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REVIEW

Uninterrupted anticoagulation with non-vitamin K antagonist oral anticoagulants in atrial fibrillation catheter ablation: Lessons learned from randomized trials

Rhanderson Cardoso[1] | Stephan Willems[2] | Edward P. Gerstenfeld[3] | Atul Verma[4] | Richard Schilling[5] | Stefan H. Hohnloser[6] | Ken Okumura[7] | Matias Nordaby[8] | Marc A. Brouwer[9] | Hugh Calkins[1]

[1]Division of Cardiology, Johns Hopkins Medical Institutions, Baltimore, Maryland

[2]Department of Cardiology-Electrophysiology, University Heart Center Hamburg, Hamburg, Germany

[3]Division of Cardiology, University of California San Francisco, San Francisco, California

[4]Division of Cardiology, University of Toronto, Toronto, Canada

[5]Division of Cardiology, Barts Heart Centre, Saint Bartholomew's Hospital, London, UK

[6]Department of Cardiology, J.W. Goethe University, Frankfurt, Germany

[7]Division of Cardiology, Saiseikai Kumamoto Hospital Cardiovascular Center, Kumamoto, Japan

[8]Boehringer Ingelheim Pharma, Ingelheim am Rhein, Germany

[9]Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands

Correspondence
Rhanderson Cardoso, MD, Johns Hopkins Medical Institutions, Sheikh Zayed Tower 7125R,1800 Orleans Street, Baltimore, MD.
Email: rhmncardoso@gmail.com

Catheter ablation has been established as a rhythm control strategy in selected patients with atrial fibrillation (AF) who have failed or wish to avoid anti-arrhythmic drugs. Uninterrupted oral anticoagulation with vitamin K antagonists (VKAs) peri-ablation is associated with a lower risk of thromboembolic and bleeding complications as compared to interrupted oral anticoagulation and bridging heparin. However, a substantial portion of patients with AF are treated with non-vitamin K antagonist oral anticoagulants (NOACs). Herein, we perform an in-depth review and comparison of three recent randomized trials of uninterrupted oral anticoagulation with NOACs vs VKAs in patients undergoing AF catheter ablation. Furthermore, we report pooled results of these randomized trials. The pooled incidence of major bleeding was significantly lower with NOACs as compared to VKAs (2% vs 4.9%, respectively; odds ratio [OR] 0.40; 95% confidence intervals [CI] 0.16-0.99). Similarly, cardiac tamponade was also reduced in the NOAC group (0.4% vs 1.5%; OR 0.27; 95% CI 0.07-0.97). Thromboembolic complications were not significantly different between groups. Overall, these findings support the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement's class I recommendation for uninterrupted NOAC use in patients undergoing AF catheter ablation.

KEYWORDS

apixaban, atrial fibrillation, catheter ablation, dabigatran, non-vitamin K antagonist oral anticoagulants, rivaroxaban, vitamin-K antagonist, warfarin

1 | INTRODUCTION

Catheter ablation is a safe and effective rhythm control strategy for selected patients with atrial fibrillation (AF), with worldwide exponential growth in recent years.[1] In the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement, catheter ablation received a class I recommendation in patients with symptomatic, paroxysmal AF, who have recurrent AF despite anti-arrhythmic drug (AAD) therapy for maintenance of sinus rhythm. A IIa recommendation was given for second-line therapy in those with persistent AF. In addition, catheter ablation received a IIa recommendation in selected patients with symptomatic paroxysmal or persistent AF before a trial of AAD, that is, as first-line therapy.[2]

In patients undergoing AF catheter ablation, periprocedural bleeding and thromboembolic complications are significantly reduced by

Abbreviations: AAD, anti-arrhythmic drug(s); ACE, asymptomatic cerebral embolism; AF, atrial fibrillation; CI, confidence interval; INR, international normalized ratio; MRI, magnetic resonance imaging; NOAC, non-vitamin K antagonist oral anticoagulant(s); TEE, transesophageal echocardiogram; TIA, transient ischemic attack; VKA, vitamin K antagonist(s).

uninterrupted anticoagulation with vitamin K antagonists (VKAs) as compared to bridging heparin.[3] The uninterrupted use of non-vitamin K antagonist oral anticoagulants (NOACs) periablation, in contrast, was not routinely recommended in guidelines until recently because of insufficient evidence from randomized studies.[4] Over recent years, however, three randomized trials were published comparing uninterrupted anticoagulation with NOACs to VKAs in patients undergoing catheter ablation for AF: VENTURE-AF,[5] RE-CIRCUIT,[6] and AXAFA-AFNET 5.[7] This review aims to provide an overview of the evidence from these randomized trials, and to contrast differences and similarities with regard to study design, patient population, and outcomes.

