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ELECTROPHYSIOLOGY

Inducibility of atrial fibrillation after catheter ablation predicts recurrences of atrial fibrillation: a meta-analysis

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Abstract

Background: Pulmonary vein isolation (PVI) is a component of standard care for patients with symptomatic atrial fibrillation (AF). Procedural inducibility of AF following PVI has been suggested as predictor of AF recurrence but is discussed controversially. This meta-analysis aimed at evaluating the relevance of electrophysiological inducibility of AF following PVI for future AF recurrences.

Methods: A literature search of MEDLINE and Web of Science was performed until April 2020. Prospective trials of PVI in patients with AF and post-procedural atrial stimulation to test for inducibility of AF as well as adequate follow-up for AF recurrence (defined as AF >10 s to >10 min at follow-up) were included. Odds ratios (ORs) were analyzed using random-effects models.

Results: A total of 11 trials with 1544 patients (follow-up 7–39 months, age 56 ± 6 years, predominantly male 74 ± 6%) were included. Inducibility of AF post-PVI was predictive for AF recurrence during follow-up (OR 2.08; 95% CI 1.25 to 3.46). Prediction for AF recurrence at follow-up was better for patients with paroxysmal AF (OR 4.06; 95% CI 1.39 to 11.91), stimulation in the CS (OR 2.82, 95% CI 1.17 to 6.79). A trend towards higher ORs was seen without the use of isoproterenol (OR 2.43; 95% CI 1.17 to 5.07), as well as few stimulations during induction and a short definition of AF in meta-regression analyses.

Conclusions: Electrophysiological inducibility of AF following PVI was predictive for future recurrence of AF, in particular in patients with paroxysmal AF, stimulation in only CS and no use of isoproterenol.

KEYWORDS
atrial fibrillation, pulmonary vein isolation, inducibility, recurrence of atrial fibrillation

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia with an estimate of 33 million patients worldwide[1] and increasing research activities in the last 20 years.[2] Pulmonary vein isolation (PVI) as an anatomical approach to isolating rapidly firing foci has become standard of care in selected patients.[3] In patients with reduced left ventricular ejection fraction (LVEF), PVI lowered the rate of the composite endpoint of all-cause death and hospitalization for heart failure compared with optimal medical therapy.[4] In

patients with new-onset or untreated AF, an association between catheter ablation and reduced recurrence of AF was shown[5] as well as a significant improvement in quality of life[6] compared with medical therapy.

AF recurrence after the blanking period following PVI occurs in 25% to 40%,[7,8] with a slow but steady decrease in arrhythmia-free survival over time.[9] Predictors for AF recurrences are, type of AF (paroxysmal vs. persistent), underlying cardiomyopathy, uncontrolled hypertension, age, and body mass index.[10] Efforts have been made to identify patients at risk for AF recurrence during the ablation procedure, by evaluating atrial vulnerability and inducibility of AF directly following PVI. While some studies suggest that inducibility of AF following PVI is predictive for long-time recurrence,[11,12] others describe no correlation.[13] Given the conflicting results, this study evaluates the role of inducibility on AF recurrence following PVI.

2 | METHODS

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard[14] as well as the scientific statement of the American Heart Association[15] and was registered with the Open Science Framework (Millenaar D. Inducibility of Atrial Fibrillation–A meta-analysis [Internet]. 2019; Available from: osf.io/fc2pv).

2.1 | Inclusion criteria

Studies had to meet the following inclusion criteria: (1) written in English, (2) published in a peer-review journal, (3) conducted with human subjects undergoing PVI for paroxysmal or persistent AF, (4) induction of AF was tested following complete PVI according to a standardized protocol, (5) no additional ablation lines were performed after the induction of AF (in case of additional ablations, only studies were included, where patients with PVI only and their follow-up results could be clearly extracted), (6) follow-up was documented with sufficient arrhythmia monitoring, and (7) information necessary for the computation of the odds ratio (OR) for the recurrence of AF between groups of inducible and non-inducible patients was available.

2.2 | Literature search

The literature search process is visualized in the PRISMA flowchart in Figure 1. It was conducted in April 2020 using the databases PubMed/MEDLINE and Web of Science Core Collection (WoS). The search terms "atrial fibrillation", "inducibility", "pulmonary vein isolation", and "recurrence of atrial fibrillation" were used in all possible combinations. Furthermore, reference lists of relevant articles were screened for additional eligible studies.

