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Uninterrupted direct oral anticoagulants vs. uninterrupted vitamin K antagonists during catheter ablation of non-valvular atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials

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Aims To assess the incremental benefit of uninterrupted direct oral anticoagulants (DOACs) vs. uninterrupted vitamin K antagonists (VKA) for catheter ablation (CA) of non-valvular atrial fibrillation (NVAF) on three primary outcomes: major bleeding, thrombo-embolic events, and minor bleeding. A secondary outcome was post-procedural silent cerebral infarction (SCI) as detected by brain magnetic resonance imaging.

Methods and results A systematic review of Medline, Cochrane, and Embase was done to find all randomized controlled trials (RCTs) in which uninterrupted DOACs were compared against uninterrupted VKA for CA of NVAF. A fixed-effect model was used, with the exception of the analysis regarding major bleeding events ($I^2 > 25$), for which a random effects model was used. The benefit of uninterrupted DOACs over VKA was analysed from four RCTs that enrolled a total of 1716 patients (male: 71.2%) with NVAF. Of these, 1100 patients (64.1%) had paroxysmal atrial fibrillation. No significant benefit was seen in major bleeding events [risk ratio (RR) 0.54, 95% confidence interval (95% CI) 0.29–1.00; $P = 0.05$]. No significant differences were found in minor bleeding events (RR 1.11, 95% CI 0.82–1.52; $P = 0.50$), thrombo-embolic events (RR 0.74, 95% CI 0.26–2.11; $P = 0.57$), or post-procedural SCI (RR 1.06, 95% CI 0.74–1.53; $P = 0.74$).

Conclusion An uninterrupted DOACs strategy for CA of NVAF appears to be as safe as uninterrupted VKA without a significantly increased risk of minor or major bleeding events. There was a trend favouring DOACs in terms of major bleeding. Given their ease of use, fewer drug interactions and a similar security and effectiveness profile, DOACs should be considered first line therapy in patients undergoing CA for NVAF.

Keyword Atrial fibrillation • Direct oral anticoagulants • Vitamin K antagonists • Warfarin • Catheter ablation • Randomized controlled trials • Meta-analysis

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What's new?

- According to our findings, there are no significant differences between uninterrupted direct oral anticoagulants (DOACs) and uninterrupted vitamin K antagonists (VKA) for catheter ablation (CA) of non-valvular atrial fibrillation (NVAF) for the studied outcomes (major bleeding, minor bleeding, thrombo-embolic events, and silent cerebral infarction).
- There was a trend for fewer major bleeding events in the DOAC group when compared to VKA.
- Given their ease of use, fewer drug interactions, the absence of need for international normalized ratio monitoring and a similar safety and effectiveness profile, DOACs should be considered first line therapy in patients undergoing CA for NVAF.

Introduction

Non-valvular atrial fibrillation (NVAF) is the most common sustained cardiac arrhythmia, with a significant impact on morbidity and mortality. Catheter ablation (CA) of atrial fibrillation (AF) is an effective therapeutic option in symptomatic, drug-refractory AF.[1] Catheter ablation is yet a challenging electrophysiology procedure, due to its technical difficulty and the associated complication risks. Due to manipulation of catheters and the creation of lesions in the left atrium (both of which are in turn associated with an increased risk of local thrombus formation), patients undergoing this procedure have a considerable risk of clinical stroke, transient ischaemic attack (TIA), or systemic embolism. The reported incidence for this complication can be as high as 7%.[2]

The COMPARE study established uninterrupted warfarin as the standard of care of patients undergoing CA of AF.[1] This randomized controlled trial (RCT) demonstrated that performing this procedure without interrupting oral anticoagulation with warfarin was associated with a decreased risk of stroke and minor bleeding complications, as long as the international normalized ratio (INR) was kept within the therapeutic range (2.0–3.0).[1]

After the introduction of direct oral anticoagulants (DOACs) several studies have tried to establish their non-inferiority to vitamin K antagonists (VKA) in CA of AF. Most have been observational, retrospective studies,[3,4] or prospective registry studies.[5,6] The VENTURE-AF was the first RCT comparing uninterrupted DOAC (rivaroxaban) to uninterrupted VKA.[7] After this study, several others followed suit.[8–12] Based on these studies, the Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) published their updated expert consensus statement regarding catheter and surgical ablation of AF in 2017.[13] Following these recommendations, the current standard of care involves the use of uninterrupted VKAs (INR goal 2.0–3.0), uninterrupted dabigatran (Evidence Class IA), or uninterrupted rivaroxaban (Class I-BR).

Nonetheless, results from these studies are limited by a small sample size, as thousands of patients in each study arm would have been required for a formal non-inferiority analysis with an acceptable confidence interval. Consequently, a descriptive comparison approach was followed, allocating just enough patients in each arm to generate clinically relevant information.[7,9] Only the AXAFA trial[14] was specifically designed to sustain a formal non-inferiority analysis by conducting the study exclusively in patients with at least one risk factor for stroke. As such, evidence supporting the use of uninterrupted DOACs in patients undergoing CA for AF is scant.