2 | HISTORICAL PERSPECTIVE

Published in 2014, the COMPARE trial randomized 1584 patients undergoing radiofrequency catheter ablation for treatment of AF to a strategy of uninterrupted VKA (on-warfarin) vs warfarin discontinuation 2 to 3 days before the ablation followed by bridging with low-molecular weight heparin (off-warfarin). There was a greater than 15-fold increase in cerebrovascular thromboembolic events in the off-warfarin (4.9%) group as compared to uninterrupted VKA (0.3%). Furthermore, bleeding complications were also lower in the on-warfarin group.[3] These findings were consistent with previously published non-randomized data.[8–10]

Although the use of uninterrupted VKA is undoubtedly simpler and more convenient than bridging with heparin, there are a few limitations to this strategy. First, it contrasts with the increasing use of NOACs for patients with AF, including those undergoing catheter ablation of AF.[11–13] Switching from a NOAC to VKA for the purpose of a procedure is as disruptive as bridging with heparin, if not more. Second, with VKA use, the ablation may have to be canceled because of a supratherapeutic international normalized ratio (INR) on the day of the procedure. In COMPARE, patients were excluded from enrollment if the INR was >3.5 on the day of the ablation. And third, with a VKA strategy, it is possible for patients to present for ablation with a subtherapeutic INR, leading either to cancellation of the procedure or the performance of catheter ablation with a subtherapeutic INR with its associated increase in stroke risk.

Considering the benefits of uninterrupted anticoagulation shown with VKAs and the convenience of NOAC use, observational studies were published on outcomes of uninterrupted NOACs for periprocedural anticoagulation in patients undergoing AF catheter ablation. An early meta-analysis including 3544 patients primarily from observational studies compared uninterrupted NOACs to uninterrupted VKAs in patients undergoing AF catheter ablation and found no difference in the rates of thromboembolic or bleeding outcomes between groups.[14]

The lack of definitive randomized data comparing uninterrupted anticoagulation strategies, however, led to substantial heterogeneity in clinical practice. This was confirmed by a survey including electrophysiologists in 13 European countries and 455 patients undergoing AF catheter ablation.[12] Although approximately 50% of patients received continuous periprocedural VKAs with a therapeutic INR, only 4% underwent catheter ablation with uninterrupted NOACs. In this context, three randomized controlled trials were designed and conducted comparing NOACs to VKAs for uninterrupted anticoagulation in patients undergoing catheter ablation for AF—VENTURE-AF (rivaroxaban), RE-CIRCUIT (dabigatran), and AXAFA-AFNET 5 (apixaban).[5–7]

3 | STUDY DESIGN

VENTURE-AF, RE-CIRCUIT, and AXAFA-AFNET 5 were multicenter, open label trials. AXAFA-AFNET and VENTURE-AF were conducted in 49 and 46 sites, respectively, in Europe and the United States. RE-CIRCUIT involved 104 centers in Japan, Europe, Russia, and North America.

In AXAFA-AFNET 5, patients were stratified by site and AF type (paroxysmal, persistent, or long-standing persistent) and then randomized in a 1:1 ratio to apixaban 5 mg twice daily (2.5 mg b.i.d. if two of the three were present: age ≥ 80 years, weight ≤ 60 Kg, or serum creatinine ≥1.5 mg/dL) or VKA with a goal INR of 2 to 3. Catheter ablation was performed after at least 30 days of continuous anticoagulation or earlier if a transesophageal echocardiogram (TEE) was performed. In the latter case, after TEE, patients were required to have either an INR ≥2.0 or a minimum of two apixaban doses in the VKA and NOAC groups, respectively.

In RE-CIRCUIT, patients were randomized, without stratification, in a 1:1 ratio to dabigatran 150 mg twice daily or warfarin with dose adjustment to achieve a target INR of 2.0 to 3.0 (<2.6 in Japanese sites for patients ≥70 years old). After randomization, all patients were treated with oral anticoagulation for 4 to 8 weeks pre-ablation to ensure a stable INR range in those receiving warfarin for at least 4 weeks prior to the ablation. In addition, all patients underwent a pre-ablation TEE to rule out left atrial thrombi.

In VENTURE-AF, patients were stratified by country and randomized in a 1:1 ratio to rivaroxaban 20 mg daily (evening dose given on the day before ablation) or to VKA with a goal INR of 2.0 to 3.0. In patients who underwent a TEE, catheter ablation was performed 1 to 7 days after exposure to the study drug. In those who did not have a TEE, catheter ablation was performed 4 to 5 weeks after randomization.