2.3 | Coding of studies

The following aspects of the final sample of studies were coded: (1) total number of patients, (2) number of patients with inducible AF, and (3) number of AF recurrences in this group, (4) number of patients without inducible AF, and (5) number of AF recurrences in this group, (6) type of AF: paroxysmal versus persistent versus both, (7) use of isoproterenol: yes versu no, (8) stimulation site: coronary sinus (CS) versus high right atrium (HRA) versus CS and HRA, (9) number of stimulations, and (10) definition of AF duration in seconds.

2.4 | Meta-analytic procedure

The statistical analyses were carried out using the metafor package[16] in R statistics 3.6.1[17] following the guidelines of Borenstein et al.[18] Due to differences in sample characteristics (e.g., age, sex distribution) and stimulation methods the analyses were conducted using a random-effects model. The OR was computed for each study based on the numbers of patients with and without AF recurrence in the inducible and non-inducible group. ORs were logarithmised before computing the meta-analysis and the results were re-transformed into the original metric. The overall OR corrected for sampling error [M(OR)], the corresponding 95% confidence interval (95% CI) and the population variance (τ^2) were computed. Significance of Cochranes Q-test as well as an I^2-statistic above 75% were regarded as indicators of substantial heterogeneity between the results of the individual studies.[19] To assess the robustness of the results against a possible file drawer, bias funnel plots were generated and inspected for asymmetry.[20] For categorial moderator variables (e.g., stimulation site) separate meta-analyses were conducted on each level of the moderator variable. Distinct mean ORs as well as non-overlapping confidence intervals were regarded as indicator of the significance of a moderating effect. To test for moderating effects of continuous study characteristics (e.g., definition of AF in seconds) random-effects meta-regression analyses were used in which the OR is predicted as a function of the moderator variable.[21] The significance of the moderator effect was assessed using a χ2-test.

3 | RESULTS

3.1 | Study selection and characteristics

The literature search resulted in 621 articles (1354 before removing duplicates). Fifteen studies seemed relevant according to title and abstract and were assessed for eligibility. One of the studies was excluded as no follow-up was reported[22] and three because different additional ablation strategies were employed.[23–25] After exclusion of ineligible studies, eleven trials with 1544 patients were used for further analysis. As information on follow-up was missing in one article, the

