	*	8
Anselme et al.	1999	*	*	*	–	*	*	*	–	*	7
Laurent et al.	2009	*	*	*	–	*	*	*	*	*	8
Tai et al.	1998	*	*	*	–	*	*	*	*	*	8
Baszko et al.	2003	*	*	*	–	*	*	*	–	*	7
Haghjoo et al.	2013	*	*	*	–	*	*	*	–	*	7
Joza et al.	2014	*	*	*	–	*	*	*	–	–	6
Romero et al.	2016	*	*	*	*	*	*	*	*	*	9
Hsieh et al.	2002	*	*	*	–	*	*	*	*	–	7
Philippon et al.	1995	*	*	*	–	*	*	*	–	*	7

Evaluation of article quality based on Newcastle-Ottawa Assessment scale. Selection criteria: 1—representativeness of the exposed cohort, 2—selection of non exposed cohort, 3—ascertainment of exposure, 4—demonstration that outcome of interest was not present at start of study. Comparability criteria: 1—study controls for the presence of previous AF, 2—study controls for additional factors. Outcome: 1—assessment of outcome, 2—was follow-up long enough for outcomes to occur, 3—adequacy of outcome of controls

Sensitivity analysis We examined every variable included in the baseline characteristics table (Tables 1 and 2) and no factor was identified with a significant influence on the total and subtotals of this meta-analysis. Albeit the study of Katritsis and colleagues met inclusion criteria, it was excluded due primarily to the fact that they reported outcomes with a very small sample size ($n = 6$) [20]. Including this study to the main meta-analysis did not affect our results [OR = 3.74 CI (2.85–4.91), $P < 0.00001$ vs. OR = 3.72, CI (2.83–4.89), $P < 0.00001$, respectively].

Publication bias Funnel plots did not suggest publication bias. As observed in Fig. 4, all studies fell inside the triangle and they are evenly distributed on both sides.

4 Discussion

In light of emerging data that AF inducibility during CTI-dependent AFL may be an important prognostic factor for the development of post-procedural AF, we systematically examined the prognostic impact of this parameter in all the available studies in the literature. Uniquely, this is the first meta-analysis to our knowledge analyzing these data. Likewise, we included 10 studies with a large group of 1299 patients with a mean follow-up of 24 months. The pertinent findings of this study were as follows:

1. This meta-analysis confirms previous observations of a moderately high incidence of symptomatic post AFL ablation AF (29% at 2 years) despite a low recurrence of typical atrial flutter in patients with CTI isthmus conduction block.
2. This meta-analysis suggests that overall, AF inducibility during CTI AFL ablation increases the probability of developing AF by 3.7-fold and 5.5-fold if only prospective studies are analyzed.

Ambulatory monitoring in patients with AFL frequently documents the coexistence of AF. Additionally, AFL may become more frequent, stable, or appear for the first time during AAD therapy of AF. Consequently, the high frequency of AF in patients referred for CTI AFL ablation (29% in the present meta-analysis), and 15 to 82% in prior reports is not unexpected. The mechanistic relation between these two arrhythmias is still not well defined. AF has been identified as a common transitional rhythm before the onset of spontaneous CTI AFL after surgical coronary revascularization as well as during the induction of typical AFL by high right atrial pacing. The transition from AF to AFL was heralded by lengthening lines of functional block, permitting the emergence of a large stable reentrant circuit. These observations suggest a potentially important role of AF in the genesis of CTI AFL. In many patients, interruption of conduction through the CTI may

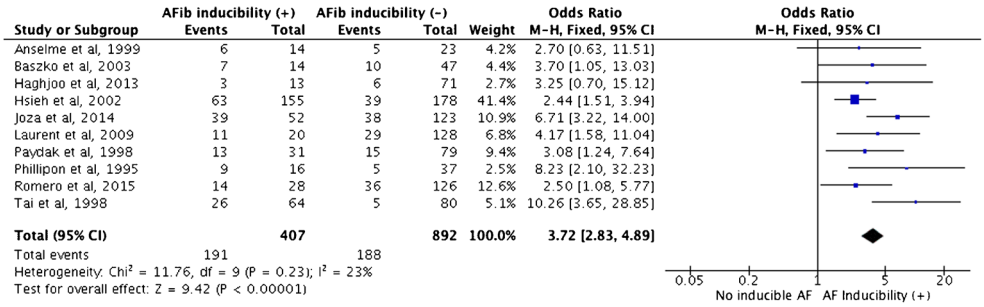

Fig. 2 Forest plot of comparison: inducibility of AF during AFL RFA predicts post-procedural clinical AF. All studies included