In this meta-analysis, our goal was to determine the existence of any statistically significant difference between uninterrupted DOACs and uninterrupted VKA for CA of NVAF. We assessed three primary outcomes (major bleeding events, minor bleeding events, and thrombo-embolic events) and one secondary outcome [silent cerebral infarction (SCI) as evidenced by post-procedural brain magnetic resonance imaging (MRI)].

Methods

The present meta-analysis was performed according to Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[15] This meta-analysis was registered in PROSPERO with registration number CRD42018089183.

Search strategy

We searched PubMed, Embase, and Cochrane Central Register of Clinical Trials (Cochrane Library, Issue 02, 2017) databases from January 2008 through February 2018 to identify RCTs comparing uninterrupted DOACs vs. uninterrupted VKA for CA of NVAF.

We used the following terms: ('direct oral anticoagulants' OR DOAC OR dabigatran OR rivaroxaban OR apixaban) AND (warfarin OR 'vitamin K antagonists' OR VKA) AND ('auricular fibrillation' OR 'atrial fibrillation') AND (ablation OR 'catheter ablation'). No language restriction was applied. The reference lists of identified articles were also reviewed for additional sources.

Eligibility criteria

Studies with the following characteristics were considered eligible: (1) RCTs comparing uninterrupted DOACs vs. uninterrupted VKA for CA of NVAF; (2) compared the clinical outcomes of major bleeding and/or minor bleeding and/or thrombo-embolic events or compared the rates of SCI by brain MRI between the uninterrupted DOACs and the uninterrupted VKA group.

Case reports, editorials, reviews, and expert opinions were excluded from our analysis. Abstracts presented in major international conferences that haven't been published as full papers were not considered in our analysis.

Primary and secondary outcomes

The primary outcomes of this study were (1) major bleeding events, (2) thrombo-embolic events, and (3) minor bleeding events. The secondary outcome was SCI as detected by post-procedural brain MRI.

Major bleeding events were defined by using the Bleeding Academic Research Consortium (BARC) criteria, with a score BARC ≥2 being considered major bleeding.[16] Studies using the ISTH (RECIRCUIT, VENTURE-AF, Kuwahara *et al.*[8]), or the GUSTO and TIMI (VENTURE-AF) classifications for bleeding each provided a full list of bleeding events. Using these lists, bleeding events were reclassified using the BARC criteria and classified as major bleeding events if BARC ≥ 2. For additional information, please see Supplementary Material.

Minor bleeding events were all reported bleeding events not fulfilling this criterion. Thrombo-embolic events were defined as stroke, TIA, systemic embolism, or development of an intracardiac thrombus

post-procedure. Finally, SCI was defined as clinically silent new brain lesions detected by brain MRI post-procedurally.

Data extractions and quality appraisal

Three investigators (J.R., R.C.R, and J.C.D.) independently screened all titles, abstracts, and manually searched the full-text versions of all relevant studies that fulfilled the inclusion criteria. References of the retrieved articles were independently reviewed for further identification of potentially relevant studies. Disagreements were resolved by consensus after discussion (J.R. and R.C.R.). We extracted characteristics of each study including methodology and baseline patient characteristics, major bleeding events, minor bleeding events and thrombo-embolic events. Silent cerebral infarction events were also extracted from the relevant studies. If the abovementioned information was not readily available in the written article, the principal investigator of that particular study was contacted to supply pertinent information.

Quality assessment

The quality and reporting of the included RCTs were assessed using the Cochrane Risk of Bias Tool. Six categories were included in the analysis: (i) selection bias: systematic differences between baseline characteristics of the groups that are compared; (ii) performance bias: systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest. After enrolment into the study, blinding of participants and staff may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcomes. Blinding is not always possible, as was the case of the RCTs included in our study, as it would've been unethical to not monitor INR in those patients randomized to the VKA arm; (iii) detection bias: systematic differences between groups in how outcomes are determined. Blinding of outcome assessors may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcome measurement; (iv) attrition bias: systematic differences

