

# Periprocedural Management of Direct Oral Anticoagulants Surrounding Cardioversion and Invasive Electrophysiological Procedures

Shannon W. Finks, PharmD,\* Paul P. Dobesh, PharmD,† Toby C. Trujillo, PharmD,‡ and George H. Crossley, MD, FHRS, FACC§

**Abstract:** As direct oral anticoagulants (DOACs) have demonstrated favorable efficacy and safety outcomes compared with vitamin K antagonists for the treatment and prevention of venous thromboembolism and the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, their role in the management of anticoagulation during electrophysiological procedures continues to evolve. At present, guidelines are limited regarding specific recommendations for the use of DOACs in these clinical settings. Here, we review available data regarding the risks and benefits associated with various periprocedural anticoagulation management approaches when patients receiving DOACs undergo electrophysiologic procedures including cardioversion, ablation, and device implantation. This discussion is intended to provide clinicians with an overview of available evidence and best practices to minimize the risk of both thromboembolic and bleeding events in the periprocedural setting.

**Key Words:** direct oral anticoagulant, anticoagulation, periprocedural management, cardioversion, cardiac ablation, device implantation

(*Cardiology in Review* 2018;26: 245–254)

There are more than 5 million patients with atrial fibrillation (AF) in the United States, a number that is expected to double over the next

From the \*College of Pharmacy, University of Tennessee, Memphis, TN; †College of Pharmacy, University of Nebraska Medical Center, Omaha, NE; ‡College of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO; and §Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN.

Disclosure: Dr P.P.D. is a consultant for Boehringer Ingelheim, Janssen Pharmaceuticals, the BMS/Pfizer Alliance, Daiichi-Sankyo, and Portola Pharmaceuticals. Dr T.C.T. is a consultant for Janssen Pharmaceuticals and the BMS/Pfizer Alliance. Dr G.H.C. is a consultant for Boston Scientific, Medtronic, and Spectranetics; speaker for Medtronic and Spectranetics. Vanderbilt University Medical Center receives fellowship support from Medtronic, Boston Scientific, St. Jude, Biotronik, and Biosense. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors received no direct compensation related to the development of the manuscript.

Writing and editorial support was provided by José L. Walewski, PhD, of Envision Scientific Solutions, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). BIPI was given the opportunity to review the manuscript for medical and scientific accuracy, as well as intellectual property considerations. BIPI had no involvement in the analysis, or interpretation of data or in writing the report.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site ([www.cardiologyinreview.com](http://www.cardiologyinreview.com)).

Correspondence: Shannon W. Finks, PharmD, College of Pharmacy, University of Tennessee, Pharmacy Building Room 459, 881 Madison Ave, Memphis, TN 38163. E-mail: [sfinks@uthsc.edu](mailto:sfinks@uthsc.edu).

Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 1061-5377/18/2605-0000

DOI: 10.1097/CRD.000000000000188

25 years.<sup>1</sup> Similar trends are anticipated for European populations.<sup>2</sup> AF is a significant contributor to morbidity and mortality, conferring a five-fold increase in the risk of stroke, a threefold increase in the risk of heart failure, and a doubling of mortality compared with patients without AF.<sup>1</sup> The direct oral anticoagulants (DOACs) are additional treatment options for the prevention of thromboembolic stroke in the setting of nonvalvular AF, demonstrating at a minimum, efficacy, and safety that is similar to vitamin K antagonists (VKAs). At present, approximately one-half of patients with AF on oral anticoagulants are taking DOACs,<sup>3</sup> and approximately 10% per year will undergo an invasive procedure.<sup>4</sup>

As familiarity with DOACs continues to grow, the use of these agents during electrophysiological procedures is expected to gain greater acceptance. Here, we review the available data regarding risks and benefits associated with periprocedural management strategies when patients who are anticoagulated with DOACs undergo invasive electrophysiological procedures such as cardioversion, ablation, or device implantation. Anticoagulation regimens can utilize VKAs or a DOAC, and can be interrupted or uninterrupted, with or without heparin bridging (Table 1).<sup>5–28</sup> Important differences in pharmacokinetics and pharmacodynamics between VKAs and DOACs underlie differences in their interruption protocols. Additional results from randomized and controlled clinical studies will ensure a better understanding of the appropriate role for DOACs, and will help refine best practices for at-risk patients undergoing cardioversion and electrophysiological procedures.

## ANTICOAGULATION PROTOCOLS FOR CARDIOVERSION

Cardioversion by electrical or pharmacological means is effective for terminating AF and restoring normal sinus rhythm. Patients with hemodynamic instability and those with a known AF onset of <48 hours can undergo immediate cardioversion.<sup>1</sup> If the duration of AF is unknown, or ≥48 hours, the periprocedural risk of thromboembolism can be as high as 7% without anticoagulant therapy.<sup>29</sup> The conventional approach is to provide anticoagulation for at least 3 weeks before, and at least 4 weeks postcardioversion.<sup>1</sup> Observational data suggest that anticoagulation lowers the risk of thromboembolism to approximately 0.5–1.6%,<sup>30</sup> and that thromboembolism is significantly more common with an international normalized ratio (INR) of 1.5–2.4 on warfarin versus an INR of 2.5 or higher before cardioversion (0.93% vs 0%;  $P = 0.012$ ).<sup>31</sup>

After cardioversion, thromboembolic risk is greatest during the first 72 hours, with the majority of events occurring within 10 days.<sup>32</sup> Although the pathophysiology of postcardioversion thrombotic events is not well understood, these may result from the migration of thrombi dislodged during the procedure, or thrombi that form while atrial function is still depressed postcardioversion. The latter is supported by transesophageal echocardiography (TEE) trials, which demonstrate despite restoration of sinus rhythm on electrocardiogram, atrial mechanical dysfunction may persist for several weeks postcardioversion.<sup>33</sup>