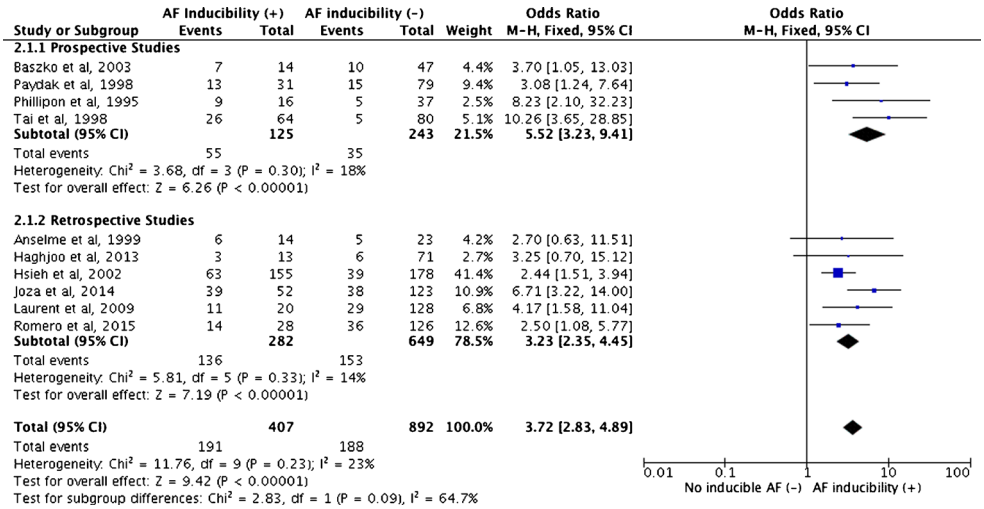

Fig. 3 Forest plot of comparison: inducibility of AF during AFL RFA predicts post-procedural clinical AF. Prospective vs. retrospective studies

prevent the organization of AF into flutter. The right atrial flutter circuit has been postulated to play a critical role in the initiation and maintenance of AF in some patients. AFL is also occasionally observed to spontaneously disorganize into AF during RFA procedures. These observations may explain the absence of recurrent AF in some patients with previous documentation of this rhythm. However, the frequent coexistence of AF and AFL in the population, and the persistent risk of AF in a substantial number of these patients despite successful long-term elimination of AFL, suggests AF as an initial trigger, rather than a consequence, of CTI AFL in our opinion.

4.1 Prior studies

Several factors have been previously reported to be associated with future development of AF after CTI AFL ablation. Yet, results from these studies showing the association of other predictors for AF have been variable, particularly the relation of LA size and LV function is limited by variable methods of assessment. Analyzing the available data on the value of LAE and LVEF as predictors of new-onset AF after CTI AFL ablation is somewhat cumbersome since these variables are continuous and not dichotomous. On the other hand, it is also difficult to consider "history of AF" as a predictor of a problem that a patient has already experienced. Chen et al. evaluated the HATCH score in the prediction of new-onset AF after RFA of CTI AFL [19]. The HATCH (hypertension, age >75 years, transient ischemic attack or stroke, chronic obstructive pulmonary disease, and heart failure) scoring system was originally developed from the Euro Heart Survey of AF to enable the detection of patients who are at high risk of progression from paroxysmal AF to more sustained forms of AF in the near future. Nearly half of patients with a HATCH score >5 progressed to persistent AF compared with 6% of patients with a HATCH score of 0. The authors demonstrated that the incidence of new-onset AF increased continuously with an