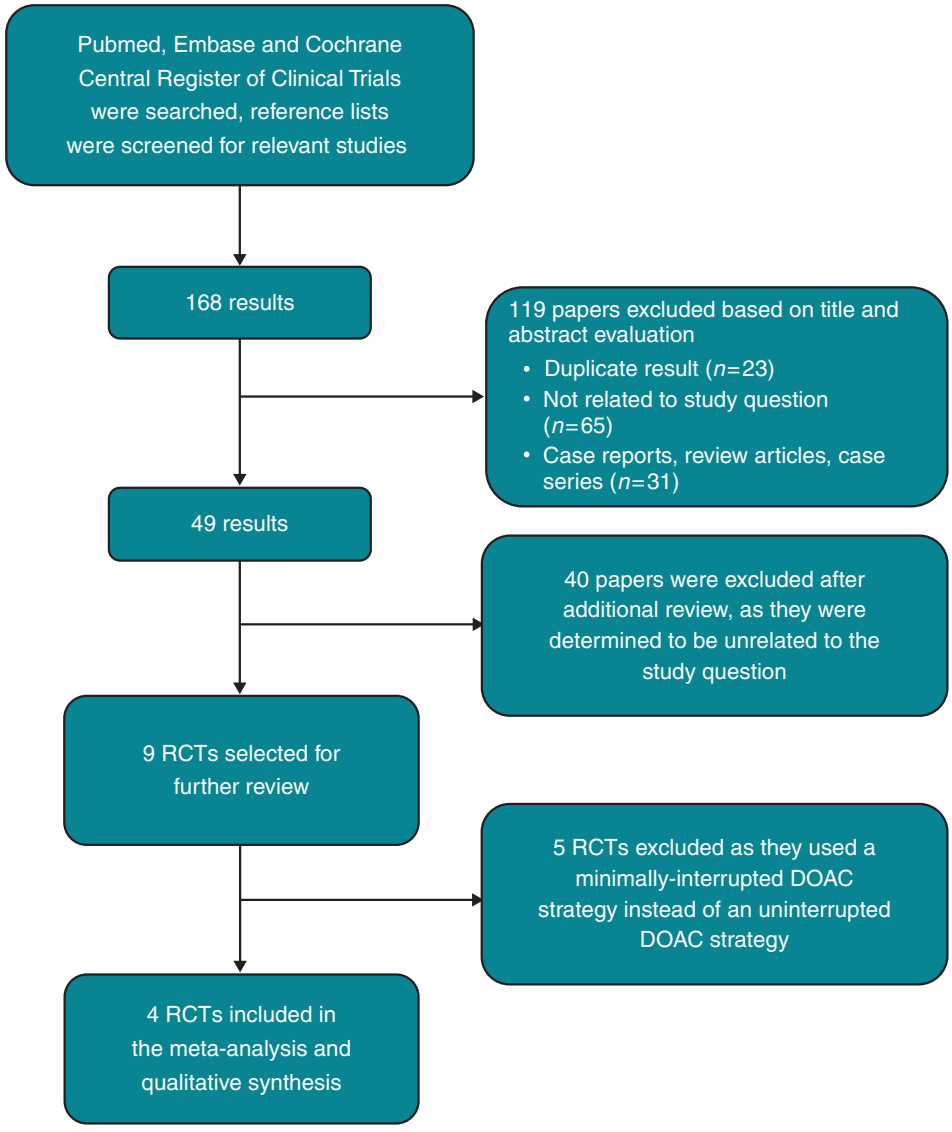

Figure 1 Study selection. DOAC, direct oral anticoagulants; RCT, randomized controlled trials.

between groups in withdrawals from a study. Withdrawals from the study lead to incomplete outcome data; (v) reporting bias: systematic differences between reported and unreported findings; (vi) other biases: other sources of bias that are relevant only in certain circumstances.[17] Quality of the included RCTs was summarized visually.

Statistical analysis

Descriptive statistics are presented as number of cases (*n*) for dichotomous and categorical variables. Statistical analysis was performed in line with recommendations from the Cochrane Collaboration and 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).[18] Data were summarized across groups using the Mantel-Haenszel Risk Ratio (RR) Fixed-Effect model if $I^2 < 25$.[19] We considered I^2 less than 25% as low and I^2 greater than 75% as high. The random effects model was used if $I^2 > 25\%$.[19] Publication bias was estimated visually by funnel plots.[19,20]

Results

A total of 168 studies were identified using the specified search criteria (*Figure 1*). After evaluation of these studies based on titles and abstracts, nine RCTs were further analysed in their full-text version, five of which were discarded leaving four RCTs that fulfilled all inclusion criteria. These four RCTs incorporated a total of 1716 participants (71.2% male, average age 61.9 ± 3.0 years). Other RCTs were excluded due to a lack of information relevant to our study questions or because they did not follow an uninterrupted DOAC strategy, using instead a minimally interrupted DOAC strategy.[2] The summary of the primary and secondary outcomes can be found in *Figure 2*.

Characteristics of included studies

The baseline characteristics of the included trials are summarized in *Table 1*. Uninterrupted dabigatran was used in 317 patients (18.5%),[9] rivaroxaban in 123 (7.2%),[7] and apixaban in 418 (24.3%).[8,14] The rest (858 participants, 50.0%) received uninterrupted VKA. The duration of oral anticoagulation before CA was approximately 4 weeks in