By practice guidelines, TEE is used to rule out the presence of a thrombus in the left atrium or left atrial appendage.<sup>1,34</sup> TEE allows

**TABLE 1.** Clinical Trials of Anticoagulation Strategies in Electrophysiology Procedures

Author/Year	Trial Design	OAC Regimen	Efficacy Endpoint*	Safety Endpoint*
<b>Anticoagulation during cardioversion for AF</b>				
Nagarakanti et al (2011) <sup>5</sup>	PHA, RE-LY (n = 1270; 7%)	Dabigatran 110 or 150 mg vs ADW	NSD; stroke and systemic embolism (30 days)	NSD; major bleeding
		TEE if cardioverted within 60 days of randomization		
Piccini et al (2013) <sup>6</sup>	PHA, ROCKET-AF (n = 321; 2.3%)	Rivaroxaban 20 or 15 mg vs ADW	NSD; stroke and systemic embolism or CV death (2.1 years)	NSD; major and clinically relevant nonmajor bleeding (2.1 years)
Flaker et al (2014) <sup>7</sup>	PHA, ARISTOTLE (n = 540; 2.8%)	Apixaban 5 or 2.5 mg BID vs ADW	No stroke or embolic events. NSD; MI or deaths (30 days)	NSD; major bleeding events NSD; deaths
Plitt et al (2016) <sup>8</sup>	PHA, ENGAGE-AF-TIMI 48 (n = 365; 1.7%)	High- (60/30 mg) or low-dose (30/15 mg) edoxaban vs ADW	NSD; stroke or embolic events	NSD; major bleeding
Cappato et al (2014) <sup>9</sup>	X-VerT, a prospective, randomized trial (N = 1504)	Rivaroxaban 20 or 15 mg vs ADW	NSD; primary efficacy endpoint (stroke, TIA, PE, MI, and cardiovascular death)	NSD; major bleeding
		Early = OAC 1–5 days before DCCV (±injectable agent); OAC continued 6 weeks postprocedure Delayed = OAC ≥3 weeks prior; OAC continued 8 weeks postprocedure		
Goette et al (2016) <sup>10</sup>	Randomized, prospective, open-label (N = 2199) (ENSURE-AF)	Edoxaban 60/30 mg daily or enoxaparin bridged to ADW for cardioversion	NSD; event rates between groups (±) TEE guidance	NSD; major bleeding (<1% each) or any bleeding (3% each)
<b>Anticoagulation during cardiac ablation of AF</b>				
<b>Interrupted DOAC therapy during AF ablation</b>				
Lakkireddy et al (2012) <sup>11</sup>	Prospective multicenter observational	Interrupted dabigatran 150 mg BID (n = 145) vs uninterrupted ADW (n = 145); all on OAC >30 days before ablation; morning dose dabigatran held; resumed 3 hours after hemostasis	Higher composite thrombotic and bleeding event rate (dabigatran vs ADW: 16% vs 6%; P = 0.009)	Higher rates of major bleeding (dabigatran vs ADW: 6% vs 1%; P = 0.019)
Bassiouny et al (2013) <sup>12</sup>	Prospective registry	Propensity scoring for baseline-matched cohort (344 patients each, interrupted dabigatran 150 mg BID vs uninterrupted ADW) 1–2 doses of dabigatran held prior, according to physician preference; resumed immediately after sheath removal or when patients were transferred to floor	NSD; thromboembolic events	NSD; major hemorrhages
Kim et al (2013) <sup>13</sup>	Case–control	Interrupted dabigatran 150 mg BID (n = 191) vs uninterrupted ADW (n = 572); all on OAC ≥4 weeks before ablation; dabigatran discontinued 24–30 hours before ablation; resumed 4 hours after hemostasis	No thromboembolic events	NSD; pericardial tamponade
Nin et al (2013) <sup>14</sup>	Randomized, controlled	Interrupted dabigatran 110 mg (n = 45) vs interrupted ADW (n = 45); both OACs held 1 day before procedure; resumed after hemostasis confirmed; no bridging with VKA	NSD; thromboembolic complications	NSD; major and minor bleeding Minor bleeding increased with ADW (OR, 3.2; 95% CI, 1.28–8.49; P = 0.015)
Imamura et al (2013) <sup>15</sup>	Prospective, observational cohort	Interrupted dabigatran (n = 101) vs interrupted VKA with bridging UFH (n = 126). Both agents dosed >1 month before ablation. TEE with both groups. Post ablation dose 3 hours after procedure. Dabigatran was discontinued 12–24 hours before ablation in patients with normal renal function	NSD; thromboembolism	NSD; major or minor bleeding

(Continued)

TABLE 1. (Continued)

