Comparison of Major Bleeding Events of Uninterrupted Novel Oral Anticoagulants Versus Uninterrupted Vitamin K Antagonist During Catheter Ablation of Atrial Fibrillation: A Meta-analysis of Randomized Controlled Trials

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Research Article

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Abstract

**Background:** Previous meta-analyses comparing efficacy and safety of uninterrupted novel oral anticoagulants (NOACs) versus uninterrupted vitamin K antagonist (VKA) during catheter ablation (CA) of atrial fibrillation (AF) had no consensus in major bleeding, and didn't perform subgroup analyses for different types of major bleeding events. This meta-analysis was performed to comprehensively evaluate the risk of major bleeding events of these two anticoagulant strategies during CA of AF.

**Methods:** We searched online databases for randomized controlled trials that compared major bleeding events of uninterrupted NOACs and VKA during CA of AF up to January 2021. A fixed-effect model was used if the chi-squared test $P$-value was $> 0.10$ and $I^2$ was $< 50\%$, otherwise a random-effect model was used.

**Results:** Six published studies including 2392 patients were identified for inclusion in the analysis. The overall incidence of major bleeding events was lower in the NOACs group than in the VKA group (OR = 0.56, 95% CI = 0.34 – 0.93, $I^2 = 38\%$, $P = 0.15$). Subgroup analyses showed that the incidence of severe puncture site complications was lower in the NOACs group than in the VKA group (OR = 0.53, 95% CI = 0.30 – 0.96, $I^2 = 16\%$, $P = 0.32$). But the incidence of cardiac tamponade (OR = 0.53, 95% CI = 0.23 – 1.26, $I^2 = 0\%$, $P = 0.46$), intracranial (OR = 0.25, 95% CI = 0.03 – 2.23, $I^2 = 0\%$, $P = 0.82$) and gastrointestinal bleeding (OR = 0.98, 95% CI = 0.18 – 5.39, $I^2 = 0\%$, $P = 0.43$) had no statistically significant differences between the two groups.

**Conclusion:** This meta-analysis suggests that compared to uninterrupted VKA, uninterrupted NOACs are superior in major bleeding and severe puncture site complications during CA of AF, but are not superior in cardiac tamponade, intracranial and gastrointestinal bleeding.

Background

Catheter ablation (CA) is an effective therapeutic option for patients with atrial fibrillation (AF) [1]. Cardiovascular guidelines recommended performing AF ablation with uninterrupted vitamin K antagonist (VKA) or uninterrupted novel oral anticoagulants (NOACs) as anticoagulant strategies [2,3]. NOACs don't need to monitor international normalized ratio (INR) and are more convenient than VKA, so they are increasingly used in recent years. At present, two latest meta-analyses including the same studies suggested that in AF patients undergoing CA, there was no difference between uninterrupted NOACs and uninterrupted VKA with regards to stroke and transient ischemic attack, however they had different conclusions with regards to major bleeding events [4,5]. In addition, neither of them did subgroup analyses for specific major bleeding events. We therefore performed this meta-analysis to compare the overall and different types of major bleeding events of uninterrupted NOACs versus uninterrupted VKA during CA of AF.

Methods

**Literature search and inclusion criteria**

We searched PubMed, EMBASE and the Cochrane Database for all published studies up to January 2021. We conducted text searches with the search terms “dabigatran”, “rivaroxaban”, “apixaban”, “edoxaban”, “novel oral anticoagulants”, “new oral anticoagulants”, “direct oral anticoagulants”, “NOACs”, “DOACs”, “warfarin”, “VKA”,...
“ablation”, “atrial fibrillation”, “uninterrupted” and “continuous”. We also manually searched references from selected clinical trials, recent meta-analyses and review articles.

We included studies that met the following specified criteria: (1) comparative studies between uninterrupted NOACs (dabigatran, apixaban, rivaroxaban, and edoxaban) and uninterrupted VKA (warfarin) during CA of AF, (2) randomized controlled trials (RCTs), (3) full-text article, (4) the number of different types of major bleeding events were reported.

**Data extraction and quality assessment**

We extracted the following information from each included study: (1) study population sample size and characteristics; (2) information on anticoagulant therapy; (3) the number of different types of major bleeding events from the start of CA to the end of follow-up. We used Cochrane Risk of Bias Tool [6] to assess the risk of bias of the included studies. One reviewer (QY) abstracted the data, and then the other (YD) checked the documentation. They finally reached an agreement on the data by consensus.

**Statistical analysis**

We performed the statistical calculations with RevMan version 5.3 (The Cochrane Collaboration, Oxford, UK). We calculated the odds ratio (OR) and 95% confidence interval (CI) in each trial separately, and for combinations of studies according to fixed-effect or random-effect models. We used the chi-squared test to assess heterogeneity and \( I^2 \) to quantify heterogeneity. If the chi-squared test \( P \)-value was > 0.10 and \( I^2 \) was < 50%, we analyzed the data using a fixed-effect model (the Mantel–Haenszel method), otherwise we used a random-effect model [7,8].