All three trials received industry funding and had an independent steering committee to oversee trial design and conduct. All three trials also used a blinded adjudication committee for endpoint events. In addition, an independent data and safety monitoring board was part of AXAFA-AFNET 5 and RE-CIRCUIT.

4 | PATIENT POPULATION

The inclusion and exclusion criteria were similar between the three trials (Table 1). The three studies included patients with paroxysmal, persistent, or long-standing non-valvular AF. All trials excluded patients with recent ischemic stroke and those with contra-indications for anticoagulation. The criteria defining recent stroke was ≤14 days in AXAFA-AFNET 5; ≤ 1 month in RE-CIRCUIT; and ≤ 6 months in VENTURE-AF. As a result, a history of prior stroke or transient

TABLE 1 Inclusion and exclusion criteria

	AXAFA-AFNET 5	RE-CIRCUIT	VENTURE-AF
Inclusion criteria	• Age ≥ 18 years • Paroxysmal, persistent, or long-standing NVAF • $CHADS_2$ ≥ 1	• Age ≥ 18 years • Paroxysmal, persistent, or long-standing NVAF • At least one episode of documented AF in <24 months	• Age ≥ 18 years • Paroxysmal, persistent, or long-standing NVAF • $CHADS_2$ or CHA_2DS_2-VASc score ≥ 1
Exclusion criteria	• Valvular AF[a] • Life expectancy <1 year • Stroke <14 days • Concomitant use of strong cytochrome P450 inhibitors • Previous ablation for AF • Indication for DAPT • Contraindication to OAC • LA thrombi <3 months • eGFR<15 mL/min or need for RRT • Premenopausal women not on contraception	• Valvular AF[a] • Reversible cause to AF • LA size ≥60 mm • OAC contra-indication • CrCl<30 mL/min • Stroke/major surgery <1 month • Previous organ transplantation • History of intracranial, intraocular, spinal, retroperitoneal, or spontaneous intra-articular bleed • GI or major bleed <1 month • Bleeding diathesis • Hb < 10 g/dL • Platelets<100×10^9/L • Malignancy ≤6 months • Active liver disease • Premenopausal women not on contraception	• Valvular AF[a] • Reversible cause to AF • MI <2 months • CABG<6 months • LVEF ≤40%, NYHA class III or IV, or ICD • LA >55 mm or thrombus • OAC contra-indication • CrCl ≤50 mL/min • ≥moderate hepatic disease • Stroke/TIA or major surgery <6 months • Major bleed or thrombo-embolism <12 months • Need for high-intensity antiplatelet therapy • Premenopausal women not on contraception

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass grafting surgery; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; Hb, hemoglobin; LA, left atrium; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation; NYHA, New York Heart Association; OAC, oral anticoagulation; RRT, renal replacement therapy.

[a] In AXAFA-AFNET 5, defined as absence of severe mitral stenosis or mechanical heart valve; in RE-CIRCUIT, defined as absence of rheumatic mitral stenosis, mechanical or bioprosthetic heart valve, hemodynamically severe valve disease, or mitral valve repair; in VENTURE-AF, defined as absence of a prosthetic heart valve (annuloplasty with or without prosthetic ring, and valvuloplasty were allowed) and hemodynamically significant mitral stenosis.

ischemic attack (TIA) was present in 7.4%, 3%, and 1.2%, of the population in AXAFA-AFNET 5, RE-CIRCUIT, and VENTURE-AF, respectively.[5–7] There were only slight differences in the patient population between the different studies, as summarized in Table 2. About one-third of the patients were women. Notably, the average age of the population was slightly higher in AXAFA-AFNET 5 as compared to the other two trials. The mean CHA_2DS_2-VASc score in patients randomized to the NOAC group was lower in VENTURE-AF (1.4), as compared to RE-CIRCUIT (2.0) and AXAFA-AFNET 5 (2.4). Hypertension was nearly universal in AXAFA-AFNET (~90%), whereas the prevalence was approximately 50% in the other studies. Similarly, heart failure was present in one-quarter of the patients in AXAFA-AFNET, which is about double of the prevalence in RE-CIRCUIT and VENTURE-AF. AF was paroxysmal in 60%, 67%, and 76% of the population in AXAFA-AFNET 5, RE-CIRCUIT, and VENTURE-AF, respectively.