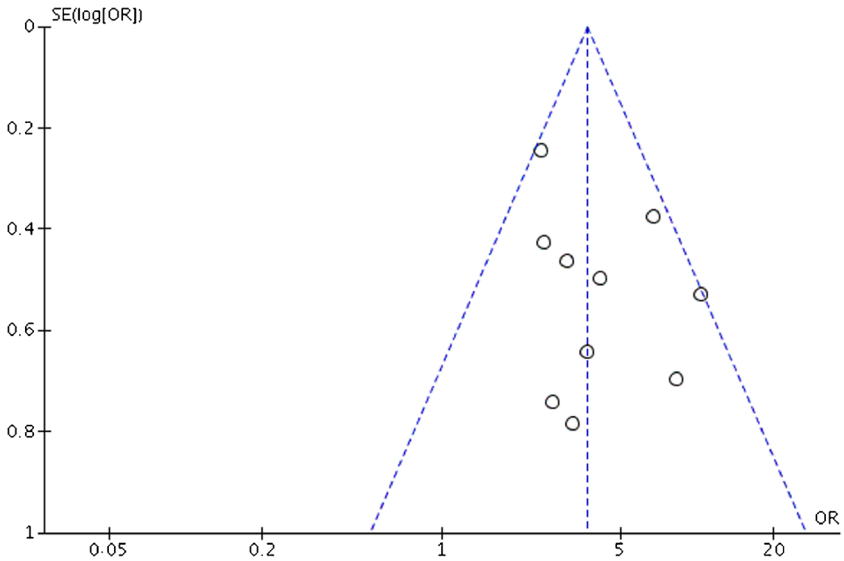

Fig. 4 Funnel plot for publication bias

increase in HATCH score ($P < 0.001$) [19]. The ROC curve for predicting AF after AFL ablation based on the HATCH score was 0.743. At a cutoff point of 2 identified by the ROC curve (sensitivity 51.8%, specificity 84.7%), patients with a HATCH score >2 were more likely to have advanced age, an LAE, and reduced LVEF. Also, as shown by Kaplan-Meier survival analysis, a HATCH score ≥2 was associated with a higher incidence of AF than a HATCH score <2 (69 vs. 27%, $P < 0.001$) during mean follow-up. Multivariate Cox regression analysis demonstrated that the HATCH score had only a Hazard Ratio (HR) of 1.784; 95% CI 1.352–2.324; $P < 0.001$ along with a low HR for LA diameter (HR 1.27; 95% CI 1.115–1.426; $P < 0.001$) [19]. AF inducibility in this meta-analysis had an OR of 3.7; 95% CI 2.83–4.89, $P < 0.00001$. Interestingly, Joza et al. elegantly demonstrated that in patients without a documented history of AF, induciblility of AF after AFL ablation is strongly associated with the future development of AF (adjusted HR 15.99; 95% CI 5.10–50.12) [11]. In contrast, in patients with a documented history of paroxysmal or persistent AF, AF inducibility was not associated with an increased risk of future development of AF (adjusted HR 1.26; 95% CI 0.74–2.14). Furthermore, a documented history of AF was strongly associated with the future development of AF (adjusted HR 9.44; 95% CI 3.61–24.64) [11]. Hsieh et al. demonstrated that positive inducibility correlated with the future development of AF; however, there was no difference among patients who had a history of AF and those who did not. Nonetheless, this conclusion may have been influenced by the fact that inducibility testing was performed before the creation of AFL line [10].

Noticeably, the presence of advanced interatrial block (aIAB), defined as a P-wave duration ≥120 ms and biphasic morphology in the inferior leads, has also been associated with an elevated risk of AF after RFA of CTI AFL and no prior history of AF (64.7 vs. 29.4%; *P*, 0.001). In multivariable analysis, aIAB was the strongest predictor of new-onset AF [OR 4.2, 95% confidence interval (CI): 1.9–9.3; *P*, 0.001]. Likewise, more recently intra-atrial conduction delay was also reported to be a significant risk factor for AF following CTI AFL ablation. Antegrade (high right atrium to coronary sinus, HRA-CS) and retrograde (CS-HRA) intra-atrial conduction times and AF inducibility were assessed in 61 patients undergoing ablation for typical AF. Patients with post-ablation AF had longer intra-atrial conduction times before (98 ± 17 vs. 68 ± 20 ms; *P*, 0.001) and after ablation (91 ± 19 vs. 73 ± 21 ms; *P*, 0.01) than those without AF. Multivariate analysis revealed that only age, previous AF, and intra-atrial conduction delay (>90 ms) were independent predictors of post-ablation AF. Patients without a history of AF and with normal intra-atrial conduction had a 3% risk of AF, while patients with both factors had a 90% risk of AF after ablation [8].

4.2 Clinical implications

This meta-analysis compares AF inducibility during CTI AFL ablation and the development AF post-ablation. Patients who were inducible for AF had a much higher incidence of post-procedural AF at follow-up when compared to those who were not, with rates of 47 vs. 21%, respectively. The data presented becomes significant in two clinical scenarios: (1) long-term post-procedural anticoagulation, particularly in patients with high stroke risk (i.e., CHADS-VASc ≥2), and (2) the role of pulmonary vein isolation during typical AFL RFA.