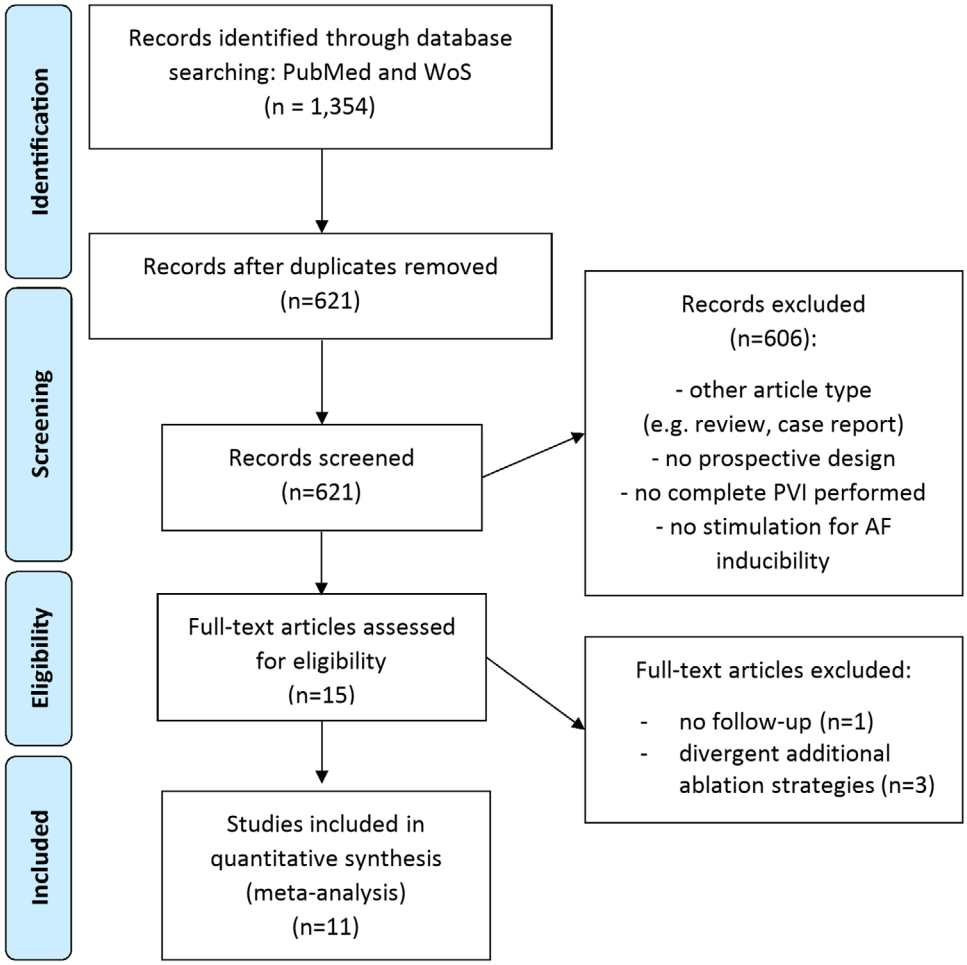

FIGURE 1 PRISMA flow diagram showing selection of studies [Color figure can be viewed at wileyonlinelibrary.com]

corresponding author was contacted for full details.[26] The complete search algorithm is depicted in Figure 1. Baseline characteristics of all included trials are shown in Table 1. All trials were designed prospectively, with alike patient populations (mean age: 56 ± 6 years, mean male percentage 74 ± 6, mean left ventricular ejection fraction (LVEF) 58 ± 4%, and mean left atrial (LA) diameter 43 ± 4 mm). The time period of publication ranged from 2004 until 2019.

Follow-up periods ranged from 7 ± 3[11] to 39 ± 21 months[27] with a mean follow-up period of 15 ± 9 months. Electrophysiological stimulation for induction of AF was performed after successful and complete PVI in all studies. Radiofrequency ablation (RFA) in combination with a three-dimensional (3D) mapping system for circumferential lesions encircling both PV ostia was utilized in all studies. Stimulation was achieved via the high right atrium (HRA)[27] or the coronary sinus (CS)[12,26,28–31] or both[11,13,32,33] (Table 2). All stimulation protocols included burst stimulation in decremental cycle lengths (CL) until reaching atrial refractoriness, the exact stimulation protocol is depicted in Table 2. In three trials, isoproterenol was used in addition to the electrophysiological stimulation. The successful inducibility of AF was defined as an episode of arrhythmic atrial activity for >10 s[32] until >10 min[27,31], depending on the study's protocol. Five trials however defined AF as >1 min. A discrepancy was observed between the definition of AF during stimulation following PVI and the definition of AF during follow-up to define AF recurrence: four studies did not define AF definition during follow-up (marked with ~ in Table 2),[11,29–31] three trials used the same definition during induction and follow-up[12,26,32], and the other four applied different definitions: >1 min versus > 30 s,[28] >2 min versus >30 s,[13] > 10 min versus >30 s,[27] >2 min versus 30 s,[33] respectively. All except one trial[31] considered a blanking period following PVI, during which AF episodes were not counted as recurrences.

3.2 | Overview of study results

Figure 2 shows the forest plot of the ORs for each individual study. ORs >1 indicate a higher rate of AF recurrence during follow-up in the group with inducible AF immediately after PVI. The ORs showed a considerable range (0.70 ≤ OR ≤11.33). Eight of the eleven ORs (72.7%) were numerically and 5 (45.5%) significantly above 1. Three studies (27.3%) showed ORs that were numerically but not significantly below 1.

TABLE 1 Patients' baseline characteristics

Study	Year	Total N	Included patients for analysis (n)	Design	Male [n] (%)	Age [y] (M, SD)	AF type (paroxysmal/ persistent)	LVEF [%] (M, SD)	LA diameter [mm] (M, SD)
Adlbrecht et al.[1]	2011	121	121	prospective	76 (63)	60 ± 10	121/0	54 ± 3	44 ± 7
Chang et al.[2]	2007	88	36[a]	prospective	61 (69)	51 ± 12	88/0	61 ± 6	31 ± 5
Essebag et al.[3]	2005	102	102	prospective	75 (74)	53 ± 11	60/42	56 ± 7	45 ± 1
Haïssaguerre et al.[4]	2004	70	70	prospective	52 (74)	53 ± 9	70/0	67 ± 12	43 ± 7
Kosiuk et al.[5]	2019	245	245	Prospective	176 (72)	59 ± 9	130/115	58 ± 10	43 ± 7
Leong-Sit et al.[6]	2012	144	107[a]	prospective	114 (79)	60	78/66	57	46 ± 8
Nagamoto et al.[7]	2012	194	194	prospective	160 (83)	55 ± 10	0/194	53 ± 7	44 ± 5
Oral et al.[8]	2004	100	70[a]	prospective	80 (80)	54 ± 10	70/0	56 ± 9	43 ± 7
Richter et al.[9]	2006	234	234	prospective	168 (72)	57 ± 11	165/69	61 ± 7	45 ± 7
Santangeli et al.[10]	2018	305	305	prospective	241 (79)	55 ± 11	104/0	59 ± 8	43 ± 7
Satomi et al.[11]	2008	60	60	prospective	45 (75)	58 ± 10	60/0	not assessed	43 ± 6

