Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants Compared With Uninterrupted Vitamin K Antagonists in Patients Undergoing Catheter Ablation for Atrial Fibrillation

Shuang Wu, MD, Yan-min Yang, PhD*, Jun Zhu, MD, Huai-bin Wan, MD, Juan Wang, PhD, Han Zhang, PhD, and Xing-hui Shao, PhD

Anticoagulation in catheter ablation (CA) of atrial fibrillation (AF) is of paramount importance for prevention of thromboembolic events, and recent studies favor uninterrupted vitamin K antagonists (VKAs). We aimed to compare the efficacy and safety of new oral anticoagulants (NOACs) to uninterrupted VKAs for anticoagulation in CA by performing a meta-analysis. PubMed, EMBASE, the Cochrane Library, and Clinicaltrials.gov databases were searched for studies comparing NOACs with uninterrupted VKAs in patients who underwent CA for AF from January 1, 2000, to August 31, 2015. Odds ratio (OR) and Peto's OR (POR) were used to report for event rates >1% and <1%, respectively. A total of 11,686 patients with AF who underwent CA in 25 studies were included in this analysis. There was no significant difference between NOACs and uninterrupted VKAs in occurrence of stroke or transient ischemic attacks (POR 1.35, 95% CI 0.62 to 2.94) and major bleeding (POR 0.87, 95% CI 0.58 to 1.31), which were consistent in subgroup analysis of interrupted and uninterrupted NOACs. A lower risk of minor bleeding was observed with NOACs (OR 0.80, 95% CI 0.65 to 1.00), and no major differences were observed for the risk of thromboembolic events, cardiac tamponade or pericardial effusion requiring drainage, and groin hematoma. NOACs, whether interrupted preprocedure or not, were associated with equal rates of stroke or TIA and major bleeding complications and less risk of minor bleeding compared with uninterrupted VKAs in CA for AF. **(Am J Cardiol 2016;■:■−■)**

Catheter ablation (CA) is a well-established rhythm-control strategy for patients with drug-refractory, symptomatic atrial fibrillation (AF); however, there is substantial risk of thromboembolic (TE) events perioperatively.[1] Rigorous anticoagulation is of paramount importance to prevent these deadly complications, whereas optimal anticoagulant strategy in the setting has not reached a consensus. Recent studies favored uninterrupted vitamin K antagonist (VKAs) therapy because of significantly less risk of TE events and bleeding complications observed with this strategy compared with interrupted VKAs.[2] With the advent of new oral anticoagulants (NOACs), increasing numbers of patients with AF are on NOACs at the time a decision to proceed with CA is made. However, it is not clear whether NOACs still hold the same efficacy and safety compared with uninterrupted VKAs in ablation procedure; therefore, we aimed to systematically evaluate all available evidence in the setting in this study.

Methods

PubMed, EMBASE, the Cochrane Library, and Clinicaltrials.gov databases were searched to identify published reports comparing NOACs to uninterrupted VKAs in patients who underwent CA for AF from January 1, 2000, to August 31, 2015. The main key words we used were "atrial fibrillation," "catheter ablation," "anticoagulants," "warfarin," "dabigatran," "rivaroxaban," "apixaban," "factor Xa inhibitor," and "factor IIa inhibitor" (refer to Supplementary File 1 for details of search strategy). The report published in English language was restricted in our search. Besides, we also manually searched reviews, meta-analyses and reference lists of all retrieved reports for additional eligible studies not found in our initial electronic database search.

Two reviewers (SW and HBW) screened and identified studies that fit the following inclusion criteria: (1) studies published in English language, (2) either full-length report or conference abstract, (3) comparing NOACs with VKAs in patients with AF presenting for CA, (4) VKAs or warfarin were continuously used through the whole procedure, (5) reporting outcomes of interest: stroke, transient ischemic attack (TIA), major bleeding, TE events, minor bleeding, cardiac tamponade or pericardial effusion requiring

Emergency and Intensive Care Center, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China. Manuscript received October 5, 2015; revised manuscript received and accepted December 16, 2015.

See page 8 for disclosure information.

*Corresponding author: Tel: (+86) 10-8839-6294; fax: (+86) 10-8836-4591.

E-mail address: yangymfuwai@163.com (Y.-m. Yang).