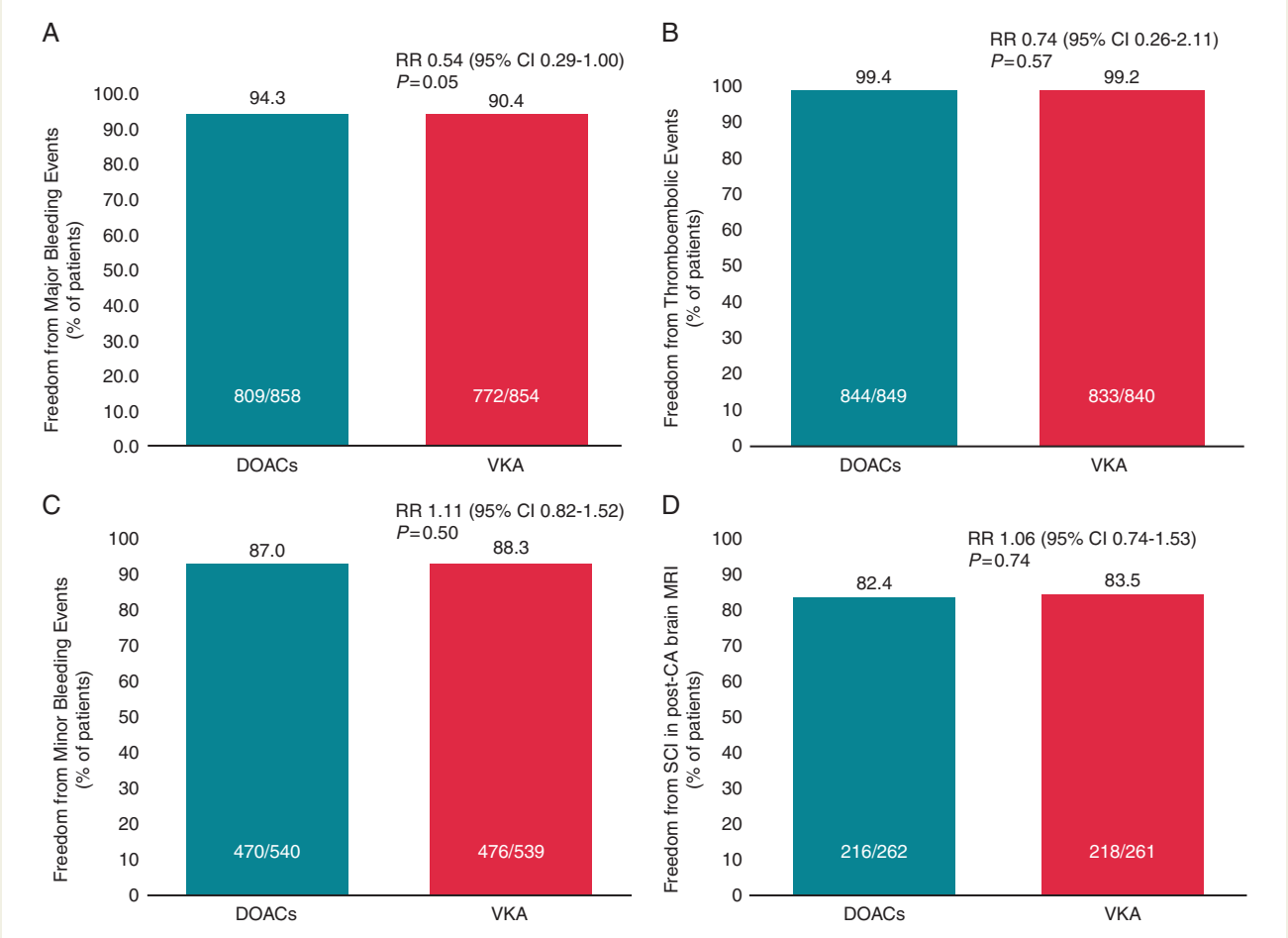

Figure 2 Study outcomes. (*A*) Freedom from major bleeding events, (*B*) freedom from thrombo-embolic events, (*C*) freedom from minor bleeding events, (*D*) freedom from SCI in post-catheter ablation brain MRI. The included RR, CI, and *P*-value refer to the values of (*A*), major bleeding events (*B*), thrombo-embolic events (*C*), minor bleeding events (*D*). 95% CI, 95% confidence interval; CA, catheter ablation; DOACs, direct oral anticoagulants; MRI, magnetic resonance imaging; RR, risk ratio; SCI, silent cerebral infarction; VKA, vitamin K antagonists.

Table 1 Baseline characteristics of included RCTs

Study	Type of study	*n*	Male	Mean age	Age 65–74	Age ≥75	Paroxysmal AF	Persistent AF	Long-standing persistent AF	DOAC used in the study	Mean CHA_2DS_2-VASc score	CHF	HTN	Diabetes mellitus	Prior stroke/TIA/embolism	Vascular disease (CAD, MI, PAD, carotid disease)	Mean BMI	Prior catheter ablation	Anti-platelet agent/NSAIDs	Brain MRI
AXAFA	RCT	633	424	63.4	240	56	367	NP	NP	Apixaban	2.4	212	571	76	47	83	29	0	30	335
Kuwahara *et al.*[8]	RCT	200	147	65.5	NP	NP	119	NP	NP	Apixaban	2.2	NP	NP	NP	NP	NP	NP	NP	NP	200
RECIRCUIT	RCT	635	475	59.2	NP	NP	432	167	36	Dabigatran	2.1	65	343	64	19	105	28.7	NP	144	NA
VENTURE-AF	RCT	248	176	59.6	75	15	182	NP	NP	Rivaroxaban	1.6	21	116	22	3	47	29.4	22	66	NA