Author/Year	Trial Design	OAC Regimen	Efficacy Endpoint*	Safety Endpoint*
<b>Uninterrupted DOAC therapy during AF ablation</b>				
Arshad et al (2014) <sup>16</sup>	Multicenter, retrospective	Uninterrupted ADW (n = 276), dabigatran 150 or 75 mg BID (n = 374), or ADW with heparin bridging (n = 232)	Major complications with ADW (4.3%) vs dabigatran (0.8%) and bridged groups (2.6%; <i>P</i> = 0.01)	Transfusion or major bleeding: (2.1%; uninterrupted ADW) (0.0%; dabigatran) and (1.2%; bridged); <i>P</i> = 0.04
Nagao et al (2015) <sup>17</sup>	Case-controlled	Uninterrupted dabigatran 110 or 150 mg BID (n = 173) vs uninterrupted ADW (n = 190)	NSD; thromboembolic events	NSD; major or minor bleeding events
Maddox et al (2013) <sup>18</sup>	Retrospective analysis	Uninterrupted dabigatran 150 mg BID (n = 212) vs uninterrupted ADW (n = 251)	NSD; thromboembolic complications	NSD; total bleeding complications
Dillier et al (2014) <sup>19</sup>	Single center, retrospective, observational	Uninterrupted rivaroxaban 20 or 15 mg (n = 272) vs uninterrupted phenprocoumon (n = 272; baseline parameter matched)	NSD; thromboembolic events	NSD; major or minor bleeding events
Cappato et al (2015) <sup>20</sup>	Prospective, randomized (VENTURE-AF)	Uninterrupted rivaroxaban 20 mg (n = 124) or uninterrupted ADW (n = 124) before ablation	NSD; thromboembolic events	NSD; major or minor bleeding events
Lakkireddy et al (2014) <sup>21</sup>	Multicenter, observational, prospective registry	Uninterrupted rivaroxaban 20 or 15 mg (n = 321) vs uninterrupted ADW (n = 321)	NSD; embolic complications	NSD; major or minor bleeding complications
Nagao et al (2015) <sup>22</sup>	Retrospective analysis of consecutive cohort	Uninterrupted apixaban 5 or 2.5 mg BID (n = 105) vs uninterrupted ADW (n = 237)	NSD; thromboembolic complications	NSD; safety complications
Di Biase et al (2015) <sup>23</sup>	Prospective multicenter registry, not randomized or controlled	Uninterrupted apixaban 5 or 2.5 mg BID (n = 200) vs uninterrupted ADW (n = 200)	No symptomatic thromboembolic complications	NSD; major or minor bleeding complications
Kaess et al (2015) <sup>24</sup>	Multicenter, retrospective, matched-cohort	Uninterrupted apixaban 5 or 2.5 mg BID (n = 105) or phenprocoumon (n = 210) matched by age, gender, and arrhythmia	NSD; primary endpoint (bleeding, thromboembolic events, and death)	NSD; major or minor bleeding
Calkins et al (2017) <sup>25</sup>	Multicenter, prospective, randomized (RE-CIRCUIT)	Uninterrupted dabigatran 150 mg BID (n = 317) vs ADW (n = 318)	Lower incidence of major bleeding events with dabigatran (1.6% vs 6.9%; <i>P</i> < 0.001)	NSD; minor bleeding events
<b>Anticoagulation during CIED surgery</b>				
Kosiuk et al (2014) <sup>26</sup>	Case-control observational cohort	Interrupted dabigatran, 110 or 150 mg (n = 93) vs interrupted rivaroxaban, 15 or 20 mg (n = 83); the last preintervention DOAC dose was omitted (dabigatran = 24 hours; rivaroxaban = 36 hours preprocedure). First postprocedure DOAC dose was left to discretion of the implanting physician	NSD; days to discharge	NSD; bleeding events
Kosiuk et al (2014) <sup>27</sup>	Prospective case-control	Interrupted dabigatran 110 or 150 mg (n = 118) vs uninterrupted ADW (n = 118) to an INR of 2–3. For dabigatran-experienced patients, anticoagulation was discontinued 12 hours before, and readministered 24 hours (IQR 0–48 hours) postprocedurally	Shorter discharge time with dabigatran (2.5 ± 2.3 vs 3.8 ± 4.1 days; <i>P</i> = 0.002)	Greater postprocedural blood loss (reduced hemoglobin) with warfarin; <i>P</i> = 0.023)
Jennings et al (2013) <sup>28</sup>	Case-control cohort	Uninterrupted dabigatran 75 or 150 mg BID (n = 48) vs uninterrupted ADW (n = 195)	NSD	NSD; bleeding complications

ADW indicates, adjusted-dose warfarin; AF, atrial fibrillation; aPTT, activated partial thromboplastin time; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BID, twice daily; CI, confidence interval; CIED, cardiac implantable electrical device; DCCV, direct-current cardioversion; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; ENSURE-AF, Edoxaban vs Enoxaparin-Warfarin in Patients Undergoing Cardioversion of Atrial Fibrillation; MI, myocardial infarction; NA, not applicable; NSD, no significant difference; OAC, oral anticoagulation; OR, odds ratio; PE, peripheral embolism; PHA, post hoc analysis; RE-CIRCUIT, Randomized Evaluation of Dabigatran Etxilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TEE, transesophageal echocardiography; TIA, transient ischemic attack; UFH, unfractionated heparin; VENTURE-AF, A Randomized, Open-label, Active-controlled Multicenter Study to Assess Safety of Uninterrupted Rivaroxaban versus Usual Care in Subjects Undergoing Catheter Ablation Therapy for Atrial Fibrillation; VKA, vitamin K antagonist; X-VerT, Explore the Efficacy and Safety of Once Daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Patients With Nonvalvular Atrial Fibrillation Scheduled for Cardioversion.

\*Thirty-day event rate.

immediate cardioversion in patients without a detectable thrombus, avoiding 3 weeks of precardioversion anticoagulation. Evidence suggests comparable risks of thromboembolic events between the TEE-guided strategy and conventional anticoagulation for 3 weeks, with significantly less bleeding risk in the precardioversion period.<sup>35</sup> A TEE-guided strategy requires periprocedural anticoagulation, traditionally involving the parenteral anticoagulants, unfractionated heparin (UFH), or low molecular-weight heparin, followed by oral anticoagulation for  $\geq 1$  month postcardioversion if no thrombus is detected.