0002-9149/16/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2015.12.027

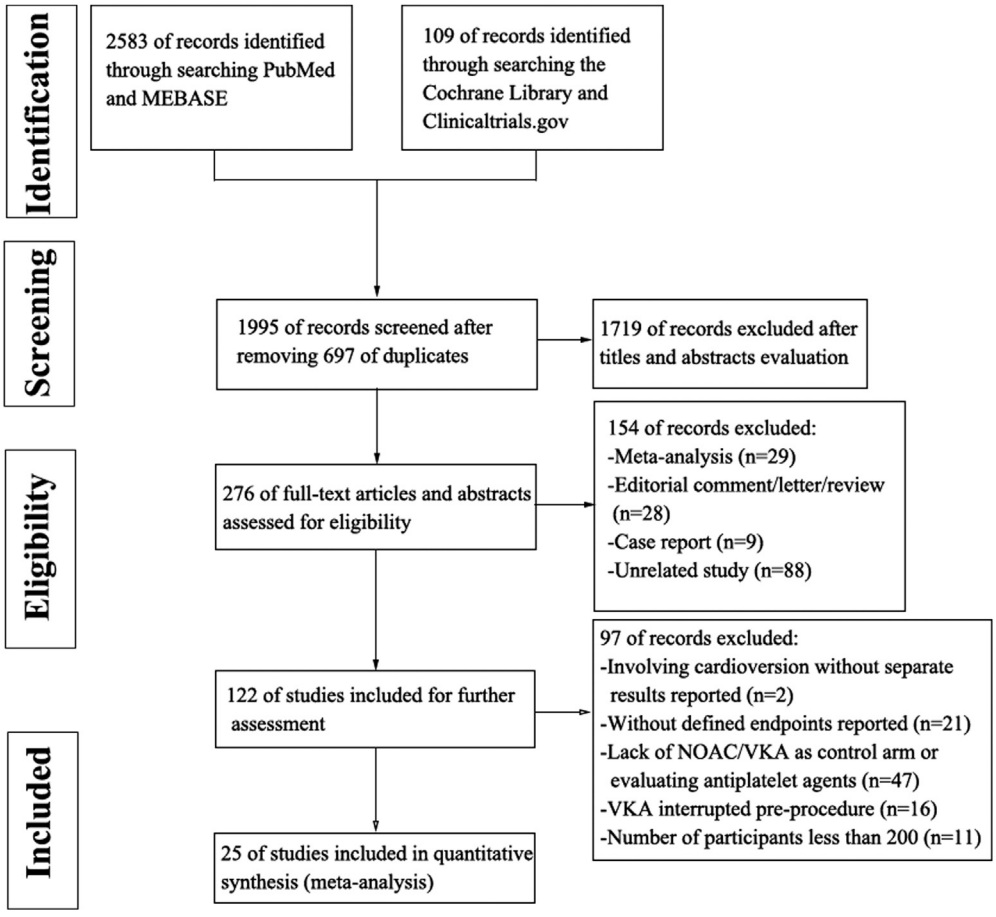

Figure 1. Flow diagram of study selection.

drainage, and groin hematoma, (6) number of participants in studies >200. The exclusion criteria were as follows: (1) studies included patients with AF both for cardioversion and ablation but without reporting respective outcomes, (2) a lack of using VKA/NOAC as comparator, (3) VKAs were interrupted and bridged with low molecular weight heparin, or unfractionated heparin during the procedure, (4) studies evaluating antiplatelet agents, (5) starting of anticoagulant treatment only after ablation, (6) evaluation of efficacy restricted to laboratory or imaging end points without reporting of desired clinical outcomes, and (7) number of participants in studies <200. We compared reports from the same investigator and excluded those identical records from the same trial or study to minimize data duplication as a result of multiple reporting. All eligible clinical trials, including case-control studies, cohort studies, and randomized controlled trials (RCTs) were formally reviewed.

Two reviewers (SW and HBW) evaluated the study quality using Newcastle-Ottawa Quality Assessment Scale for observational studies and Delphi consensus criteria for RCTs. Baseline characteristics and numbers of events were extracted from the eligible studies by 2 independent reviewers (SW and HBW) and checked by another (YMY). Any disagreement was resolved through discussion with additional investigator (YMY). We abstracted and tabulated details for each study on senior investigator, year of publication, publication type, design, details of the anticoagulant protocols, follow-up data, baseline characteristics of participants, and information related to clinical outcomes.

The primary efficacy outcome was stroke or TIA. The primary safety outcome was major bleeding. Secondary outcomes included TE events, minor bleeding, cardiac tamponade or pericardial effusion requiring drainage, and groin hematoma. Stroke was defined as sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery, whereas outcomes as positive imaging finding on magnetic resonance imaging or computed tomography without clinical symptoms were excluded for this analysis. TE events included ischemic stroke, TIA, pulmonary embolism, and systemic embolism such as deep vein thrombosis and peripheral arterial embolism. Major bleeding was defined as excessive bleeding requiring transfusion or intervention, cardiac tamponade or pericardial effusion requiring drainage, intracranial hemorrhage, hemothorax, retroperitoneal bleeding, massive hemoptysis, and bleeding extending hospital stay. Minor bleeding was defined as the occurrence of a hematoma or any bleeding that did not require transfusion or other particular interventions or prolong hospitalization. The longest available follow-up data from individual studies were selected into analysis.