Abbreviations: AF, atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction; M, mean; N, number; SD, standard deviation.
[a]only selected patients were included for analysis, as other patients received additional ablation procedures in addition to a PVI.

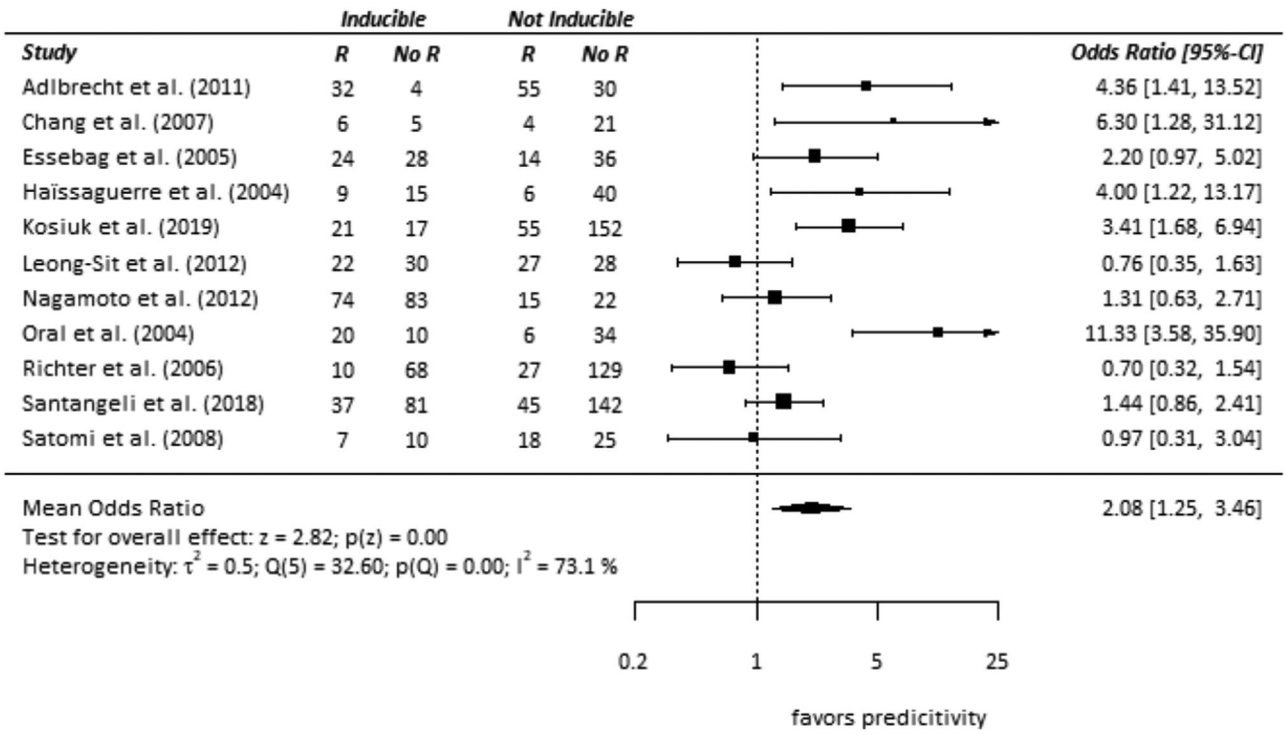

FIGURE 2 Forest plot of all included trials showing the overall predictivity of AF during follow-up after successful inducibility of atrial fibrillation post-PVI. R, recurrence; No R, no recurrence; OR, odds ratio; τ^2, population variance; 95%-CI, 95% confidence interval; I^2, I^2-statistic; Q(df), Q-value with degrees of freedom; p(Q), significance of the Q-value