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHA_2DS_2-VASc score, age 65–74 years (+1) or ≥75 (+2), female (+1), congestive heart failure history (+1), hypertension history (+1), stroke/transient ischaemic attack/thromboembolism history (+2), vascular disease history (+1); CHF, congestive heart failure; DOAC, direct oral anticoagulant; HTN, hypertension; MI, myocardial infarction; MRI, magnetic resonance imaging; NA, not applicable; NP, not provided; NSAIDs, non-steroidal anti-inflammatory drugs; PAD, peripheral artery disease; RCT, randomized controlled trials; TIA, transient ischaemic attack.

most studies. The target INR for patients receiving VKA was between 2.0 and 3.0.

Quality assessment and publication bias

Funnel plots did not suggest publication bias for the selected outcomes of major bleeding events, minor bleeding events, thrombo-embolic events, and SCI (*Figure 3*). All the RCTs included in this meta-analysis had good methodological quality indicating 'low risk of bias' (*Figures 4* and *5*).

Impact on major bleeding events

Although a trend towards fewer major bleeding events (as defined by a BARC ≥ 2) was found in patients assigned to uninterrupted DOAC group (5.7%) as compared to the uninterrupted VKA group (9.6%), this did not reach statistical significance [RR 0.54, 95% confidence interval (95% CI) 0.29–1.00; $P = 0.05$] (*Figures 2* and *6*).

Impact on thrombo-embolic events

There were no significant differences between groups regarding thrombo-embolic events. The stroke rates in the DOAC and VKA groups were 0.6% and 0.8%, respectively (RR 0.74, 95% CI 0.26–2.11; $P = 0.57$) (*Figures 2* and *6*).

Impact on minor bleeding events

The minor bleeding rates in the DOAC and VKA groups were 13% and 11.7%, respectively. There were no significant differences between groups (RR 1.11, 95% CI 0.82–1.52; $P = 0.50$) (*Figures 2* and *6*).

Impact on silent cerebral infarction

Two out of the four included RCTs included a component to assess for post-CA SCI using brain MRI. In our analysis, we could not find any statistically significant difference between the uninterrupted DOAC group and the uninterrupted VKA group regarding SCI as detected by brain MRI (RR 1.06, 95% CI 0.74–1.53; $P = 0.74$) (*Figures 2* and *6*).

Discussion

Catheter ablation of NVAF is an important rhythm control strategy for improvement of quality of life in patients with drug-refractory AF. Even though this procedure carries the risk of embolization, an uninterrupted VKA strategy has shown to decrease this risk to <1% with no associated increase in the rate of bleeding complications. These benefits were demonstrated in a well-designed, large clinical trial which randomized 1584 patients to either uninterrupted VKA during CA for NVAF vs. the common practice of bridging patients with heparin in and out of a therapeutic INR for the procedure.[1]

In spite of having been in the market for years now, the use of uninterrupted DOACs during CA of AF has been limited. Several factors have contributed to this situation. First, the concern of having no readily available reversal agent in case a life-threatening bleeding (such as a pericardial tamponade) occurs. But also, the fact that RCTs that support this method have had only small sample sizes. Previously published small RCTs demonstrated a favourable safety and efficacy profile of uninterrupted DOACs during CA of AF,[3,4] and published meta-analysis looking at observational data in over 7900 patients