## THE ROLE OF DOACS IN CARADIOVERSION

Evidence supporting the use of DOACs during cardioversion procedures has been generated by both retrospective and randomized trials. Each pivotal phase 3 DOAC trial in AF included a posthoc subanalysis of patients undergoing cardioversion<sup>5–8</sup> (Table 1, Figure 1A). Thrombotic event rates ranged from 0.0% in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, to 0.9% in the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial (due to different patient risk profiles).<sup>36–38</sup> Since most patients had persistent or permanent AF (68%–84%), proportions undergoing cardioversion were low (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY], 7%; ROCKET AF, 2%; ARISTOTLE, 3%).<sup>36–38</sup>

In the posthoc analysis of the RE-LY trial, there were 1983 cardioversions in 1270 patients (dabigatran 110 mg,  $n = 647$ ; dabigatran 150 mg,  $n = 672$ ; and warfarin  $n = 664$ ).<sup>5</sup> Continuous treatment with study drug for  $\geq 3$  weeks before cardioversion was lower in patients receiving dabigatran 110 mg (76.4%) or dabigatran 150 mg (79.2%) when compared with patients receiving warfarin (85.5%;  $P < 0.01$  for both).<sup>5</sup> No significant differences were reported in the rates of stroke and systemic embolism at 30 days (0.8% for dabigatran 110 mg,  $P = 0.7087$  vs warfarin; 0.3% for dabigatran 150,  $P = 0.4048$  vs warfarin; and 0.6% for warfarin), with or without TEE.

Data from the other posthoc analyses suggest the efficacy and safety of the direct Xa inhibitors in cardioversion are similar to those demonstrated with dabigatran. While the outcomes in patients receiving cardioversion or catheter ablation procedures were only provided at the end of the 2.1 years of follow-up and not at 30 days in the ROCKET-AF trial, the incidence of all efficacy outcomes were low and not significantly different between patients receiving rivaroxaban compared with warfarin, including stroke, systemic embolism, and cardiovascular death (3.1% vs 4.4%).<sup>6</sup> No stroke events were noted in either group (apixaban versus warfarin) in the ARISTOTLE trial at 30 days.<sup>7</sup> There was 1 death and 2 myocardial infarctions in each group. There were also no stroke events with the use of edoxaban at 30 days in the ENGAGE-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48), with 1 death in the edoxaban group compared to warfarin at 30 days.<sup>8</sup> None of the posthoc analyses of the DOAC trials demonstrated a difference in bleeding events compared with warfarin in patients undergoing cardioversion.<sup>5–8</sup>

The first prospective trial to evaluate a DOAC for cardioversion was the Explore the Efficacy and Safety of Once Daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Patients With Nonvalvular Atrial Fibrillation Scheduled for Cardioversion trial (X-VerT).<sup>9</sup> Patients with hemodynamically stable AF  $\geq 48$  hours ( $n = 1504$ ) were randomized 2:1 to open-label

rivaroxaban (20 mg or 15 mg daily based on renal function) or VKA with a goal INR of 2–3. The early cardioversion protocol included TEE, and rivaroxaban or a VKA ( $\pm$ injectable anticoagulant) 1–5 days precardioversion, through 6 weeks postcardioversion. For delayed cardioversions, patients received rivaroxaban or a VKA for 3–8 weeks prior, and continued for 6 weeks postcardioversion. The primary efficacy endpoint was the composite of stroke, systemic embolism, myocardial infarction, or cardiovascular death.<sup>9</sup> The primary safety analysis was major bleeding by ISTH (International Society of Thrombosis and Haemostasis) criteria.<sup>39</sup>

Of 1167 patients cardioverted, 87% achieved normal sinus rhythm.<sup>9</sup> With the early approach, the median time from randomization to cardioversion was 1 day for both groups ( $P = 0.628$ ). With the delayed approach, the median time was significantly shorter with rivaroxaban versus VKA [22 days (21–26) vs 30 days (23–42);  $P < 0.001$ ]. At 3 weeks, more patients on rivaroxaban in the delayed group cardioverted successfully versus those on VKA (77% vs 36%;  $P < 0.001$ ), most likely due to the fact that more patients in the VKA-treated group were unable to achieve adequate anticoagulation before cardioversion by this time point (95 patients compared with 1 patient in the rivaroxaban group).<sup>9</sup>

At 6 weeks postcardioversion, no significant differences were reported between rivaroxaban and VKA for the primary endpoint (early or delayed cardioversion), nor were there significant differences in major, critical site, intracranial, or fatal bleeding rates.<sup>9</sup>