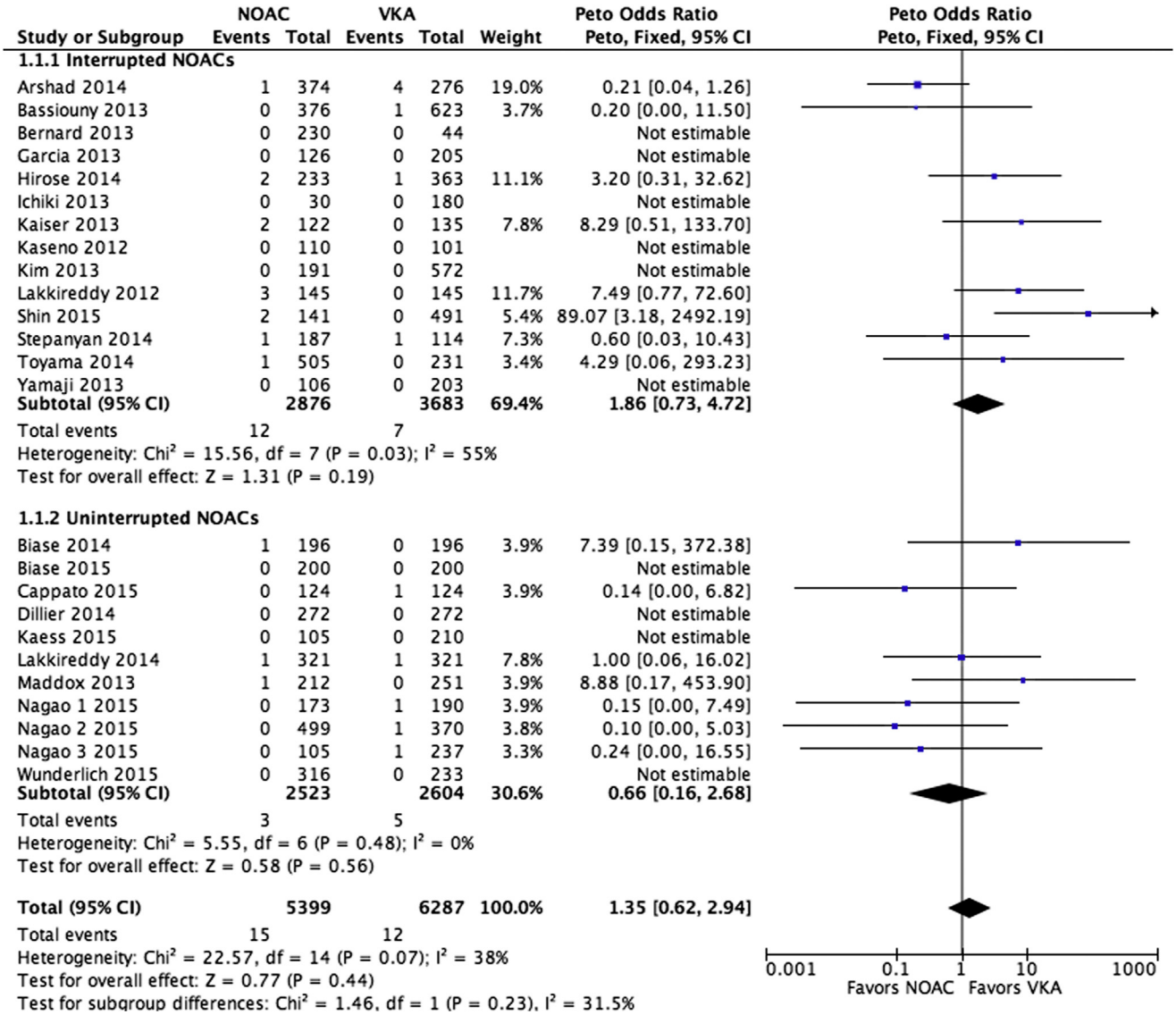

Figure 2. Primary efficacy outcome of stroke or TIA with periprocedural NOACs versus uninterrupted VKAs in patients with AF who underwent CA.

The statistical analysis was performed according to the recommendations from Cochrane Collaboration using Review Manager, version 5.3, for Mac (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark). Outcomes were reported as odds ratio (OR) and their respective 95% CIs. We calculated Peto's OR (POR) estimates and associated 95% CI using fixed effects models for event rates <1%. The Mantel–Haenszel method using fixed effects model and the DerSimonian–Laird method using random effects model were respectively used to combine results from individual studies for event rates >1%, depending on study heterogeneity. Subgroup analyses, according to different strategies of NOACs, that is, interrupted or not preprocedure, were also conducted for the primary outcomes. We used the Cochrane Q statistic and I^2 statistic to assess heterogeneity across studies. A p value <0.05 of Cochran Q statistic and I^2 statistic >50% were considered statistical significant to demonstrate heterogeneity for each outcome in this meta-analysis. Publication bias was assessed by visual inspection of the symmetry in Begg's funnel plot and Egger's linear regression test. All the p values were 2-tailed with statistical significance level at 0.05, and associated 95% CIs were also calculated.

Sensitivity analyses were performed by sequentially decreasing each individual study for the primary efficacy and safety outcomes. Further sensitivity analysis was carried out as follows: (1) full-text published studies, (2) studies with low/intermediate risk of bias, and (3) studies whose follow-up was at least 30 days. Stata, version 12.1, for Mac (StataCorp LP, College Station, Texas) was used for sensitivity analysis.

In addition, we used the trial sequential analysis (TSA) to calculate a diversity-adjusted required information size to avoid false positive and test for futility of this meta-analysis by establishing monitoring boundaries using O'Brien–Fleming method according to the required information size to detect or reject an intervention effect of a 150% increase in POR with control group event proportion (CEP) of 0.19% for stroke or TIA outcome, and