5 | PROCEDURAL DATA

In all three studies, patients randomized to the NOAC group received anticoagulation in an uninterrupted fashion following the approved posology of each medication, that is, including the morning of (for twice-daily medications) or the evening prior (for once-daily medications) to the procedure. In VENTURE-AF, once daily rivaroxaban was given daily in the evening, and administered post-procedure at least 6 hours following hemostasis. In RE-CIRCUIT, dabigatran was given on the morning of the procedure, and continued in the evening, with a minimum delay of 3 hours after sheath removal and hemostasis. In AXAFA-AFNET 5, apixaban was administered on the morning and evening of the procedure, though a time frame for resuming apixaban after ablation or sheath removal was not specified.

VENTURE-AF did not report the number of additional lesion sets or the proportion of radiofrequency vs cryoablation. In AXAFA-AFNET 5 and RE-CIRCUIT, about 10% and 20%, respectively, of patients received other ablation lesions in addition to pulmonary vein isolation. Radiofrequency was the predominant energy source, though roughly one-quarter of patients underwent cryoablation in both AXAFA-AFNET 5 and RE-CIRCUIT.

Unfractionated heparin was administered before or immediately after transseptal puncture. The activated clotting time (ACT) goal was >300 seconds in AXAFA-AFNET 5 and RE-CIRCUIT, and 300 to 400 seconds in VENTURE-AF. As shown in Table 2, the mean intra-procedural ACT was lower in the NOAC group as compared to VKA-

TABLE 2 Baseline and procedural characteristics

	AXAFA-AFNET 5 NOAC vs. VKA	RE-CIRCUIT NOAC vs. VKA	VENTURE-AF NOAC vs VKA
Number of patients	318/315	317/318	124/124
Age (years), mean or median	64/64	59.1/59.3	58.6/60.5
Age ≥ 75 years	8.8%/8.9%	NR	4%/8.1%
Female gender	31%/35%	27.4%/23%	31.6%/27.4%
BMI, kg/m^2, mean or median	28.4/28.2	28.5/28.8	29.8/28.9
CHA_2DS_2-VASc, mean	2.4/2.4	2/2.2	1.5/1.7
Hypertension	89%/91.4%	52.4%/55.7%	47.6%/46%
Congestive heart failure	24.5%/22.9%	9.8%/10.7%	9.7%/7.3%
Diabetes mellitus	12.9%/11.1%	9.5%/10.7%	6.5%/11.3%
Prior stroke or TIA	7.5%/7.3%	3.2%/2.8%	0%/2.4%
Coronary artery disease	12.3%/12.1%	10.1%/15.1%	NR
Beta-blocker	72.3%/70.2%	57.7%/60.4%	52.4%/49.2%
Paroxysmal AF	59.4%/56.5%	67.2%/68.9%	76.6%/70.2%
Persistent AF	40.6%/43.5%	32.8% / 31.2%	23.4%/29.8%
Prior catheter ablation	0%	NR	8.9%/8.9%
TEE prior to ablation	84.6%	100%	NR
Other lesion sets in addition to PVI	9.1%	21%	NR
Cryoablation	28.9%	28%	NR
Estimated NOAC compliance[a]	97%	97.6%	99.9%
INR, time in therapeutic range[b]	84%	85.7%	79.8%
INR on day of ablation	NR	NR	65%, 1.8-3.2
ACT (seconds), mean or median	310/348	330/340	302/332

Abbreviations: ACT, activated clotted time; AF, atrial fibrillation; BMI, body mass index; INR, International Normalized Ratio; NOAC, novel oral anticoagulant; NR, not reported; PVI, pulmonary vein isolation; TIA, transient ischemic attack; TEE, transesophageal echocardiogram; VKA, vitamin K antagonist.

[a] Compliance reported as follows: in AXAFA-AFNET 5, by the % of patients who took all or all but one apixaban doses per week; in RE-CIRCUIT, by the % of patients who took between 80% to 120% of the expected dose; in VENTURE-AF, by % of patients with documented compliance of at least 80% as determined by physician assessment or patient interview.

[b] The time in therapeutic range was calculated by the Rosendaal method in AXAFA-AFNET 5 and RE-CIRCUIT, but not specified in VENTURE-AF. Median reported in AXAFA-AFNET and RE-CIRCUIT; mean vs. median not specified in VENTURE-AF.

treated patients in all three studies. In the VENTURE-AF trial, the total heparin dose needed to achieve the goal ACT was higher with rivaroxaban (13 871 ± 6516 units) compared to VKA treatment (10 964 ± 5912 units). Post-ablation, anticoagulation with the study drug was mandatory for 3 months in AXAFA-AFNET 5, 8 weeks in RE-CIRCUIT, and 30 days in VENTURE-AF. Thereafter, anticoagulation management was at the discretion of the treating physicians.