**Results**

**Characteristics of the included studies**

Six published studies [9-14] including 2392 patients were identified for inclusion in the analysis. The process of study selection is summarized in Figure 1. The target INR of 2.0-3.0 was used in the warfarin arm in all studies. The characteristics of the studies included in the meta-analysis were shown in Table 1.

**Results of the meta-analysis**

The major bleeding events of uninterrupted NOACs and uninterrupted warfarin groups were reported in all included studies. Five studies [9-11,13,14] applied the International Society on Thrombosis and Hemostasis (ISTH) definition [15] for major bleeding, except the ASCERTAIN study [12]. There was a moderate heterogeneity, so a fixed-effect model was used. The overall incidence of major bleeding events was lower in the NOACs group than in the VKA group (OR = 0.56, 95% CI = 0.34 – 0.93, \( I^2 = 38\%\), \( P = 0.15 \)). When the ASCERTAIN study [12] was excluded, the incidence of major bleeding events still had no statistically significant differences between the two groups (OR = 0.53, 95% CI = 0.32 – 0.88, \( I^2 = 43\%\), \( P = 0.13 \)). Results are shown in Figure 2.

**Subgroup analysis**

Six included studies all reported different types of major bleeding events, and these were shown in Table 2. Subgroup analyses of cardiac tamponade, severe puncture site complications, intracranial bleeding and
gastrointestinal bleeding were performed to reduce the heterogeneity and provide some evidences for clinical work. These subgroup analyses all had a low heterogeneity, so a fixed-effect model was used.

1. Cardiac tamponade

Five\textsuperscript{[10-14]} studies reported cardiac tamponade requiring drainage. The VENTURE-AF study\textsuperscript{[9]} only reported pericardial effusion classified as non-major bleeding, and didn’t observed cardiac tamponade. The incidence of cardiac tamponade had no statistically significant differences between the NOACs and VKA groups (OR = 0.53, 95% CI = 0.23 – 1.26, $I^2 = 0\%$, $P = 0.46$). Results are shown in Figure 3.

2. Severe puncture site complications

Five\textsuperscript{[9,11-14]} studies reported severe puncture site complications, including puncture site bleeding, hematoma and pseudoaneurysm. The AXAFA-AFNET study\textsuperscript{[13]} reported more severe puncture site complications than major bleeding events. That’s because the major bleeding was defined according to ISTH and the severe puncture site complication was defined according to the Bleeding Academic Research Consortium (BARC $\geq 2$)\textsuperscript{[16]}. The incidence of severe puncture site complications was lower in the NOACs group than in the VKA group, no matter whether the AXAFA-AFNET study was included (OR = 0.53, 95% CI = 0.30 – 0.96, $I^2 = 16\%$, $P = 0.32$) or not (OR = 0.32, 95% CI = 0.12 – 0.82, $I^2 = 9\%$, $P = 0.35$). Results are shown in Figure 4.

3. Intracranial bleeding

Two\textsuperscript{[11,13]} studies reported intracranial bleeding. The ELIMINATE-AF study\textsuperscript{[14]} also reported a case of intracranial bleeding in the NOACs group, but it happened before CA. The incidence of intracranial bleeding had no statistically significant differences between the NOACs and VKA groups (OR = 0.25, 95% CI = 0.03 – 2.23, $I^2 = 0\%$, $P = 0.82$). Results are shown in Figure 5.

4. Gastrointestinal bleeding

Two\textsuperscript{[11,14]} studies reported gastrointestinal bleeding. The incidence of gastrointestinal bleeding had no statistically significant differences between the NOACs and VKA groups (OR = 0.98, 95% CI = 0.18 – 5.39, $I^2 = 0\%$, $P = 0.43$). Results are shown in Figure 6.

Quality assessment and bias assessment

All the included studies are RCTs, so they have high quality. Risk of bias was assessed using the methods described in Cochrane collaboration’s handbook and results are summarized in Figure 7.

Discussion

At present, CA of AF as an important rhythm control strategy is widely used in clinic\textsuperscript{[1,2]}. Cardiovascular guidelines recommended performing AF ablation with uninterrupted VKA or uninterrupted NOACs in order to reduce the risk of thromboembolism complications\textsuperscript{[2,3]}. The main complication of uninterrupted anticoagulation during CA is bleeding, and major bleeding events, such as cardiac tamponade, can be very serious even life-threatening\textsuperscript{[17]}. So it is very important to optimize perioperative anticoagulant therapy to reduce major bleeding events. The meta-analysis by Romero et al.\textsuperscript{[5]} including six RCTs showed that uninterrupted NOACs appeared to be safer than
uninterrupted VKA with a decreased rate of major bleeding events. However the other meta-analysis by Brockmeyer et al. [4] including the same RCTs showed that uninterrupted NOACs was not superior to VKA with regards to major bleeding. We found that the two different results were due to their different definitions of major bleeding. In addition, neither of them did subgroup analyses for specific bleeding events, so we performed this meta-analysis.