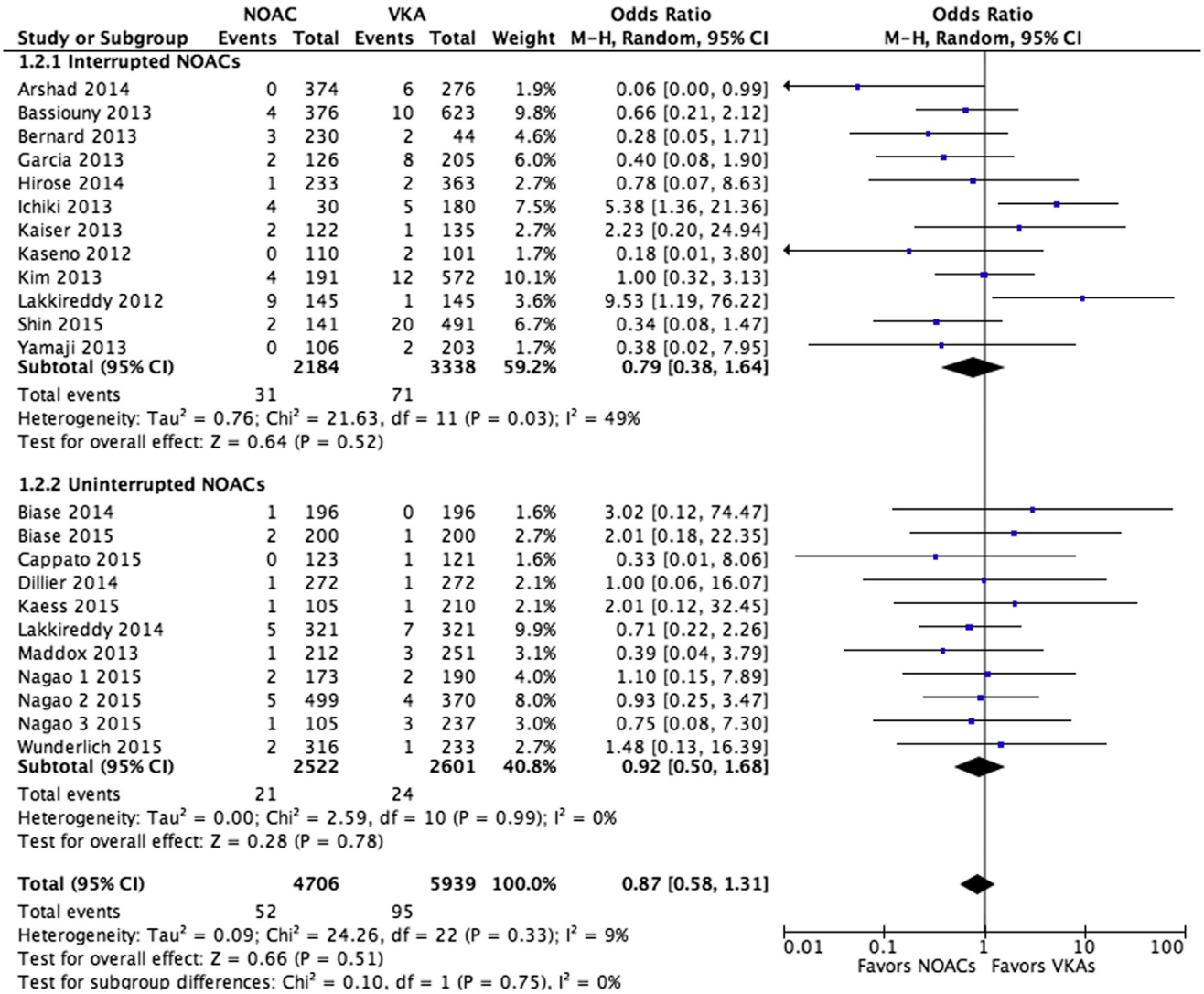

Figure 3. Primary safety outcome of major bleeding with periprocedural NOACs versus uninterrupted VKAs in patients with AF who underwent CA. M-H = Mantel-Haenszel.

intervention group event proportion of 1.6% and CEP of 1.1% for major bleeding outcome to challenge ORs estimated from conventional meta-analyses with a type II error of 20% (power of 80%). The TSA-adjusted 95% CIs were also calculated and provided. TSA, version 1.0, for Mac (Copenhagen Trial Unit, Center for Clinical intervention Research, Rigs Hospitalet, Copenhagen, Denmark) was used for TSA analyses.

Results

The flowchart of detailed search process was illustrated in Figure 1. From a total of 2,692 potentially relevant reports, 25 citations, involving 11,686 patients, fulfilled selection criteria and were finally included in this meta-analysis.[3–27] Of the identified studies, only one was RCT,[20] and the remaining were observational studies. Eighteen studies were published as full-text studies,[3–11,19–27] whereas the rest were conference abstracts.[12–18] Baseline data of selected studies, anticoagulation strategies periprocedure and clinical information of patients in the 2 groups were listed in Supplementary File 2. Difference in terms of overall design and outcome definitions existed in these studies. NOACs were continuously used during ablation in 11 studies,[17–27] whereas interrupted in 14 studies.[3–16] Unbalanced clinical characteristics of patients between the 2 groups presented in part of those studies with relevant information reported.[16,20] Particularly, 2 of 25 studies were considered as high risk of bias after quality assessment.[16,17]

Quantitative synthesis indicated that NOACs had comparable efficacy to uninterrupted VKAs in prevention of ischemic stroke or TIA in patients presenting with CA for AF (0.28% vs 0.19%; POR 1.35, 95% CI 0.62 to 2.94, $p = 0.44$; $I^2 = 38\%$; Figure 2). And the incidence of major bleeding was also well matched between the 2 groups (1.10% vs 1.60%; POR 0.87, 95% CI 0.58 to 1.31, $p = 0.51$; $I^2 = 9\%$; Figure 3). Subgroup analyses showed that both interrupted and uninterrupted NOAC agents had similar efficacy and safety as VKAs as anticoagulant

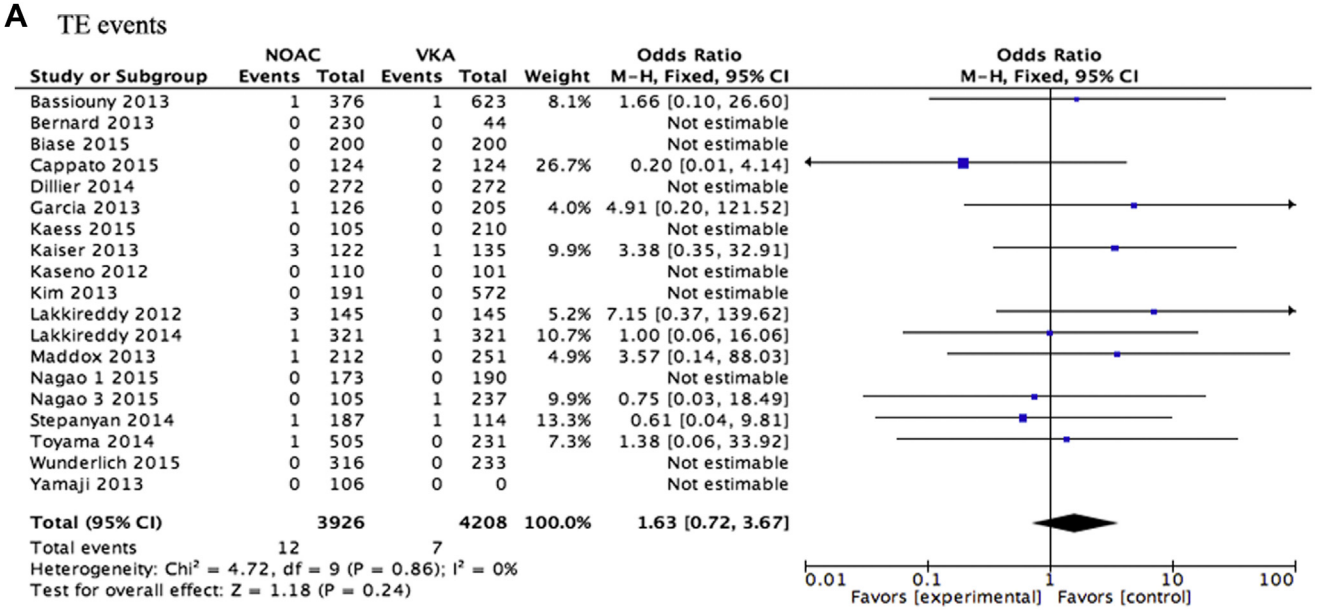

Figure 4. Secondary outcomes with periprocedural NOACs versus uninterrupted VKAs in patients with AF who underwent CA, *(A)* TE events; *(B)* minor bleeding. M-H = Mantel-Haenszel.

therapy in CA for AF, despite a higher heterogeneity existed in interrupted NOACs subgroup (Figures 2 and 3).