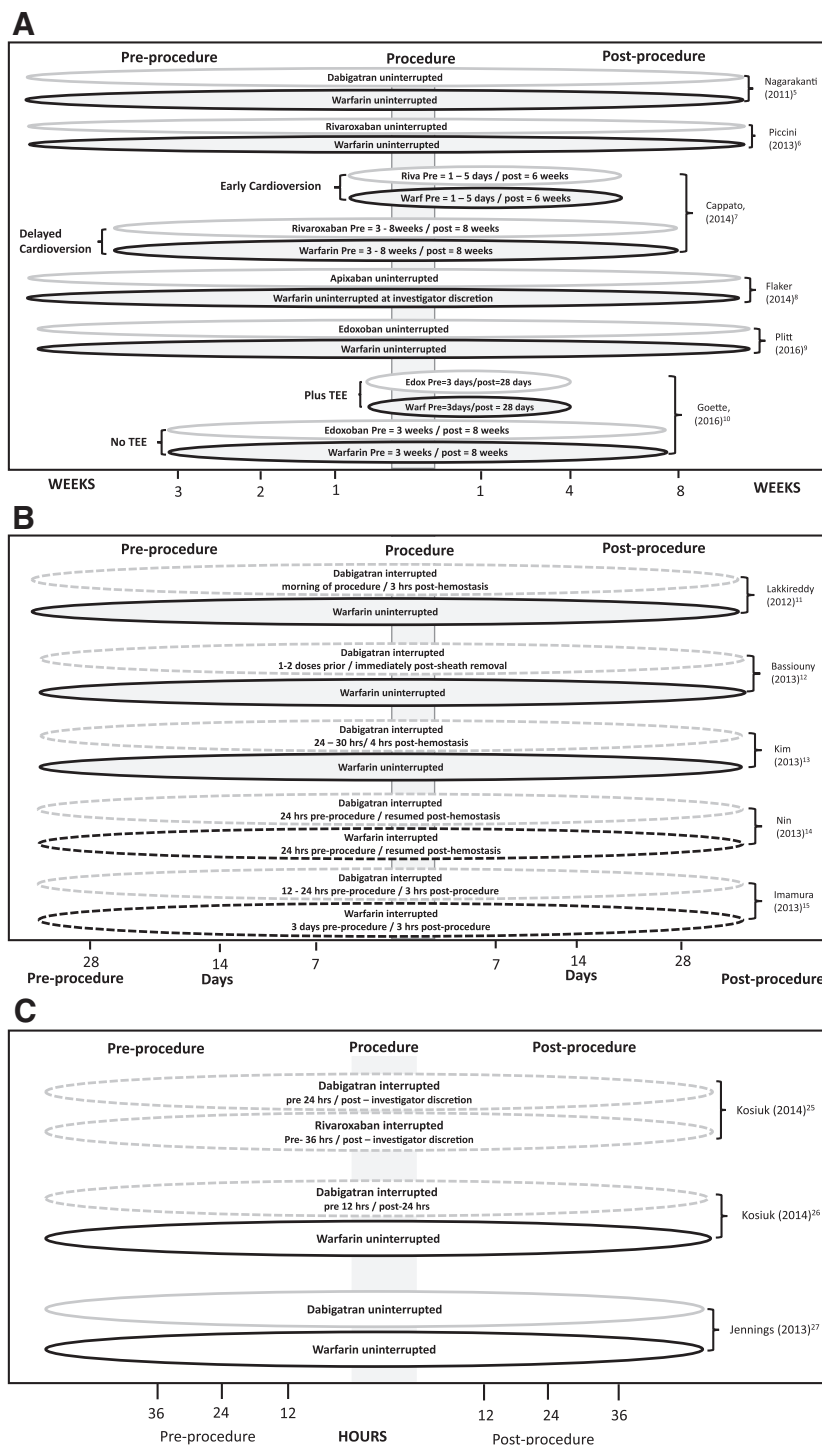
Edoxaban was evaluated in the prospective, open-label Edoxaban versus Enoxaparin-Warfarin in Patients Undergoing Cardioversion of Atrial Fibrillation (ENSURE-AF) trial.<sup>10</sup> Patients ( $n = 2199$ ) with nonvalvular AF  $\geq 48$  hours with planned electrical cardioversion were randomized 1:1 to edoxaban 60 mg daily or enoxaparin bridged to warfarin. Patients underwent TEE-guided early cardioversion, or delayed cardioversion, both followed by 28 days of postcardioversion anticoagulation. The primary efficacy endpoint was the composite of stroke, systemic embolism, myocardial infarction, or cardiovascular death 4 weeks after cardioversion. The primary safety endpoint was the combination of major and clinically relevant nonmajor bleeding by International Society on Thrombosis and Haemostasis criteria.<sup>39</sup>

Normal sinus rhythm was achieved by 89% of patients.<sup>10</sup> The primary efficacy endpoint incidence 4 weeks after cardioversion was not significantly different between edoxaban and warfarin [0.46% vs 1.0%; odds ratio, 0.46; 95% confidence interval, 0.12–1.43]. There were no significant differences in event rates in the TEE-guided stratum (0.34% vs 0.84%) or the non-TEE-guided stratum (0.59% vs 1.12%; edoxaban vs warfarin, respectively). The primary safety endpoint occurred in 1% of both groups at 4 weeks postcardioversion, and there were no significant differences in rates of major, or any, bleeding events.<sup>10</sup>

Finally, patient satisfaction may be greater with DOAC-associated cardioversion. In the X-VerT (X-VerT) trial, patients undergoing delayed cardioversion on rivaroxaban reported greater convenience (80.3% vs 66.7%), better effectiveness (38.8% vs 34.4%), and higher global satisfaction (81.7% vs 67.5%; all  $P$  values  $< 0.0001$ ) compared with patients receiving VKA. No significant differences were noted in rates of side effects. Similar results were reported with the early approach.<sup>40</sup>

Advantages associated with DOAC use during cardioversion include faster therapeutic anticoagulation, reduced time to cardioversion, avoidance of periprocedural parenteral bridging, and improved patient satisfaction versus VKAs.<sup>1,41</sup> Shorter times to cardioversion have been reported in studies with dabigatran<sup>42</sup> and with rivaroxaban,<sup>9</sup> that can reduce delays in care, potentially reducing costs.<sup>40</sup>





**FIGURE 1.** A, Anticoagulation during cardioversion for AF: ovals represent periods of anticoagulation; those that extend beyond the marked timeframes on the x axis indicate ongoing treatment. Where applicable, dosing timeframes are listed within individual ovals. B, Anticoagulation during cardiac ablation of AF (protocols with at least 1 interrupted treatment arm). Ovals represent periods of anticoagulation; those that extend beyond the marked timeframes on the x axis indicate ongoing treatment. Protocols with interrupted anticoagulation dosing are noted by dashed line boundaries. Where applicable, dosing interruption timeframes are listed within individual ovals. C, Anticoagulation during cardioversion during CIED procedures. Ovals represent periods of anticoagulation. Those that extend beyond the marked timeframes on the x axis indicate ongoing treatment. Protocols with interrupted anticoagulation dosing are noted by dashed line boundaries. Where applicable, dosing interruption timeframes are listed within individual ovals. AF indicates atrial fibrillation; CIED, cardiac implantable electric devices; TEE, transesophageal echocardiography.