4.3 Anticoagulation

Anticoagulation therapy should be especially considered for patients with elevated CHADS-VASc scores (≥2) who have had AF inducibility during CTI AFL ablation, as the increased risk of future AF implies higher probabilities of thromboembolic stroke. As mentioned above, some studies have shown a 6% cumulative incidence of stroke during mean follow-up of 30 months after ablation for typical AFL, which might be due to the fact that a significant amount of these patients will experience post-procedural AF. The 2014 AHA/ACC/HRS Guidelines for the Management of Patients With AF recommend the same antithrombotic therapy for patients with AFL according to the same risk profile used for AF (Class I, Level of Evidence: C). Similarly, the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of AF recommends systemic anticoagulation at least 2 months following an AF/AFL RFA. Decisions regarding the continuation of systemic anticoagulation agents more than 2 months following ablation should be based on the patient's risk factors for stroke and not on the presence or type of AF. Although, the same principle should be applied for patients undergoing RFA of AFL based on current guidelines, in clinical practice oral anticoagulation is usually stopped after 3 months of a successful procedure for AFL.

4.4 Prophylactic PVI

Studies have assessed the addition of PVI to CTI ablation in patients with atrial flutter without previously identified AF. "Navarrete et al. in 2011 reported absence of recurrent atrial arrhythmias in 87% of 20 patients that underwent CTI line plus PVI (87%) compared to 44% of 11 patients in whom only a CTI line was performed ($P < 0.05$) [21]. The PREVENT-AF study was also a randomized clinical trial of 50 patients in whom only typical AFL had been observed clinically, the addition of PVI to CTI ablation resulted in a marked reduction of new-onset AF during follow-up as assessed by a continuous implantable cardiac monitor (52 vs. 12%; $P = 0.003$) [22]. Moreover, Schneider and collaborators recently published a study in 2015 in the same population (lone AFL) comparing

PVI vs. CTI ablation. They suggested that pulmonary vein triggers play an important role in AFL and that PVI can prevent the recurrence of AFL, even without CTI ablation (14 of 23 patients (60.9%) in the CTI group, and 2 of 20 patients (10%) in the PVI group had recurrence of any atrial arrhythmia (*P*, 0.001)) [23]. Others have observed that in some patients with both AF and AFL, PVI alone may be sufficient to control both arrhythmias [24, 25]. Further research is required to determine whether inducibility of AF at time of AFL ablation may help in identifying those patients in whom the benefits are most likely to outweigh the risks of additional ablation for PVI with its associated risks of transseptal puncture, increased procedure time, atrioesophageal fistula, cardiac tamponade, phrenic nerve injury, pulmonary vein stenosis, and stroke [26, 27]. Current AHA/ACC guidelines do not have recommendations for this prophylactic approach (i.e., PVI ablation). Before recommending a complex prophylactic procedure such as RFA of AF in this subset of patients, large well-designed prospective studies must be conducted with assessment of cost-benefit and risk-benefit [27]."

5 Limitations

There are many limitations common to retrospective studies and meta-analyses. Many of the included studies have relatively small sample sizes. Studies used different pacing protocols and the induction of AF was performed prior to the CTI line creation in some studies. The occurrence of AF may have been underestimated. Although electrocardiographic documentation of symptomatic arrhythmias was available before ablation and was routinely obtained after ablation, arrhythmia monitoring was variable among studies. Asymptomatic atrial arrhythmias are frequent in this population.

6 Clinical implications

AF induced by pacing protocols in patients undergoing CTI ablation for common AFL is a strong predictor for future AF. This may be useful to consider in decisions of the intensity of follow-up for arrhythmias and whether to continue long-term anticoagulation after successful typical AFL ablation especially in patients with elevated CHADS-VASc scores (≥2). AF inducibility may also be helpful in deciding whether or not to perform prophylactic pulmonary vein isolation for AF during CTI AFL ablation.

Compliance with ethical standards

Conflict of interest Dr Di Biase is a consultant for Biosense Webster, Boston Scientific, and St. Jude Medical and has received speaker honoraria/travel from Medtronic, Atricure, EPiEP, and Biotronik. Dr. Kumar is a recipient of the Neil Hamilton Fairley Overseas Research scholarship co-funded by the National Health and Medical Research Council and the National Heart Foundation of Australia; and the Bushell Travelling Fellowship funded by the Royal Australasian College of Physicians and the Postdoctoral Research Fellowship by the American Heart Association. Dr. Tedrow receives consulting fees/honoraria from Boston Scientific Corp. and St. Jude Medical and research funding from Biosense Webster, Inc., and St. Jude Medical. Dr. John receives consulting fees/honoraria from St. Jude Medical. Dr. Michaud receives consulting fees/honoraria from Boston Scientific Corp., Medtronic, Inc., and St. Jude Medical, and research funding from Boston Scientific Corp. and Biosense Webster, Inc. Dr. Stevenson is co-holder of a patent for needle ablation that is consigned to Brigham and Women's Hospital. The remaining authors have no disclosures.

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