6 | ENDPOINTS AND SAMPLE SIZES

There were important differences in the study design between trials with regard to endpoints (Table 3). AXAFA-AFNET 5 planned to enroll 650 patients to demonstrate non-inferiority of the uninterrupted NOAC strategy at a pre-specified margin of 7.5% with regard to the primary composite endpoint of all-cause mortality, stroke, or major bleeding per Bleeding Academic Research Consortium (BARC 2 or higher) criteria. Of note, this margin was wide, as physicians and patients may not consider the uninterrupted NOAC strategy as an acceptable alternative to uninterrupted VKA if it were associated with an absolute risk increase of up to 7.5% in the composite endpoint of death, stroke, or major bleeding. Furthermore, the power calculation was based on an anticipated overall event rate of 17%, whereas the results showed a much smaller event rate of 7.1%. AXAFA-AFNET 5 was unique in performing a systematic evaluation of quality-of-life and cognitive function at baseline and during follow-up. In addition, 25 out of the 49 centers participated in a magnetic resonance imaging (MRI)-substudy protocol, where all patients underwent a brain MRI within 48 hours of the ablation procedure to detect acute brain lesions.

RE-CIRCUIT and VENTURE-AF, however, compared the two uninterrupted anticoagulation strategies for the primary endpoint of major bleeding. Both studies were designed as exploratory analyses only because the sample sizes required to demonstrate non-inferiority in bleeding endpoints were considered to be prohibitive and the absence of a commonly accepted non-inferiority margin. VENTURE-AF planned on enrolling 250 patients to demonstrate a clinically relevant difference between groups, if any. In RE-CIRCUIT, assuming a major bleeding rate between 0.59% and 4.55% in both groups and a sample size of 580 patients, power calculations estimated the upper limit of the confidence interval (CI) for major bleeding to be between 2.48% and 4.98%. All three studies reported major bleeding outcomes using International Society on Thrombosis and Hemostasis (ISTH) criteria; AXAFA-AFNET 5 and VENTURE-AF reported additional criteria for major bleeding (Table 3).

TABLE 3 Outcomes and endpoint definitions

	AXAFA-AFNET 5	RE-CIRCUIT	VENTURE-AF
Primary outcome	All-cause mortality, stroke, or major bleeding (BARC ≥2)	ISTH major bleeding events	Major bleeding events
Analysis	Modified ITT, all randomized patients who underwent CA	Ablation set, all patients who received study drug and underwent CA	PPA, all patients who received study drug and underwent CA
Secondary outcomes	Length of stay; all bleeding events; tamponade; need for transfusion; quality of life; cognitive function; and prevalence of MRI-detected acute brain lesions	Composite of stroke, TIA, and systemic embolism; minor bleeding events; and composite of major bleeding and thromboembolic events	Composite (and individual) events of ischemic stroke, systemic embolism, myocardial infarction, and vascular death; other bleeding events; procedure-attributable adverse events
Follow-up	3 months	8 weeks	30 days
Major bleeding definitions	BARC, ISTH, TIMI	ISTH	GUSTO, ISTH, TIMI

Abbreviations: BARC, Bleeding Academic Research Consortium; CA, catheter ablation; GUSTO, Global Use of Strategies to Open Occluded Arteries; ISTH, International Society on Thrombosis and Hemostasis; ITT, intention-to-treat; PPA, per protocol analysis; TIA, transient ischemic attack; TIMI, thrombolysis in myocardial infarction.

- BARC—type 2: any overt, actionable sign of hemorrhage requiring non-surgical evaluation by a healthcare professional or hospitalization; type 3a: overt bleeding requiring transfusion or associated with hemoglobin drop of 3–5 g/dL; type 3b: cardiac tamponade or bleeding requiring surgery, vasoactive agents, or associated with a hemoglobin drop ≥5 g/dL; type 3c: intracranial, intraspinal, or intraocular bleed; type 4: CABG-related bleeding; type 5: fatal bleeding.
- GUSTO severe or life-threatening—intracerebral hemorrhage or bleeding resulting in hemodynamic compromise requiring treatment.
- ISTH major bleeding—fatal bleeding, symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular), or bleeding associated with a hemoglobin drop of ≥2 g/dL or requiring transfusion of ≥2 red cell units.
- TIMI major bleeding—intracranial bleeding, clinically overt hemorrhage associated with a hemoglobin drop ≥5 g/dL, or fatal bleeding.

7 | OUTCOMES

7.1 | Major bleeding

In AXAFA-AFNET 5, bleeding with apixaban was comparable to the VKA group according to BARC 2 to 5 criteria (6.2% vs 7.9%, respectively), thrombolysis in myocardial infarction (TIMI) major bleeding criteria (0.3% vs 1%, respectively), and ISTH criteria (3.1% vs 4.4%, respectively) (Table 3). In VENTURE-AF, there was only one major bleeding event in the VKA group vs none in the NOAC group.