Our meta-analysis also included six RCTs [9-14]. Different from the previous two meta-analyses, we used a fixed-effect model rather than a random-effect model, for the reason that the chi-squared test P-value was > 0.10 and $I^2$ was < 50%. Except the the ASCERTAIN study [12], they all used the ISTH standard to define major bleeding [15]. No matter whether the ASCERTAIN study was included, the result showed that uninterrupted NOACs was superior to VKA, especially dabigatran (1.6% vs. 6.9%) [11]. Then we did subgroup analyses of specific major bleeding events, which further reduced heterogeneity. Cardiac tamponade is a relatively infrequent and potentially fatal complication, and sometimes needs emergency surgical intervention [17,18]. Five [10-14] studies reported cardiac tamponade, which only needed pericardial drainage and administration of protamine and vitamin K. Subgroup analysis showed that uninterrupted NOACs was not superior to uninterrupted VKA. However the incidence of cardiac tamponade was relatively lower in the NOACs group than in the warfarin group (0.7% vs. 1.3%), especially in dabigatran (0.3% vs. 1.9%) and apixaban (0.6% vs. 1.6%) groups. The largest sample size of these included studies just exceeded 600. The effective of NOACs may emerge as the number of large scale RCTs increasing. Puncture site complications are most common during CA of AF. Five [9,10-14] studies reported severe puncture site complications, which were classified as major bleeding events. Subgroup analysis showed that uninterrupted NOACs, especially dabigatran, were superior to VKA in severe puncture site complications. The intracranial and gastrointestinal bleeding are infrequent complications. Both of them were reported only in two studies. Subgroup analyses showed that uninterrupted NOACs was not superior to uninterrupted VKA in intracranial and gastrointestinal bleeding during CA of AF.

**Limitations**

This meta-analysis has the following limitations. Only published RCTs were included in our meta-analysis, so publication bias was unavoidable. The sample size of the included studies was limited, and the number of studies in some subgroups were limited. These were the main limitations of our analysis, so the results were less persuasive.

**Conclusion**

Compared to uninterrupted VKA, uninterrupted NOACs are superior in major bleeding and severe puncture site complications during CA of AF, but are not superior in cardiac tamponade, intracranial and gastrointestinal bleeding.

**Abbreviations**

AF: atrial fibrillation; BARC: the Bleeding Academic Research Consortium; CA: catheter ablation; CI: confidence interval; INR: international normalized ratio; ISTH: the International Society on Thrombosis and Hemostasis; NOACs: novel oral anticoagulants; OR: odds ratio; RCTs: randomized controlled trials; VKA: vitamin K antagonist.
Declarations

Acknowledgments

None.

Authors’ contributions

QY conceived the study, participated in the design, collected the data, performed statistical analyses and drafted the manuscript. YD conceived the study, collected the data, and helped to draft the manuscript. XFC and JLZ performed statistical analyses and helped to draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

[1] January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation. 2019;140:e125-51.

[2] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42:373-498.

[3] Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2018;20:e1-160.
[4] Brockmeyer M, Lin Y, Parco C, Karathanos A, Krieger T, Schulze V, et al. Uninterrupted anticoagulation during catheter ablation for atrial fibrillation: no difference in major bleeding and stroke between direct oral anticoagulants and vitamin K antagonists in an updated meta-analysis of randomised controlled trials. Acta Cardiol. 2020; doi:10.1080/00015385.2020.1724689.

[5] Romero J, Cerrud-Rodriguez RC, Alviz I, Diaz JC, Rodriguez D, Arshad S, et al. Significant Benefit of Uninterrupted DOACs Versus VKA During Catheter. JACC Clin Electrophysiol. 2019;5:1396-405.

[6] Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. New York: Wiley; 2011.

[7] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7:177-88.

[8] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J. 2003;327:557-60.

[9] Cappato R, Marchlinski FE, Hohnloser SH, Naccarelli GV, Xiang J, Wilber DJ, et al. VENTURE-AF Investigators. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. Eur Heart J. 2015;36:1805-11.

[10] Kuwahara T, Abe M, Yamaki M, Fujieda H, Abe Y, Hashimoto K, et al. Apixaban versus Warfarin for the prevention of periprocedural cerebral thromboembolism in atrial fibrillation ablation: multicenter prospective randomized study. J Cardiovasc Electrophysiol. 2016;27:549-54.