TABLE 2 Electrophysiological characteristics of included studies

Study	Definition of AF	Stimulation location: stimulation protocol (number of repetitions)	Isopro-terenol	Monitoring during follow-up	Follow-up [months] (M, SD)	Blanking period
Adlbrecht et al.[28]	>1 min	CS: CL slightly shorter than SR until atrial refractoriness or 200 ms, pacing maintained for 5 s (2)	No	3-month-interval: clinical evaluation, 12-lead ECG, Holter monitoring (24 or 48 h). ([a]) AF > 30 s	12	3 months
Chang et al.[12]	>1 min	CS: CL 250 ms to 150 ms in 10-ms decrements, pacing maintained for 5-10 s (4)	No	2 months following ablation: 12-lead ECG, Holter monitoring (24 h). AF > 1 min	12 ± 6	2 months
Essebag et al.[32]	> 10 s	HRA & CS: burst pacing at CL 200 ms, pacing maintained for 5 s (3)	Yes	1, 3, 6, 12 months: 2-week trans-telephonic event recorder, Holter monitor (24 h). AF > 10 s	16 ± 10	30 days
Haïssaguerre et al.[11]	≥ 1 min	HRA & CS: programmed extrastimuli, then CL 250 ms until atrial refractoriness in 10-ms decrements (6)	No	1, 3, 6, 12 months: Transthoracic echocardiography, ambulatory monitoring, stress testing. [b]	7 ± 3	1 month
Kosiuk et al.[26]	> 30 s	CS: CL 300, 250, 200 ms or shortest CL > 200 ms with 1:1 atrial capture, 10 s at each CL (1)	No	First week, 3, 6, 12, 24, 36 months: Holter monitoring (7 days)	max. 36[c]	3 months
Leong-Sit et al.[13]	> 2 min	HRA & CS: CL 250 ms until 2:1 atrial capture or 180 ms, pacing maintained for 15 beats for each 10-ms increment (3)	No	6-12 weeks, 6, 12 months: 12-lead ECG, 2-4-week trans-telephonic looping monitor. AF > 30 s	12	8 weeks
Nagamoto et al.[27]	> 10 min	HRA: CL 250 ms until atrial refractoriness or 160 m, pacing maintained for 8 s (5)	Yes	1 week, 1, 3, 6, 9, 12, months: 12-lead ECG, 3, 6, 9 months: Holter monitoring (24 or 48 h). ([a]) AF > 30 s	39 ± 21	3 months
Oral et al. [29]	> 1 min	CS: shortest CL with 1:1 atrial capture, pacing maintained for 15 s (5)	No	3, every 6 months: 12-lead ECG, every 4 weeks: trans-telephonic surveys. ([a],[b])	8 ± 2	6 weeks
Richter et al.[30]	> 1 min	CS: CL slightly shorter than SR until atrial refractoriness or 200 ms, pacing maintained for 5 s (2)	No	6 weeks, then 3-month-intervals: 12-lead ECG, Holter monitoring (24 or 48 h). ([a],[b])	13	2 months
Santangeli et al.[33]	> 2 min	HRA & CS: CL 250 ms to atrial refractoriness or 180 ms, pacing maintained for 15-beats per 10-ms increment (1)	Yes	6 weeks, 6, 12 months: 12-lead ECG; 6, 12 months: 30 days trans-telephonic monitoring, self-guided pulse palpation[a]. AF > 30 s	19 ± 7	90 days
Satomi et al.[31]	> 10 min	CS: CL 250 ms until atrial refractoriness, pacing maintained for 10 s (5)	No	1, 3, 6, 12, 18, 24 months: 12-lead ECG, Holter monitoring (24 h), transthoracic echocardiography. ([b])	16 ± 8	None

AF, atrial fibrillation; CL, cycle length; CS, coronary sinus; h, hours; HRA, high right atrium; M, mean; min, minute; ms, milliseconds; SD, standard deviation; sec,seconds, SR, sinus rhythm.

[a]further monitoring in case of symptoms suggestive for AF.

[b]no additional information on AF definition at follow-up.

[c]no information on mean follow-up time available.

3.3 | Outcomes

The results of outcome of interest are presented in Figures 2 and 3. The mean OR of 2.08 (95% CI 1.25–3.46) indicates that patients with inducible AF immediately after PVI showed a higher rate of AF recurrence during follow-up. A population variance of $\tau 2 = 0.5$, a significant Q-test [$Q(10) = 32.6$; $p < .01$] as well as a I^2 - value of 73.1% indicate a substantial amount of heterogeneity between the results of the individual studies. Thus, additional moderator analyses were performed.