In RE-CIRCUIT, ISTH-defined major bleeding outcomes were significantly reduced by uninterrupted dabigatran (1.6%) as compared to uninterrupted warfarin (6.9%), with a hazard ratio of 0.22 (95% CI 0.08-0.59). The mean intraprocedural ACT among patients who had major bleeding was higher in the dabigatran group as compared to the warfarin group (374 vs 314 seconds, respectively). There was no difference between bleeding rates in patients who received dabigatran within 4 hours vs between 4 and 8 hours before ablation. Similarly, in the VKA group, the INR at the time of ablation was not different between the patients with (2.4) vs without (2.3) major bleeding.

A pooled analysis of the three studies (Figure 1A) shows a lower rate of ISTH-defined major bleeding with NOAC (2%) vs VKA (4.9%) (OR 0.40; 95% CI 0.16-0.99; $P = 0.05$). The incidence of cardiac tamponade was also lower with NOAC vs VKA therapy (Figure 1B; OR 0.27; 95% CI 0.07-0.97; $P = 0.04$). Patients with cardiac tamponade (n = 14) were managed with pericardiocentesis (n = 14) and protamine administration (n = 12). Only 2 of the 11 patients with tamponade in the VKA group required reversal with prothrombin complex concentrate. No patient required surgical intervention for tamponade in either group. Idarucizumab, a specific reversal agent for dabigatran, was not used to reverse any major bleeding episode in the RE-CIRCUIT trial.

7.2 | Mortality and thromboembolic outcomes

In AXAFA-AFNET 5, one patient in the VKA group died from intracerebral hemorrhage and another one in the NOAC group died from an unknown cause. In VENTURE-AF, there was a sudden death in the VKA group of unknown cause. No patient died in RE-CIRCUIT. Strokes or TIA were also infrequent: two patients receiving apixaban in AXAFA-AFNET 5, and one patient treated with warfarin in both RE-CIRCUIT and VENTURE-AF. The timing of strokes or TIA in reference to the AF catheter ablation was as follows: same day (1 patient), within the same hospitalization (1 patient), 27 days post-procedure (1 patient), and not specified in one patient.

At least mild cognitive dysfunction was seen in nearly one-third of patients enrolled in AXAFA-AFNET 5 at baseline. Though there was a 7% absolute reduction in the number of patients with cognitive dysfunction at follow-up after ablation, there was no significant difference in cognitive function between groups. Similarly, in their MRI-substudy including 335 patients, acute MRI lesions post-ablation were seen in 27% of apixaban-treated patients vs 25% of those who were randomized to VKAs ($P = 0.63$).

7.3 | Composite outcomes

The primary endpoint of all-cause death, stroke, or major bleeding was not significantly different between apixaban- (6.9%) and VKA- (7.3%) treated patients in the AXAFA-AFNET 5 trial, meeting the pre-specified non-inferiority criteria ($P < 0.01$ for non-inferiority).[7] In RE-CIRCUIT, the composite of thromboembolic events and major bleeding was lower in the dabigatran group (1.6%) vs the warfarin group (7.2%), which was driven entirely by major bleeding because no strokes or deaths were observed in the dabigatran group.[6] In VENTURE-AF, the composite of thromboembolic events (stroke, systemic embolism, myocardial infarction, and vascular death) occurred in