For the outcome of TE events reported in 19 studies, there was no statistical difference between the NOACs group and VKAs group (0.31% vs 0.17%; POR 1.63, 95% CI 0.72 to 3.67, p = 0.24, I^2 = 0%; Figure 4). For the outcome of minor bleeding, a significantly lower risk was observed in the NOACs group (3.68% vs 4.38%; OR 0.80, 95% CI 0.65 to 1.00, p = 0.05, I^2 = 0%; Figure 4). Besides, no statistically significant difference was indicated in cardiac tamponade or pericardial effusion requiring drainage (0.85% vs 0.89%; OR 1.11, 95% CI 0.72 to 1.71, p = 0.64, I^2 = 14%; Figure 5) and groin hematoma (2.98% vs 3.14%; OR 0.90, 95% CI 0.71 to 1.15, p = 0.41, I^2 = 0%; Figure 5). All outcomes were summarized in Supplementary File 3.

Sensitivity analyses failed to identify any of the individual study as having influenced the outcomes to a significant extent, and the results of subgroups were also concordant with the overall analyses (Supplementary File 4). No evidence of publication bias existed by visual inspection of Funnel plots (Figure 6) and Egger's test (t = 0.48, p = 0.640).

TSA was conducted to test the futility of the results obtained in this meta-analysis. With a 150% increase in POR and CEP of 0.19%, the calculated information size was 13,172 for stroke or TIA outcome; with intervention group

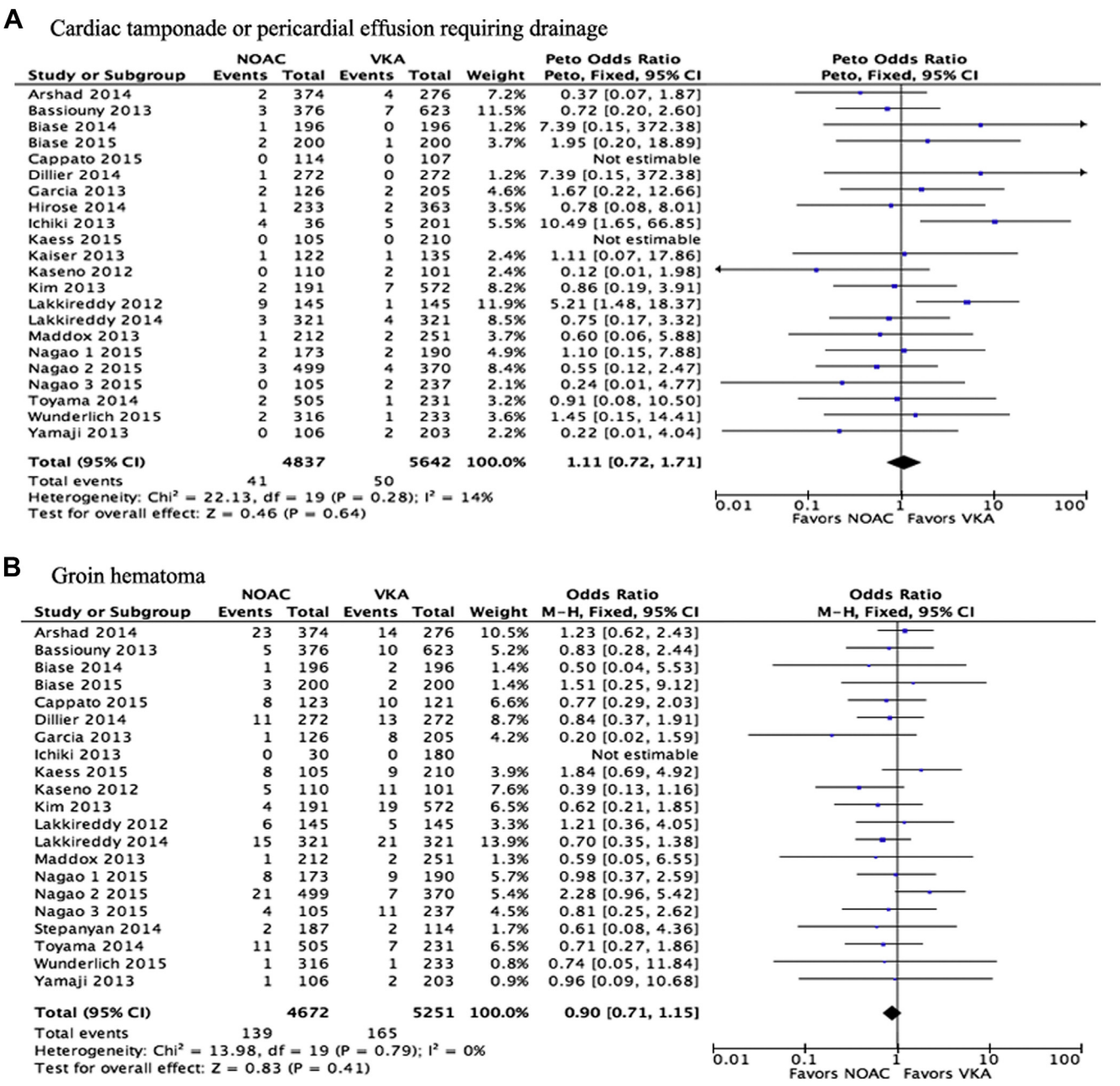

Figure 5. Secondary outcomes with periprocedural NOACs versus uninterrupted VKAs in patients with AF who underwent CA. *(A)* cardiac tamponade or pericardial effusion requiring drainage; *(B)* groin hematoma. M-H = Mantel-Haenszel.

event proportion of 1.6% and CEP of 1.1%, the calculated information size was 18,379 for major bleeding outcome. Both cumulative Z-curves crossed the futility boundaries and further confirmed that NOACs were as effective and safe as uninterrupted VKAs for thrombosis prevention during ablation for AF (Supplementary File 5).