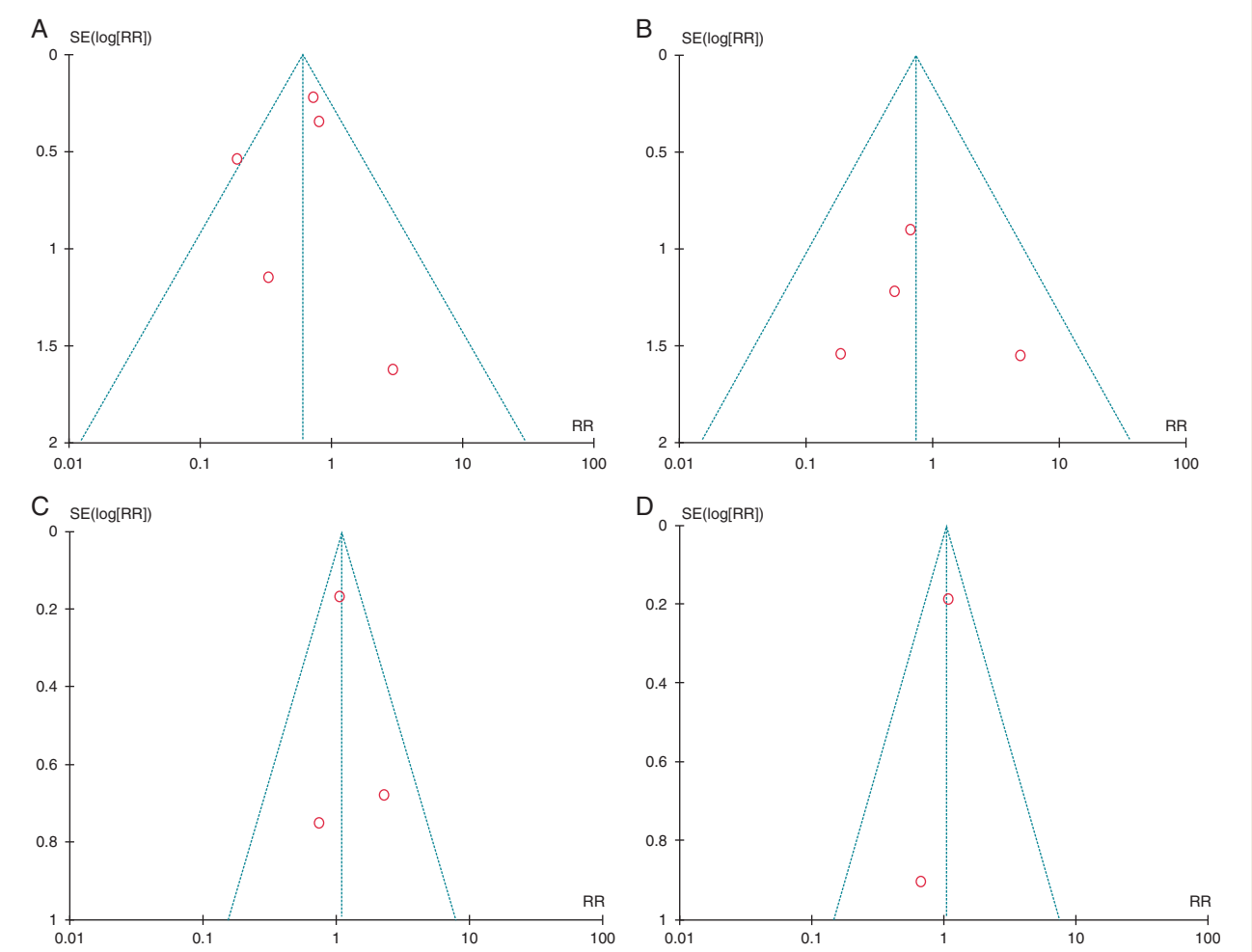

Figure 3 Funnel plots for publication bias—(*A*) major bleeding events, (*B*) thrombo-embolic events, (*C*) minor bleeding events, (*D*) silent cerebral infarction as demonstrated by post-catheter ablation brain MRI. MRI, magnetic resonance imaging; RR, risk ratio; SE, standard error.

comparing uninterrupted DOACs vs. uninterrupted warfarin showed no difference with respect to preventing thrombotic events and were in fact associated with a lower risk of bleeding.[21]

This is the first meta-analysis available using all published RCT data that compares the outcomes of uninterrupted DOACs vs. uninterrupted VKA on major bleeding events, minor bleeding events, thrombo-embolic events, and SCI. We included a total of 1716 participants undergoing CA of NVAF. The pertinent findings of this study were:

(1) Our results show that, overall, although uninterrupted DOACs demonstrated a trend towards fewer major bleeding events, this did not reach statistical significance over uninterrupted VKA.
(2) There were no statistically significant differences between groups in the outcomes of minor bleeding events and thrombo-embolic events.
(3) No significant difference was found between the uninterrupted DOACs and the uninterrupted VKA arm in the SCI outcome.

Catheter ablation of AF has been associated with post-operative cognitive dysfunction.[22] It has been speculated that SCI occurring during the procedure might be the cause of this adverse consequence; the reported incidence of SCI is between 2 and 14%.[8–10] Two out of the four RCTs included in our meta-analysis incorporated a brain MRI component to assess if there was any difference in the incidence of SCI when comparing uninterrupted DOACs and uninterrupted VKA. None of them found any significant difference between groups.

Given our findings, it is conceivable to offer patients who need to undergo CA of NVAF uninterrupted anticoagulation with a DOAC. These conclusions fall in line with the recent consensus statement on the use of uninterrupted DOACs for CA of NVAF which gave a Class I recommendation for the use of uninterrupted dabigatran or rivaroxaban. Direct oral anticoagulants are more convenient for both the patient and the physician, as they have fewer interactions with medications and food than VKAs. They also have the additional advantage of offering a fixed dose and not requiring constant monitoring of the INR, which can adversely impact the quality of life of these patients. A strategy of uninterrupted dabigatran also has the benefit of the availability of idarucizumab, a dabigatran-specific reversal agent. Moreover, in case of major bleeding during the procedure,

prothrombin complex concentrate (Kcentra®) can reverse the effect of DOACs.

The results of our meta-analysis prove that there is no significant difference in the risk of major bleeding between patients receiving uninterrupted DOACs and patients receiving uninterrupted VKA. Furthermore, though our results did not reach statistical significance (*P*-value equal to 0.05), a clear trend towards a reduction in major bleeding events associated with uninterrupted DOAC use was observed in our study when compared to VKA (i.e. 5.7% vs. 9.6%). Failure to reach statistical significance could be explained by a small sample size, and a larger RCT could help define whether or not DOACs are associated with a reduced risk of major bleeding.