3.4 | Moderator analyses

The analyses concerning the categorical moderator variables are presented in Figure 3. The mean ORs indicated that the prediction of the recurrence of AF was significantly better for trials including only patients with paroxysmal AF [M(OR) = 4.06, 95% CI 1.39 to 11.91] than for trials including patients suffering from either paroxysmal or persistent AF [M(OR) = 1.61, 95% CI 0.92 to 2.83]. There was no statistically significant difference between the mean ORs of studies that used or did not use isoproterenol. However, in studies using no isoproterenol [M(OR) = 2.43, 95% CI 1.17 to 5.07] the prediction of AF was numerically better than in studies using isoproterenol [M(OR) = 1.53, 95% CI 1.06 to 2.23]. Studies conducting stimulation via the CS showed a significantly better prediction of the recurrence of AF [M(OR) = 2.82, 95% CI 1.17 to 6.79] than studies additionally conducting stimulation via the HRA [M(OR) = 1.59, 95% CI 0.89 to 2.85].

The results of the random-effects meta-regression analysis concerning the definition of AF as well as the number of stimulation repetitions during electrophysiological induction of AF is depicted in Figure 4. The visual inspection of the regression plots shows that the ORs tend to decrease with longer AF definitions (Figure 4A) and tend to increase with the number of repetitions (Figure 4B). Nevertheless, the results of the $\chi 2$-test indicate that the effect regarding the definition of AF [$\chi 2(1) = 0.45$; $p = .50$] as well as the effect regarding the number of repetitions [$\chi 2(1) = 0.43$; $p = .51$] cannot be regarded as significant.

3.5 | Bias assessment

The funnel plot of all included trials is shown in Figure S1. The ORs of the individual studies scatter symmetrically around the mean effect. A substantial publication bias is rather unlikely. A risk of bias assessment was not applicable as there were no randomized controlled trials or non-randomized interventional studies included.

4 | DISCUSSION

In this systematic meta-analysis investigating the predictive value of inducibility of AF following PVI in 1544 patients, a significant correlation between electrophysiological inducibility of AF immediately following PVI and recurrence of AF during a mean follow-up period of 15 ± 9 months was found.

AF associates with adverse outcomes such as stroke, dementia, congestive heart failure, and impaired quality of life.[34] Bilateral electrical isolation of the PVs with circumferential lesion placement has become standard of care[35,36] and is recommended during all AF ablation procedures according to current guidelines.[3]The use of a 20-min monitoring period for PV reconnection following PVI (class IIA) and an entrance block into the PVs (class IB) have been suggested as markers for successful and complete electrical isolation. However, despite these attempts, AF recurrence following PVI is common.[37] Indeed, intraprocedural techniques for the assessment of PV reconnection did not improve long-term success of PVI.[38] So far, no reliable parameter predicting long-term freedom of AF following PVI has been identified. This meta-analysis showed a significantly increased risk for recurrence of AF following when AF was inducible immediately after PVI, regardless of the heterogeneity of included trials. The predictability of AF was even more pronounced in trials including patients with paroxysmal AF only. One may speculate that this is related to the fact that patients with persistent AF are at risk of more pronounced atrial fibrosis which itself represents a trigger for AF.[39] Moreover, the triggers for persistent AF are frequently located outside the PVs. In these clinical scenarios benefits of additional ablative procedures of non-PV focal triggers of AF, like specific ablation of complex fractionated atrial electrograms (CFAE) or adding empirical linear ablations after PVI, have been reported.[40] Persistent AF often presents clinically asymptomatic, which can challenge the identification of patients with AF recurrence.[41] Data supporting the use of the above-mentioned additional procedures are conflicting.[3,42] Herein, we only included patients after PVI without additional ablations in the left or right atrium.

According to the current Consensus Statement on Catheter Ablation of AF,[3] non-inducibility of AF is defined as a lack of induction with common stimulation approaches including high doses of isoproterenol. In the studies included herein, electrophysiological stimulation both with and without additional isoproterenol led to a statistically significant prediction of AF. The use of isoproterenol gave a distinct and homogenous information yet with a numerically lower predictive power for AF recurrences in comparison to no use of isoproterenol (OR 1.53, 95% CI 1.06 to 2.23 vs. 2.43, 95% CI 1.17 to 5.07). Thus, the bare electrophysiological stimulation in the absence of isoproterenol increased the prediction of future AF recurrences.