## ANTICOAGULATION PROTOCOLS FOR ABLATION OF AF

Catheter ablation has emerged as a viable option for the control of AF and atrial flutter.<sup>43</sup> However, this procedure increases the risk of thromboembolism via several mechanisms, including cardioversion, thrombus formation after transseptal puncture, thrombus formation on the ablation catheter, endothelial damage, and “stunning” of the atrial myocardium.<sup>44</sup>

Periprocedural OAC protocols involve balancing the risks of bleeding, mainly due to cardiac perforation, versus systemic thrombosis. Historical management of periprocedural anticoagulation involved warfarin discontinuation 3–5 days before ablation, with heparin or enoxaparin bridging, followed by re-establishing warfarin (INR 2–3) for at least 8 weeks. However, the failure to maintain a therapeutic INR over the preceding 3 weeks or to maintain an activated clotting time (ACT) of >300 seconds during ablation were associated with elevated thrombosis risk in the periprocedural window.<sup>45</sup> Current guidelines recommend 3 weeks of anticoagulation before catheter ablation in patients with AF ≥48 hours to mitigate thrombosis risk.<sup>1,2</sup> Alternatively, TEE may allow ablation to proceed without delay.<sup>1,2</sup> Results from the COMPARE (Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation Patients Undergoing Catheter Ablation), a randomized prospective trial, demonstrated that uninterrupted periprocedural warfarin lowers bleeding complications and reduces clinical and silent thromboembolic events versus interrupted warfarin in this setting.<sup>43,46</sup> Therefore, current guidelines allow patients on warfarin to continue therapy (INR 2–3) throughout the procedure.<sup>2,34</sup>

As experience with DOACs has become more widespread in AF, both minimally interrupted therapy (withholding 1–2 DOAC doses prior, then resuming 4–6 hours postprocedure pending hemostasis), or uninterrupted DOAC therapy have been proposed for ablation.<sup>1,41</sup> Studies have evaluated DOACs versus VKAs in this setting, most utilizing both minimally interrupted, or uninterrupted approaches, and no adverse safety signal has been identified (Table 1).<sup>47,48</sup>

Most reports regarding dabigatran for ablation are non-randomized studies (almost all with interrupted dabigatran). Two meta-analyses comparing outcomes between dabigatran versus warfarin in the setting of catheter ablation reported no differences in bleeding or thromboembolic events.<sup>49,50</sup> Both analyses highlighted the limitations of nonrandomized observational study designs and variable therapeutic protocols. Within that context, the Randomized Evaluation of Dabigatran Etexilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy (RE-CIR-CUIT) trial, a randomized, controlled open-label trial examined the safety of uninterrupted dabigatran (n = 317) versus warfarin (n = 318) in patients undergoing AF ablation.<sup>25</sup> Regimen adherence to dabigatran was high (mean = 97.6%), and INR-adjusted warfarin patients were in the target INR range of 2.0–3.0 for 66% of the time.<sup>25</sup> Uninterrupted anticoagulation began 4–8 weeks before ablation, and continued for 8 weeks postprocedure in 635 patients. UFH was used intraprocedurally to achieve an ACT of >300 seconds in both arms. The primary endpoint was major bleeding, with minor bleeding and thrombotic events as secondary endpoints from initial femoral puncture, through 8 weeks postprocedure. Dabigatran-treated patients had a lower incidence of major bleeding [n = 5 (1.6%)] compared to those receiving warfarin [n = 22 (6.9%)], an absolute risk difference of –5.3% [95% confidence interval, –8.4% to –2.2%; *P* < 0.001]. Dabigatran-treated patients experienced fewer pericardial tamponades than patients treated with warfarin (n = 1 vs n = 6, respectively), and groin hematomas (n = 0 vs n = 8), although minor bleeding event rates were similar.

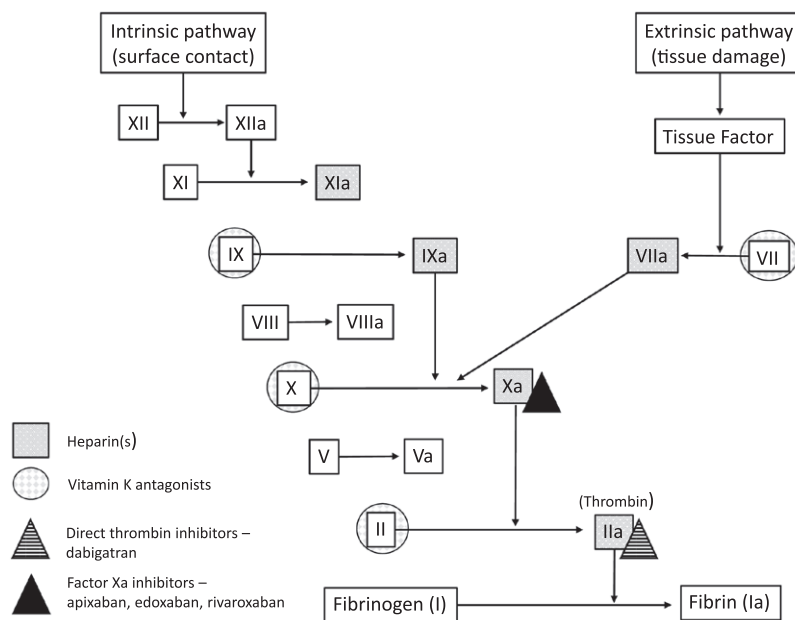
No differences were noted in thromboembolic event [stroke, systemic embolism, or transient ischemic attack (TIA)] rates between groups (none with dabigatran, 1 TIA with warfarin).<sup>25</sup> Patients on INR-adjusted warfarin were within the guideline-defined target INR range (2.0–3.0) 66% of the time. However, their incidence rates for major bleeding events were independent of the mean INR at the time of ablation, which was similar in both patients who experienced a major bleed, and those who did not (2.4 and 2.3, respectively).<sup>25</sup>