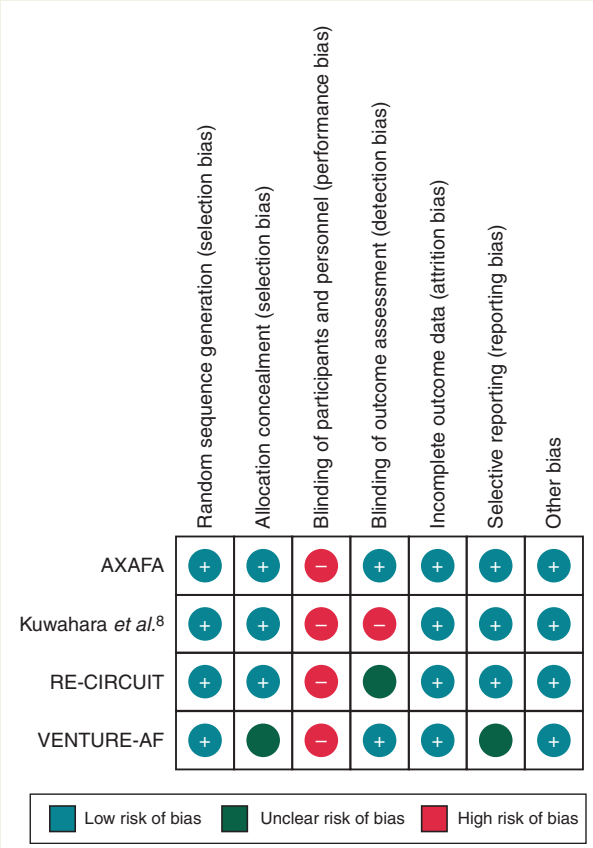

Figure 4 Risk of bias summary.

Limitations

Our meta-analysis has some limitations; in particular, there is the fact that the majority of the RCTs included in our meta-analysis were conducted as exploratory trials with administratively determined trial sizes, because the sample required to provide sufficient power to establish formal non-inferiority would have made them unfeasible. Only one of the included studies, AXAFA,[14] was designed to accumulate sufficient events for a formal non-inferiority analysis by selecting the study population from patients with at least one risk factor for stroke. We hope the results of our study will generate interest in the design of larger, well-designed RCT. Second, the number of patients assessed for SCI might not have been enough to determine if there was a real difference between the uninterrupted DOACs and the uninterrupted VKA group. Third, some studies did not include information regarding minor bleeding events and as such no clear difference could be found. Finally, we believe that the main limitation of our analysis lies on the low number of events.

Conclusions

An uninterrupted DOACs strategy for CA of NVAF appears to be as safe as uninterrupted VKA without significantly increased risk of minor or major bleeding events. There was a trend favouring DOACs in terms of major bleeding. Direct oral anticoagulants should be

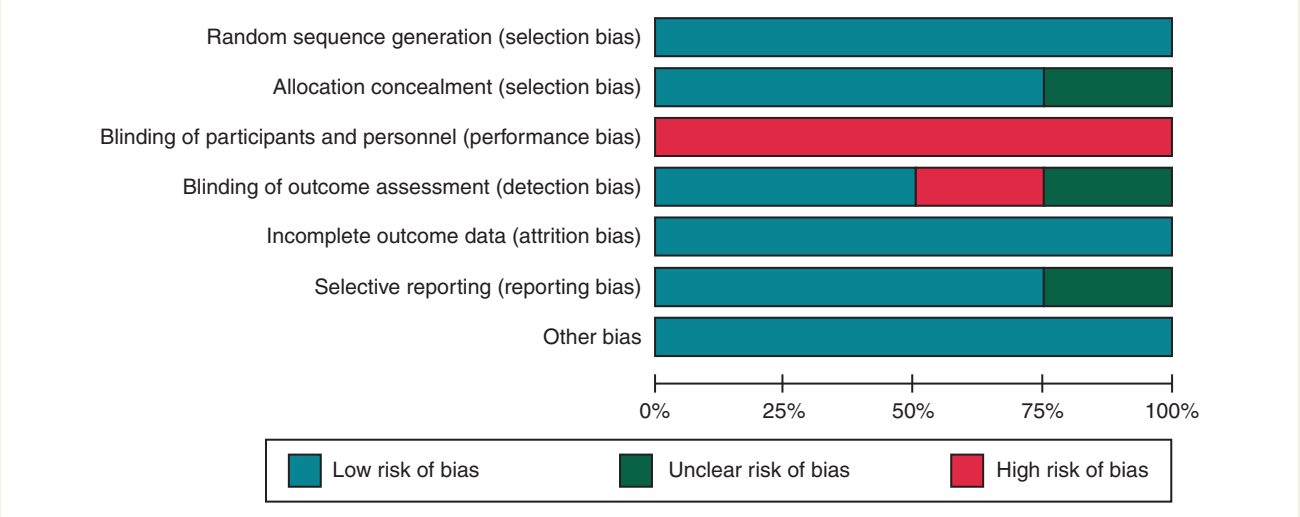

Figure 5 Risk of bias graph. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