Isoproterenol provides limited information on dormant PV reconnections, yet leads to a prolonged procedure time.[3] On the other hand, intravenously administrated adenosine has been shown to offer a possible additional benefit for discrimination of dormant PV conduction following PVI.[43] As none of the included trials used adenosine, the utility of electrophysiological stimulation of AF in the context of adenosine remains elusive.

Our findings revealed a significantly higher predictive value when stimulating in the CS alone, rather than stimulating in both the CS as well as the HRA (OR 2.82, 95% CI 1.17 to 6.79 vs. 1.59, 95% CI 0.89 to 2.85, respectively). As the site of stimulation in the atrium has been shown to be equally effective for the induction of AF during

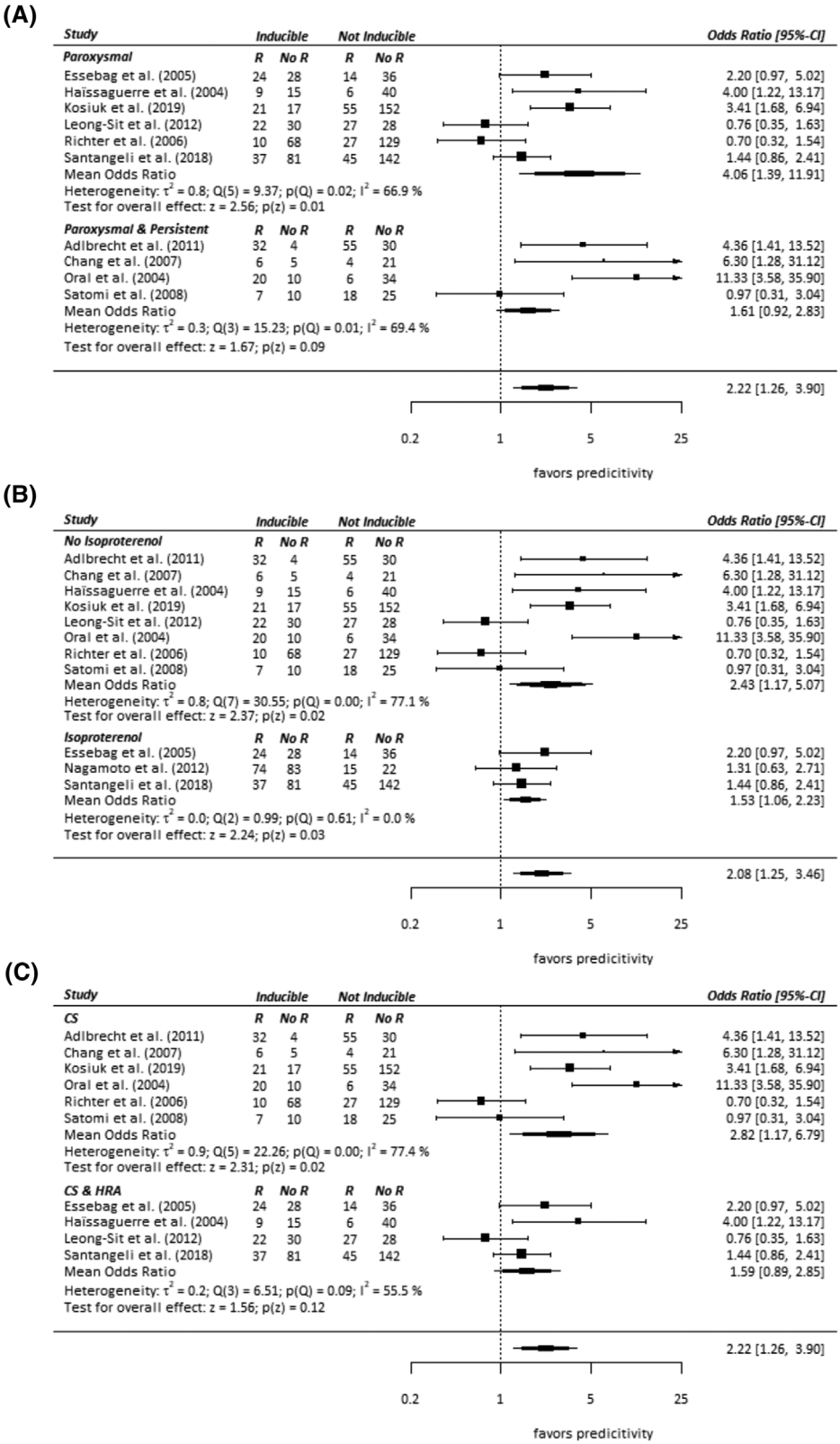

FIGURE 3 Forest plots of moderator analyses investigating the underlying type of AF (A), the use of additional isoproterenol for AF induction (B) and the stimulation site (C). R, recurrence; No R, no recurrence; OR, odds ratio; τ^2, population variance; 95% CI, 95% confidence interval; I^2, I^2-statistic; Q(df), Q-value with degrees of freedom; p(Q), significance of the Q-value