Discussion

The present study was the first and most comprehensive meta-analysis so far comparing the efficacy and safety of NOACs to uninterrupted VKAs in patients undergoing rhythm control management of AF by CA, with 25 selected studies that included 11,686 participants. This meta-analysis incorporating all these studies showed that NOACs, whether discontinued preprocedure or not, had comparable efficacy in terms of ischemic stroke or TIA prevention and similar safety with respect to the occurrence of major bleeding compared to continuous VKAs administration. Besides, a significantly lower risk of minor bleeding was observed in the NOACs group. Particularly, we also verified the futility of the negative results by TSA. The comparable low rate of TE events and bleeding complications seen with NOACs provided favorable support for their use, as an alternative to uninterrupted VKAs, in the setting of CA for AF.

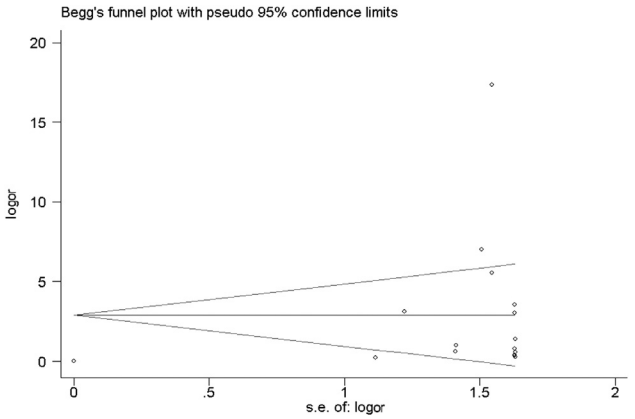

Figure 6. Begg's funnel plot of publication bias in a selection of studies on the rates of stroke or TIA between NOACs and uninterrupted VKAs. Log (OR), natural logarithm of OR. S.E = standard error. Horizontal line means magnitude of the effect.

As an invasive and thrombogenic procedure, CA carries a risk of TE events as high as 5%.[1] So far, no consensus on the optimal anticoagulant strategy in CA procedures has been reached, and a series of observational studies and meta-analyses preferred uninterrupted VKAs to interrupted therapy because of significantly lower risk of TE and bleeding events observed with this strategy.[2] Compared with VKAs, NOACs have several advantages, including rapid onset of therapeutic anticoagulation, predictable anticoagulant effect, and relatively abbreviated time to reversal of anticoagulation after the medication is held.[28] Previous study reported that as many as 50% or more of patients on uninterrupted warfarin present for CA of AF were with an interquartile range outside the therapeutic range,[1] and it is reasonable to estimate NOACs might be noninferior, or even superior to uninterrupted VKAs in this setting because of the previously mentioned advantages. However, sparse is known about the feasibility and safety of NOACs compared with uninterrupted VKAs during CA procedure, on account of small sample sizes of the existing studies and lack of power to detect any difference between the 2 strategies, and it is well worth to perform this meta-analysis.

In our study, the pooled rate of stroke or TIA with uninterrupted VKAs was 0.19%, <1.2% with interrupted VKAs reported by Nairooz et al[2] in their meta-analyses, indirectly favoring uninterrupted VKAs strategy; moreover, an equally low risk of 0.28% was detected with NOACs, revealing their comparable efficacy in prevention of TE events. As for major bleeding, a matched rate of 1.10% in NOACs group versus 1.60% in uninterrupted VKAs group was observed in our analysis, lower than a rate of 2.03% with interrupted VKAs reported by Nairooz et al, showing that both NOACs and uninterrupted VKAs were more riskless than interrupted VKAs. Besides, NOACs were also associated with significantly lower risk of minor bleeding than uninterrupted VKAs, whereas equal risk was observed between the 2 groups as for TE events, cardiac tamponade or pericardial effusion requiring drainage, and groin hematoma. We further explored whether significant discrepancy existed in terms of different anticoagulant protocols with NOACs in the subgroup analysis, resulting that NOACs, whether interrupted or uninterrupted, had comparable efficacy and safety to continuous VKAs during CA. These results did not show major statistical heterogeneity and also consistent in the sensitivity analyses. Importantly, the futility of the results was also verified by TSA.

Previous meta-analyses without defining specific anticoagulant protocols have been conducted and came into conflicting results.[29,30] In the meta-analysis performed by Sardar et al,[29] dabigatran therapy was associated with higher risk of stroke or TIA and all TE complications without significant difference for the risk of major bleeding compared with warfarin, whereas a recently published meta-analysis performed on larger number of studies indicated no significant difference existed between NOACs and warfarin during CA procedure.[30] Unlike previously mentioned meta-analyses, we restricted VKAs to continuous administration and evaluated the efficacy and safety of NOACs compared with this superior strategy, resulting comparable risk of TE events and bleeding complications. Notably, the futility of these results was further verified by TSA. Contrary to our results, subgroup analyses conducted by Santarpia et al[30] indicated that uninterrupted VKAs therapy was associated with lower risk of stroke or TIA than NOACs while with similar risk of major bleeding. In that study, silent cerebral ischemia was defined as a component of the primary safety outcome while we excluded those outcomes, and this discrepancy in end point definitions might be one possible reason for the inconsistent results. In addition, we included 25 studies into analysis, whereas Santarpia et al selected only 15 trials in the subgroup analysis of uninterrupted VKAs, and it was possible that the addition of more studies might affect the results.