Similar to dabigatran, trials with rivaroxaban suggest comparable safety to uninterrupted warfarin. Two meta-analyses, each incorporating 8 studies, showed equivalent periprocedural efficacy, bleeding risks, and thromboembolic risks between VKA and rivaroxaban.<sup>51,52</sup>

A VENTURE-AF (Randomized, Open-label, Active-controlled Multicenter Study to Assess Safety of Uninterrupted Rivaroxaban versus Usual Care in Subjects Undergoing Catheter Ablation Therapy for Atrial Fibrillation) trial, a prospective randomized study in patients undergoing catheter ablation for AF, compared safety and efficacy in 124 patients receiving uninterrupted rivaroxaban 20 mg once daily to 124 patients titrated to an INR of 2.0–3.0 on uninterrupted warfarin, beginning before, and extending 4 weeks postprocedure.<sup>20</sup> This target INR range was achieved by 79.8% of patients on warfarin during the primary endpoint period. UFH was used intraprocedurally to achieve an ACT of 300–400 seconds in both arms. There was no significant difference between groups in the primary endpoint, the incidence of major bleeding in the first 30 ± 5 days postprocedure (0.4%, 1 event for VKA; 0.0% for rivaroxaban). Thromboembolic events were also low (0.8%; 1 ischemic stroke and 1 vascular death, both with VKA; 0.0% with rivaroxaban). In addition, the number of any adjudicated events (26 vs 25), any bleeding events (21 vs 18), or any other procedure-attributable events (5 vs 5), rivaroxaban versus VKA, respectively, were low and not statistically different between groups.<sup>20</sup>

Apixaban also demonstrated safety and efficacy comparable to VKA in a prospective, open-label, randomized, multicenter study monitoring complications after catheter ablation for AF in Japanese patients.<sup>53</sup> Patients were randomized to uninterrupted apixaban (5 or 2.5 mg twice daily; n = 100) or warfarin (INR, 2–3; n = 100) ≥1 month before AF ablation. More heparin was administered to maintain an ACT >300 seconds with apixaban (14,000 ± 4000 units) than with warfarin (9000 ± 3000 units; *P* < 0.0001).<sup>53</sup> Primary outcomes were stroke, TIA, silent cerebral infarction, or major bleeding that required intervention. Three primary outcome events were reported in each group (*P* = 1.00). In addition, 3 secondary outcome events occurred with apixaban and 4 with warfarin (*P* = 0.70).<sup>53</sup> It is anticipated that the ongoing AXAFA AFNET 5 (Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy) study will provide additional insights regarding the relative safety and efficacy of periprocedural anticoagulation with either apixaban or a VKA in patients undergoing catheter ablation of AF.<sup>54</sup>

Intraprocedural UFH is utilized during cardiac ablation regardless of therapy interruption strategy. Most algorithms to determine specific dosing of UFH and subsequent ACT monitoring for use during the procedure have been extrapolated from patients receiving VKA (with INR data). Although failure to achieve and maintain an ACT ≥ 300 seconds intraprocedurally is associated with thrombotic events, an optimal ACT threshold for when patients receive DOACs has yet to be defined. In the VENTURE-AF trial, slightly higher doses of heparin were required with rivaroxaban (13,871 vs 10,964 units for warfarin; *P* < 0.001); however, this did not equate to an increased number of bleeding events.<sup>20</sup> Likewise, observational experience suggests that higher doses of UFH are required with minimally interrupted DOAC therapy (in comparison to protocols utilizing uninterrupted VKA).



**FIGURE 2.** The intrinsic and extrinsic clotting pathways, including the sites of action (clotting inhibition by VKAs, heparins, and DOACs). Reproduced with permission from *Clin Ther* 2012;34:2051–2060.

The 2017 HRS/EHRA/ECAS/APHS/SOLAECE consensus statement on catheter and surgical ablation of AF recommends performing ablation for AF with uninterrupted dabigatran or rivaroxaban (level of evidence A, or B-R recommendations, respectively), or the other factor Xa inhibitors (apixaban, edoxaban; each with level of evidence 2A recommendations).<sup>34</sup> In addition, new and ongoing trials with larger sample sizes are expected to provide further information regarding best practices for AF ablation-related anticoagulation. These experimental protocols include uninterrupted or minimally interrupted DOAC regimens, whether intraprocedural anticoagulation should include dosing and monitoring of UFH, when is the appropriate time to resume interrupted DOAC therapy postprocedure, and the management of any bleeding complications, especially in patient subgroups with different risk factors. Ongoing and recently completed clinical trials to assess the safety and efficacy of periprocedural DOACs during ablation are summarized in Supplementary Table 1; <http://links.lww.com/CIR/A14>.