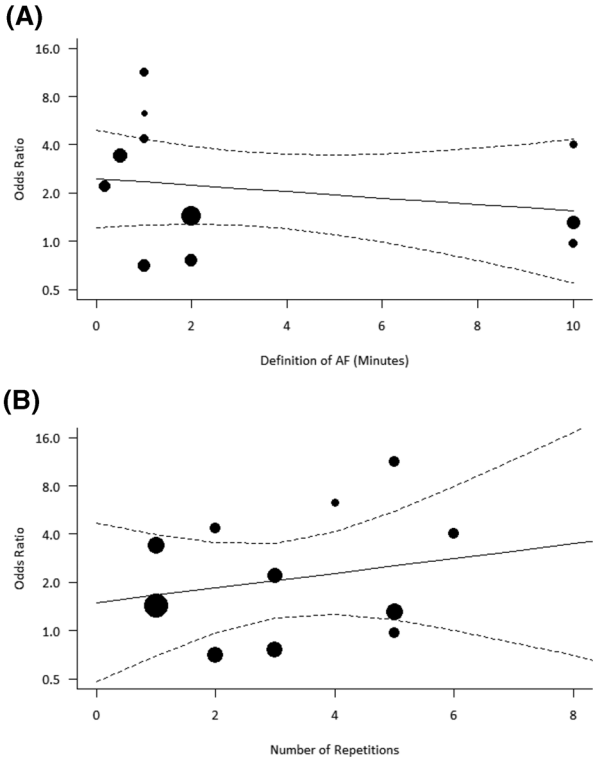

FIGURE 4 Random-effects regression concerning definition of AF during electrophysiological induction of AF (A, $p = .68$) and stimulation repetitions following PVI (B, $p = .29$). AF, atrial fibrillation; PVI, pulmonary vein isolation

electrophysiological studies,[44] our data suggest that stimulation in more than location may not increase predictive power of induced of AF for AF recurrences. Stimulation of both HRA and CS decreases predictivity, yet extending the duration of the stimulation process.

Another factor was the required duration of AF during the electrophysiological induction of AF, defined by the investigators. According to previous consensus statements, a cut off time of 30 sec has been defined as clinically relevant AF.[45] However, the analyzed trials used various definitions of AF during stimulation. Our results show a slight trend for higher ORs when the AF definition is rather short (Figure 4A). Nevertheless, this trend cannot be regarded as significant. Even though this 30-s threshold is discussed controversially in regards to its clinical consequences,[46] it remains the most commonly used definition of AF.[36] Likewise, the number of repetitions of electrophysiological stimulations showed a slight tendency for higher ORs in studies with more repetitions that cannot be regarded as significant (Figure 4B).

4.1 | Limitations

There are some limitations to this meta-analysis. First of all, different pacing protocols with diverging definitions of AF in some trials poses a potential bias. Using moderator analyses, we addressed these important factors, showing an impact of stimulation duration on sensitivity. Furthermore, even though follow-up was conducted exceeding standard of care with often trans-telephonic monitoring, especially asymptomatic AF recurrences may have been missed due to varying arrhythmia monitoring. Patient populations were surprisingly akin according to age, sex, LA diameter and LVEF; however, type of AF (paroxysmal vs. persistent) was differing, due to individual inclusion criteria. There was no exhaustive information on the use of general anesthesia during the procedure or the use of anti-arrhythmic drugs before and after the ablations.

5 | CONCLUSION

In conclusion, this meta-analysis underlines the importance of electrophysiological induction of AF following PVI to evaluate the risk of AF recurrence over time. Patient selection is essential, with favorable predictive results in patients with paroxysmal AF. According to the present data, predictivity of future AF recurrence is increased by no use of isoproterenol during the electrophysiological stimulation and decreased by multiple locations for stimulation in the atrium. Future trials are warranted to investigate how to proceed with patients following the induction of AF after successful PVI, in order to reduce the risk of AF recurrences.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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