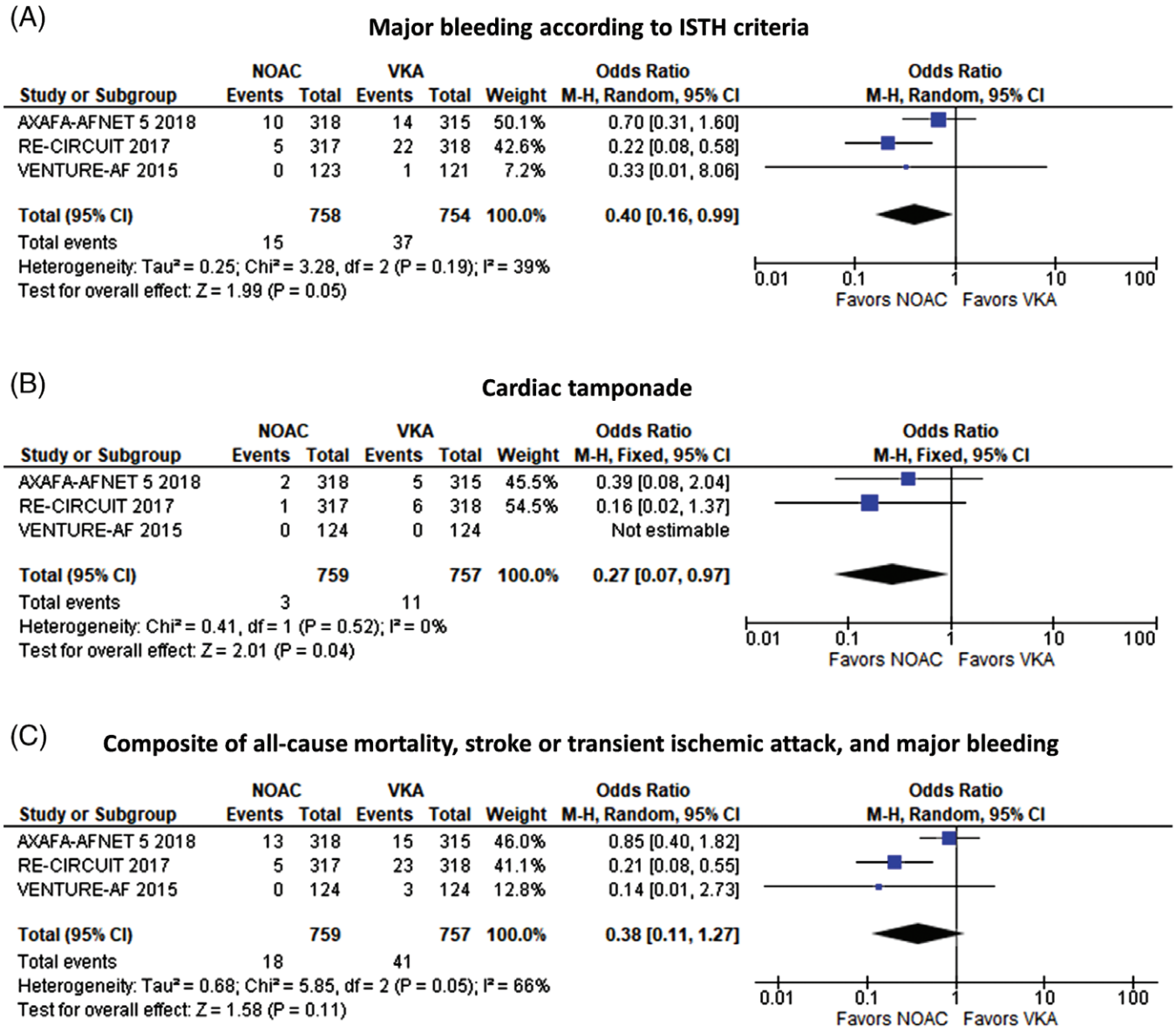

FIGURE 1 The incidence of major bleeding (A) and cardiac tamponade (B) were significantly lower in the non-vitamin K antagonist oral anticoagulants group as compared to vitamin K antagonists. No significant difference between groups was noted in the composite outcome of mortality, stroke or transient ischemic attack, and major bleeding

2 patients treated with VKAs and in none of the rivaroxaban-treated patients.[5] The pooled composite endpoint of mortality, stroke or TIA, and major bleeding between the three studies is reported in Figure 1C, showing no significant difference between groups (OR 0.38; 95% CI 0.11-1.27; P = 0.11).

8 | DISCUSSION

These results attest to the efficacy and safety of an uninterrupted NOAC strategy in patients undergoing AF ablation. The lower numerical incidence of all bleeding endpoints in the NOAC group is reassuring to physicians and patients who wish to avoid switching from a NOAC to warfarin merely for catheter ablation.

Of note, the low incidence of strokes or TIA in these three randomized trials (4/1516; 0.2%) is similar to reports including observational data, which may be more reflective of real-world practice, and substantially lower than the incidence of stroke in studies of interrupted oral anticoagulation. In a meta-analysis of nearly 5000 patients, the incidence of stroke was 0.08% and 0.16% with uninterrupted NOACs and VKAs, respectively.[15] In the COMPARE trial, nearly 5% of patients randomized to warfarin discontinuation with heparin bridging had periprocedural stroke or TIA.[3] Similarly, observational data of NOAC interruption even for less than 24 to 48 hours has been associated with a substantially higher incidence of stroke or TIA (0.5-2%).[16,17]

The recently published AEIOU trial randomized 300 patients undergoing catheter ablation for AF to a strategy of holding one preprocedural dose of apixaban (minimally interrupted) vs uninterrupted anticoagulation with apixaban.[18] There was one TIA in each group, and no stroke or systemic embolism with either strategy. The incidence of major bleeding was similar between the minimally interrupted (2.1%) and uninterrupted (1.3%) strategies. This approach

should be studied further before widely adopted. Until then, clinicians should consider using uninterrupted anticoagulation with NOACs on the basis of the three randomized trials here reported, with a lower incidence of major bleeding compared to uninterrupted VKAs and a lower incidence of thromboembolism compared to historical controls of interrupted anticoagulation.