NOACs related major bleeding is one of the most terrible complications for their usage in CA of AF, as it is tough to be properly handled because of a lack of experience and the absence of available specific antidotes. Strategy with holding several doses of NOACs preprocedure has been attempted to maximally reduce bleeding complications.[3–16] Nevertheless, no significant difference in terms of major bleeding was detected between interrupted and uninterrupted NOACs administration in our study, and both strategies had comparable incidence of major bleeding compared with uninterrupted VKAs, providing some reassurance about the safety of NOACs in the periprocedural setting. Antidotes, including neutralizing monoclonal antibody fragment against dabigatran and recombinant variant of factor Xa serving as decoy for rivaroxaban and apixaban, are in development.[28] When the antidotes are available, we will have more guarantees to use NOACs for periprocedural anticoagulation in patients undergoing CA.

There inevitably were several limitations in this meta-analysis. First, the vast majority of the studies included in our analysis were observational design, which had inherent biases. Second, 7 of 25 selected studies were conference abstracts with limited information about anticoagulation protocols, procedural data, and patients' characteristics. However, accordant results were obtained when refining full-text studies into analysis. Third, heterogeneity existed in study protocols and definitions for safety and efficacy outcomes, and baseline characteristics of the patients in these

selected studies, which might affect our results to some extent. Finally, well-designed and large-scale RCTs are certainly required to confirm our findings.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.amjcard.2015.12.027.

1. Kok LC, Mangrum JM, Haines DE, Mounsey J. Cerebrovascular complication associated with pulmonary vein ablation. *J Cardiovasc Electrophysiol* 2002;13:764−767.
2. Nairooz R, Sardar P, Payne J, Aronow WS, Paydak H. Meta-analysis of major bleeding with uninterrupted warfarin compared to interrupted warfarin and heparin bridging in ablation of atrial fibrillation. *Int J Cardiol* 2015;187:426−429.
3. Bassiouny M, Saliba W, Rickard J, Shao M, Sey A, Diab M, Martin DO, Hussein A, Khoury M, Abi-Saleh B, Alam S, Sengupta J, Borek PP, Baranowski B, Niebauer M, Callahan T, Varma N, Chung M, Tchou PJ, Kanj M, Dresing T, Lindsay BD, Wazni O. Use of dabigatran for periprocedural anticoagulation in patients undergoing catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2013;6:460−466.
4. Kaiser DW, Streur MM, Nagarakanti R, Whalen SP, Ellis CR. Continuous warfarin versus periprocedural dabigatran to reduce stroke and systemic embolism in patients undergoing catheter ablation for atrial fibrillation or left atrial flutter. *J Interv Card Electrophysiol* 2013;37:241−247.
5. Arshad A, Johnson CK, Mittal S, Buch E, Hamam I, Tran T, Shaw RE, Musat D, Preminger M, Sichrovsky T, Herweg B, Shivkumar K, Hummel J, Steinberg JS. Comparative safety of periablation anticoagulation strategies for atrial fibrillation: data from a large multicenter study. *Pacing Clin Electrophysiol* 2014;37:665−673.
6. Ichiki H, Oketani N, Ishida S, Iriki Y, Okui H, Maenosono R, Namino F, Ninomiya Y, Miyata M, Hamasaki S, Tei C. The incidence of asymptomatic cerebral microthromboembolism after atrial fibrillation ablation: comparison of warfarin and dabigatran. *Pacing Clin Electrophysiol* 2013;36:1328−1335.
7. Kaseno K, Naito S, Nakamura K, Sakamoto T, Sasaki T, Tsukada N, Hayano M, Nishiuchi S, Fuke E, Miki Y, Nakamura K, Yamashita E, Kumagai K, Oshima S, Tada H. Efficacy and safety of periprocedural dabigatran in patients undergoing catheter ablation of atrial fibrillation. *Circ J* 2012;76:2337−2342.
8. Lakkireddy D, Reddy YM, Di Biase L, Vanga SR, Santangeli P, Swarup V, Pimentel R, Mansour MC, D'Avila A, Sanchez JE, Burkhardt JD, Chalhoub F, Mohanty P, Coffey J, Shaik N, Monir G, Reddy VY, Ruskin J, Natale A. Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation. *J Am Coll Cardiol* 2012;59:1168−1174.
9. Yamaji H, Murakami T, Hina K, Higashiya S, Kawamura H, Murakami M, Kamikawa S, Hirohata S, Kusachi S. Usefulness of dabigatran etexilate as periprocedural anticoagulation therapy for atrial fibrillation ablation. *Clin Drug Investig* 2013;33:409−418.
10. Kim J-S, She F, Jongnarangsin K, Chugh A, Latchamsetty R, Ghanbari H, Crawford T, Suwanagool A, Sinno M, Carrigan T, Kennedy R, Saint-Phard W, Yokokawa M, Good E, Bogun F, Pelosi F, Morady F, Oral H. Dabigatran vs warfarin for radiofrequency catheter ablation of atrial fibrillation. *Heart Rhythm* 2013;10:483−489.
11. Stepanyan G, Badhwar N, Lee RJ, Marcus GM, Lee BK, Tseng ZH, Vedantham V, Olgin J, Scheinman M, Gerstenfeld EP. Safety of new oral anticoagulants for patients undergoing atrial fibrillation ablation. *J Interv Card Electrophysiol* 2014;40:33−38.
12. Bernard M, Brabham W, Netzler P, Rowley C, Gold M, Leman R, Sturdivant J, Wharton JM, Cuoco F. Comparison of atrial fibrillation ablation bleeding and thrombotic complications with dabigatran, rivaroxaban and warfarin. *J Am Coll Cardiol* 2013;61:E276.