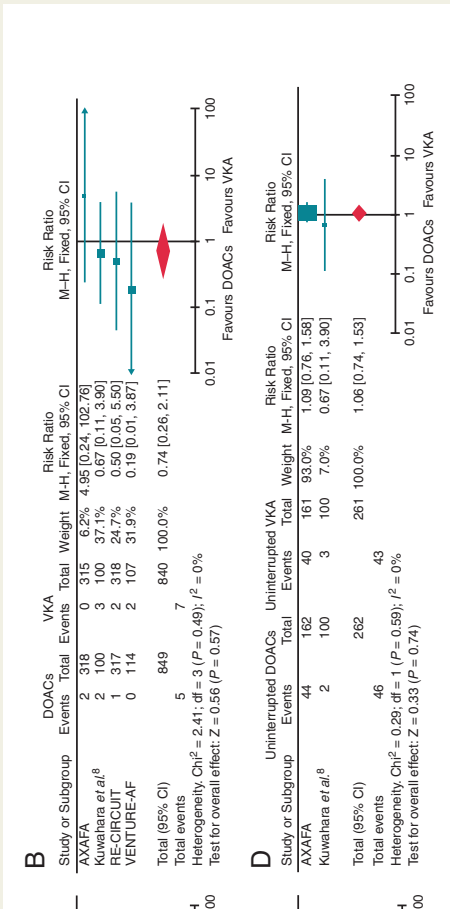

Figure 6 Forest plots of study outcomes. (*A*) Major bleeding events, (*B*) thrombo-embolic events, (*C*) minor bleeding events, and (*D*) SCI in post-CA brain MRI. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI); width of the shaded square, size of the population. Random effects model was used in the major bleeding events outcome as $I^2 > 25$, the fixed effect model was used in all other outcomes. CA, catheter ablation; CI, confidence interval; DOAC, direct oral anticoagulants; MH, Mantel–Haenszel; MRI, magnetic resonance imaging; SCI, silent cerebral infarction; VKA, vitamin K antagonists.

considered as first-line agents over VKA in patients undergoing CA of NVAF, due to their ease of use and a lower number of interactions.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: L.D.B. is a consultant for Biosense Webster and Stereotaxis and received speaker honoraria/travel from Medtronic, Pfizer, Boston Scientific, Abbott, and Biotronik. All remaining authors declared no conflicts of interest.

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Atrial decremental evoked potentials accurately determine the critical isthmus of intra-atrial re-entrant tachycardia

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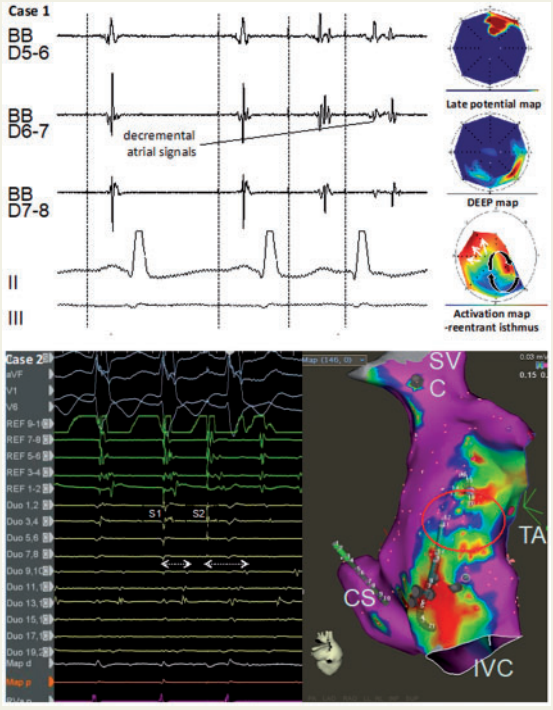
We have shown before, the utility of DEEP mapping in identifying critical isthmus of scar VT. We hypothesized that, as intra-atrial re-entrant tachycardia (IART) substrate is similar to scar VT by virtue of surgical scars, DEEP mapping could be useful in identifying critical targets for ablation. Two patients with corrected transposition of great arteries (cc TGA) and previous cardiac surgery were selected for the study. Both had recurrent symptomatic IART prompting multiple hospital visits. A decapolar coronary sinus catheter was used for both patients. For the first patient a 64-electrode basket array and for the second patient a duo-decapolar catheter was used for mapping. The late potentials and decremental local potentials were annotated on the electro-anatomical map (CARTO, Biosense Webster, Israel). In sinus rhythm, a pacing train was applied from the CS proximal electrode, and extra stimulus was introduced. The site with maximum local electrogram decrement was considered the critical isthmus and was ablated. The arrhythmia was non-inducible after ablation at this DEEP site for both patients. DEEP mapping was useful in localizing the critical ablation target in IART.



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