The incidence of asymptomatic cerebral embolism (ACE) assessed by routine imaging following catheter ablation for AF varies between 2 to 41% in the literature, depending on the definition of ACE and imaging criteria.[19] In AXAFA-AFNET 5, 335 patients underwent brain MRI within 3 to 48 hours of ablation including diffusion-weighted imaging and fluid-attenuated inversion recovery methodology. Approximately one-quarter of patients had an acute brain lesion detected by MRI within 48 hours of catheter ablation, despite a strategy of strict uninterrupted anticoagulation.[7] These findings suggest that some embolic mechanisms may not be preventable with anti-thrombotic therapy, such as air embolism, thermal thrombus related to radiofrequency delivery, or debris from ablation lesions. Of note, in the FIRE and ICE trial, the ablation method did not affect the incidence of stroke or TIA among 762 patients randomized to cryoballoon or radiofrequency ablation. In addition, though the duration of pre-procedure interruption of anticoagulation was not specified, the incidence of stroke or TIA (0.5%) in FIRE and ICE was also numerically higher than the cumulative incidence with uninterrupted anticoagulation (0.2%), as reported here.[20]

With regards to the choice of specific NOAC, two separate drug classes are available. Dabigatran etexilate is a prodrug, converted to the active form in plasma and in the liver. It is a competitive, direct inhibitor of free thrombin and fibrin-bound thrombin, preventing the conversion of fibrinogen to fibrin and therefore clot formation. In contrast, rivaroxaban and apixaban are direct, potent and selective competitive inhibitors of factor Xa. Head-to-head comparisons between thrombin and factor Xa inhibitors, however, are lacking. Nevertheless, factors such as patient age, renal function, and drug interactions can guide individualized treatment.

There is yet another direct factor Xa inhibitor being studied for uninterrupted anticoagulation in patients undergoing AF catheter ablation. The ongoing Edoxaban Compared with VKA in Subjects Undergoing Catheter Ablation of Non-valvular Atrial Fibrillation (ELIMINATE-AF) randomized trial plans to enroll 560 patients to compare uninterrupted edoxaban vs VKA for the primary endpoint of all-cause death, stroke, and major bleeding.[21]

The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of AF supports uninterrupted anticoagulation before catheter ablation for AF in patients treated with warfarin (class I, level of evidence - LOE - A), dabigatran (class I, LOE A), rivaroxaban (class I, LOE B-randomized), and apixaban (class IIa, LOE B-non-randomized).[2] Of note, these guidelines preceded the publication of AXAFA-AFNET 5, which has added randomized evidence supporting uninterrupted anticoagulation with apixaban at the time of AF catheter ablation.[7]

Though the need for hemostatic surgical intervention was not reported in any of the patients receiving NOACs, major bleeding still occurred in 2% of those patients. Therefore, electrophysiologists may consider the use of NOACs with specific reversal agents when planning catheter ablation. At present, only dabigatran has a widely available direct reversal agent, idarucizumab.[22] A reversal agent for factor Xa inhibitors, andexanet alpha, has been recently approved in the US; however, it is not yet widely available.[23]

Finally, the absence of head-to-head comparison and the different risk profiles between the three trials do not allow for a direct comparison between factor IIa (ie, dabigatran) over factor Xa inhibitors. However, dabigatran was the only drug which showed a significantly decreased incidence of major bleeding as compared to VKA in patients undergoing catheter ablation for AF on uninterrupted anticoagulation.

9 | CONCLUSION

In summary, data from three randomized trials including more than 1500 patients attest to the safety and efficacy of uninterrupted anticoagulation with NOACs in patients undergoing catheter ablation for AF. Though the trials had different primary endpoints and objectives, overall findings were consistent between studies. Uninterrupted NOAC therapy was associated with a low incidence of major bleeding (2%), cardiac tamponade (0.4%), and clinical cerebrovascular events (0.2%). These findings support the use of uninterrupted NOACs at the time of AF ablation, as recommended by the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of AF.

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CONFLICTS OF INTEREST

The authors declare no potential conflict of interests.

ORCID

Rhanderson Cardoso https://orcid.org/0000-0003-3622-7605

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