13. Garcia LI, Ahuja K, Mascarenhas MA, Aizer A, Bernstein N, Bernstein SA, Fowler SJ, Holmes DS, Park DS, Chinitz L. The safety of dabigatran versus warfarin in patients undergoing atrial fibrillation ablation. *Heart Rhythm* 2013;10:S236−S237.
14. Hirose S, Miyamoto K, Nakajima I, Ishibashi K, Okamura H, Noda T, Aiba T, Kamakura S, Kusano K. Discontinuation period and periprocedural events of novel oral anticoagulation in patients undergoing catheter ablation of atrial fibrillation. *Eur Heart J* 2014;35:30.
15. Shin DG, Kim TH, Park J, Lee H, Park JK, Uhm JS, Kim JY, Joung B, Lee MH, Pak HN. Novel oral anticoagulants reduces preprocedural anticoagulation duration, but increases intra-procedural heparin requirement compared to uninterrupted warfarin in atrial fibrillation catheter ablation. *Heart Rhythm* 2015;12:S260.
16. Toyama H, Kumagai K. Relationship between oral anticoagulants and dose of heparin during procedure in patients undergoing catheter ablation of atrial fibrillation. *Heart Rhythm* 2014;11:S310−S311.
17. Di Biase L, Trivedi C, Mohanty P, Mohanty S, Bai R, Santangeli P, Sanchez J, Horton R, Joseph Gallinghouse G, Zagrodzky J, Hao S, Hongo R, Beheiry S, Lakkireddy DR, Reddy M, Viles-Gonzalez JF, David Burkhardt J, Natale A. Feasibility and safety of uninterrupted rivaroxaban in patients undergoing radiofrequency ablation for long standing persistent atrial fibrillation. *Circulation* 2014;130; A16402.
18. Wunderlich C, Christoph M, Huo Y, Forkmann M, Gaspar T, Salmas J, Pohl M, Mayer J, Piorkowski C. Ablation of atrial fibrillation with uninterrupted NOAC treatment during ablation of atrial fibrillation is not associated with severe peri- and postprocedural complications. *Europace* 2015;17:iii234−iii236.
19. Di Biase L, Lakkireddy D, Trivedi C, Deneke T, Martinek M, Mohanty S, Mohanty P, Prakash S, Bai R, Reddy M, Gianni C, Horton R, Bailey S, Sigmund E, Derndorfer M, Schade A, Mueller P, Szoelloes A, Sanchez J, Al-Ahmad A, Hranitzky P, Gallinghouse GJ, Hongo RH, Beheiry S, Purerfellner H, Burkhardt JD, Natale A. Feasibility and safety of uninterrupted periprocedural apixaban administration in patients undergoing radiofrequency catheter ablation for atrial fibrillation: results from a multicenter study. *Heart Rhythm* 2015;12:1162−1168.
20. Cappato R, Marchlinski FE, Hohnloser SH, Naccarelli GV, Xiang J, Wilber DJ, Ma CS, Hess S, Wells DS, Juang G, Vijgen J, Hugl BJ, Balasubramaniam R, De Chillou C, Davies DW, Fields LE, Natale A. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. *Eur Heart J* 2015;36:1805−1811.
21. Dillier R, Ammar S, Hessling G, Kaess B, Pavaci H, Buiatti A, Semmler V, Kathan S, Hofmann M, Lennerz C, Kolb C, Reents T, Deisenhofer I. Safety of continuous periprocedural rivaroxaban for patients undergoing left atrial catheter ablation procedures. *Circ Arrhythm Electrophysiol* 2014;7:576−582.
22. Kaess BM, Ammar S, Reents T, Dillier R, Lennerz C, Semmler V, Grebmer C, Bourier F, Buiatti A, Kolb C, Deisenhofer I, Hessling G. Comparison of safety of left atrial catheter ablation procedures for atrial arrhythmias under continuous anticoagulation with apixaban versus phenprocoumon. *Am J Cardiol* 2015;115:47−51.
23. Lakkireddy D, Reddy YM, Di Biase L, Vallakati A, Mansour MC, Santangeli P, Gangireddy S, Swarup V, Chalhoub F, Atkins D, Bommana S, Verma A, Sanchez JE, Burkhardt JD, Barrett CD, Baheiry S, Ruskin J, Reddy V, Natale A. Feasibility and safety of uninterrupted rivaroxaban for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. *J Am Coll Cardiol* 2014;63:982−988.
24. Maddox W, Kay GN, Yamada T, Osorio J, Doppalapudi H, Plumb VJ, Gunter A, McElderry HT. Dabigatran versus warfarin therapy for uninterrupted oral anticoagulation during atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2013;24:861−865.
25. Nagao T, Inden Y, Yanagisawa S, Kato H, Ishikawa S, Okumura S, Mizutani Y, Ito T, Yamamoto T, Yoshida N, Hirai M, Murohara T. Differences in activated clotting time among uninterrupted anticoagulants during the periprocedural period of atrial fibrillation ablation. *Heart Rhythm* 2015;12:1972−1978.
26. Nagao T, Inden Y, Shimano M, Fujita M, Yanagisawa S, Kato H, Ishikawa S, Miyoshi A, Okumura S, Ohguchi S, Yamamoto T, Yoshida N, Hirai M, Murohara T. Efficacy and safety of apixaban in the patients undergoing the ablation of atrial fibrillation. *Pacing Clin Electrophysiol* 2015;38:155−163.

27. Nagao T, Inden Y, Shimano M, Fujita M, Yanagisawa S, Kato H, Ishikawa S, Miyoshi A, Okumura S, Ohguchi S, Yamamoto T, Yoshida N, Hirai M, Murohara T. Feasibility and safety of uninterrupted dabigatran therapy in patients undergoing ablation for atrial fibrillation. *Intern Med* 2015;54:1167−1173.
28. Jackson Ii LR, Becker RC. Novel oral anticoagulants: pharmacology, coagulation measures, and considerations for reversal. *J Thromb Thrombolysis* 2014;37:380−391.
29. Sardar P, Nairooz R, Chatterjee S, Wetterslev J, Ghosh J, Aronow WS. Meta-analysis of risk of stroke or transient ischemic attack with dabigatran for atrial fibrillation ablation. *Am J Cardiol* 2014;113:1173−1177.
30. Santarpia G, De Rosa S, Polimeni A, Giampa S, Micieli M, Curcio A, Indolfi C. Efficacy and safety of non-vitamin K antagonist oral anticoagulants versus vitamin K antagonist oral anticoagulants in patients undergoing radiofrequency catheter ablation of atrial fibrillation: a meta-analysis. *PLoS One* 2015;10:e0126512.