[11] Calkins H, Willems S, Gerstenfeld EP, Verma A, Schilling R, Hohnloser SH, et al. RE-CIRCUIT Investigators. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. N Engl J Med. 2017; 376:1627-36.

[12] Kimura T, Kashimura S, Nishiyama T, Katsumata Y, Inagawa K, Ikegami Y, et al. Asymptomatic cerebral infarction during catheter ablation for atrial fibrillation: comparing uninterrupted rivaroxaban and warfarin (ASCERTAIN). JACC Clin Electrophysiol. 2018;4:1598-609.

[13] Kirchhof P, Haeusler KG, Blank B, De Bono J, Callans D, Elvan A, et al. Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. Eur Heart J. 2018; 39:2942-55.

[14] Hohnloser SH, Camm J, Cappato R, Diener HC, Heidbüchel H, Mont L, et al. Uninterrupted edoxaban vs. vitamin K antagonists for ablation of atrial fibrillation: the ELIMINATE-AF trial. Eur Heart J. 2019;40:3013-21.

[15] Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithemostatic medicinal products in nonsurgical patients. J Thromb Haemost. 2005;3:692-4.

[16] Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation. 2011;123:2736–47.

[17] Hamaya R, Miyazaki S, Taniguchi H, Kusa S, Nakamura H, Hachiya H, et al. Management of cardiac tamponade in catheter ablation of atrial fibrillation: single-centre 15 year experience on 5222 procedures. Europace. 2018;20:1776-82.
Table 1 Baseline characteristics of the studies included in the meta-analysis

| Study, year         | No. of patients | Age* (y) | Male patients (%) | CHA₂DS₂-VASc score* | NOAC/VKA regimen | Target ACT (sec) | Follow-up time |
|---------------------|-----------------|----------|-------------------|----------------------|------------------|-----------------|----------------|
| VENTURE-AF 2015 [9] | 244             | 59/61    | 69/73             | 1.5/1.7              | Riv 20mg qd      | 300-400         | 30 days        |
| Kuwahara et al.2016 [10] | 200         | 65/66    | 75/72             | 2.1/2.4              | Api 5/2.5mg bid | ≥ 300           | 7 days         |
| RE-CIRCUIT 2017 [11] | 635            | 59/59    | 73/77             | 2.0/2.2              | Dab 150mg bid    | > 300           | 8 weeks        |
| ASCERTAIN 2018 [12] | 127            | 59/62    | 83/84             | -                    | Riv 15/10mg qd   | 300-350         | 30 days        |
| AXAFA-AFNET 2018 [13] | 633            | 64/64    | 69/65             | 2.4/2.4              | Api 5/2.5mg bid  | > 300           | 3 months       |
| ELIMINATE-AF 2019 [14] | 553           | 60/61    | 71/73             | -                    | Edo 60/30mg qd   | 300-400         | 90 days        |

*: mean or median; ACT: activated clotting time; Api: apixaban; bid: twice daily; Dab: dabigatran; NOAC: novel oral anticoagulant; Edo: edoxaban; qd: once daily; Riv: rivaroxaban; VKA: vitamin K antagonist.

Table 2 Different types of major bleeding events
| Study, year               | No. of major bleeding NOAC/VKA | No. of cardiac tamponade NOAC/VKA | No. of vascular pseudoaneurysm NOAC/VKA | No of severe puncture site bleeding and hematoma NOAC/VKA | No. of intracranial bleeding NOAC/VKA | No. of gastrointestinal bleeding NOAC/VKA |
|--------------------------|--------------------------------|-----------------------------------|----------------------------------------|----------------------------------------------------------|--------------------------------------|-----------------------------------------|
| VENTURE-AF 2015 [9]      | 0/1                            | -/-                               | 0/1                                    | -/-                                                      | -/-                                  | -/-                                     |
| Kuwahara et al. 2016 [10]| 1/0                            | 1/0                               | -/-                                    | -/-                                                      | -/-                                  | -/-                                     |
| RE-CIRCUIT 2017 [11]     | 5/22                           | 1/6                               | 0/1                                    | 2/12                                                     | 0/2                                  | 1/2                                     |
| ASCERTAIN 2018 [12]      | 2/1                            | 1/0                               | -/-                                    | 1/1                                                      | -/-                                  | -/-                                     |
| AXAFA-AFNET 2018 [13]    | 10/14                          | 2/5                               | -/-                                    | 12/15                                                    | 0/1                                  | -/-                                     |
| ELIMINATE-AF 2019 [14]   | 9/3                            | 3/2                               | -/-                                    | 3/1                                                      | -/-                                  | 2/0                                     |

NOAC: novel oral anticoagulant; VKA: vitamin K antagonist.