## ANTICOAGULATION PROTOCOLS FOR CARDIAC IMPLANTABLE ELECTRIC DEVICES

The management of anticoagulation during a cardiac implantable electric devices (CIED) procedure can present challenges for electrophysiologists. Bleeding complications can significantly increase the risk for pocket hematomas, extended hospital stays, and elevated overall costs.<sup>1,26,28</sup>

The traditional approach has been interrupted OAC for the procedure, and UFH or enoxaparin as a bridge until therapeutic OAC is reestablished, which has been associated with significant hematoma formation and infection.<sup>55</sup> The current standard-of-care is to perform pulse generator replacements on fully anticoagulated patients. For CIED, uninterrupted warfarin therapy is superior to interrupted warfarin with heparin bridging with regard to bleeding complications.<sup>56</sup> At present, reports of DOAC safety and efficacy for CIED are limited to case-control and cohort studies; therefore, randomized and controlled studies are needed in this area. DOAC use during CIED procedures is expected to expand as data from randomized studies emerge.

## BEST PRACTICES APPROACH TO USE DOAC AGENTS

### Pharmacokinetic Considerations

Unlike warfarin's indirect mechanism-of-action (inhibition of clotting factor synthesis), DOACs rapidly and directly inhibit key components of the coagulation cascade (Figure 2). After oral administration, all DOACs achieve peak concentrations within 1–3 hours, providing quick, predictable, and concentration-dependent anticoagulation.<sup>57</sup> This is advantageous particularly at the time of therapy initiation, as bridging with UFH or low molecular-weight heparin can be avoided. Key considerations for withholding periprocedural DOACs include the dosing interval, primary route of elimination, concomitant use of antiplatelet agents or other drugs influencing plasma concentrations, and baseline bleeding risk of the surgical/procedural intervention. Renal function is important because all DOACs are eliminated at least in part via the kidney (Table 2).<sup>58–61</sup> Creatinine clearance should be determined to assess baseline risk for drug accumulation. With half-lives of 7–14 hours, DOACs typically reach subtherapeutic concentrations 24–48 hours after the last dose, allowing patients to be unprotected for shorter periods than with warfarin.<sup>57</sup> Dabigatran, which is most dependent on renal function (80% renal clearance) may need to be withheld for longer periods, depending on baseline creatinine clearance and bleeding risk associated with the upcoming procedure. Like other drugs that are metabolized at least in part by the liver, the DOACs should not be coadministered with P-glycoprotein inducers like rifampin (which reduces exposure to DOACs<sup>58,59</sup>) and prescribed with caution or avoided in patients with renal insufficiency who are comedicated with P-glycoprotein inhibitors (dabigatran<sup>58</sup>). Similar precautions are noted for comedication with strong inducers of the P-glycoprotein and 3A4 pathways, where dosing with apixaban,<sup>60</sup> and rivaroxaban<sup>61</sup> should be avoided. Apixaban doses should be lowered or avoided,<sup>60</sup> and rivaroxaban should be avoided<sup>61</sup> when coadministered with strong dual inhibitors of P-glycoprotein and 3A4 (Table 2).

### Therapy Interruption Considerations

The American College of Cardiology classifies AF ablation and CIED as low risk for bleeding with possible intermediate risk

**TABLE 2.** Basic Pharmacological Properties of Approved DOACs

DOAC	Onset (hours)	T1/2 (hours)	Protein Binding (%)	Renal Excretion (%)	Metabolic Pathways
Apixaban <sup>60</sup>	3–4	~12	~87	~27	3A4 + P-gp
Dabigatran <sup>58</sup>	2	12–17	~35	~80	P-gp
Edoxaban <sup>59</sup>	1–2	10–14	~55	~50	P-gp
Rivaroxaban <sup>61</sup>	3	11–13	92–95%	~36	3A4 + P-gp

3A4 indicates cytochrome P450 3A4; DOAC, direct oral anticoagulant; P-gp, P-glycoprotein.

under extreme circumstances, supporting continuous periprocedural OAC.<sup>62</sup> There is early evidence supporting uninterrupted therapy during cardiac procedures such as cardioversion, AF ablation, and device implantation with minimal bleeding. Yet, interruptions in therapy may be considered for patients at highest risk for bleeding based on factors including renal and hepatic function, potential drug–drug interactions, and the availability of anticoagulation reversal agents.

When anticoagulant interruption is desired, the timing of such is important. Both European<sup>41</sup> and US<sup>62</sup> guidelines suggest performing surgeries with minimal to no bleeding risk at trough OAC plasma concentrations (12 or 24 hours after the last dose depending on dosing interval), with resumption 6–8 hours later.<sup>41</sup> Peak OAC plasma concentrations should be avoided. Most studies addressing AF ablation, where therapy was interrupted, held the morning dose of the DOAC, thereby providing the requisite 12- to 24-hour pause. For interventions with risk of increased or major bleeding events, DOACs should be discontinued 24 or 48 hours preoperatively, respectively, in patients with normal renal function, and longer with renal insufficiency.<sup>41</sup>

For procedures where complete hemostasis is expected, the DOAC can safely be resumed 6–8 hours after the intervention.<sup>41</sup> Protocols for electrophysiological procedures include resumption of anticoagulation 3–4 hours after vascular hemostasis has been achieved after sheath removal. For higher risk procedures, resumption may be delayed up to 48 hours, while acknowledging that the risk for cardioembolism increases with time. To date, no safety or efficacy data support a reduced periprocedural DOAC dose in patients with AF.

### Reversal of DOACs

Although major or cerebrovascular bleeds are less likely to occur with DOACs than with warfarin, rapid reversal of DOAC-induced anticoagulation may be needed in rare instances such as severe bleeding situations, or when emergency surgeries are required. With non–life-threatening periprocedural bleeding, interruption of DOAC therapy for 12–24 hours may restore hemostasis in patients with normal renal function.<sup>41</sup> For patients on dabigatran, in cases of life-threatening bleeding or when an emergency surgical procedure is required, idarucizumab can rapidly and specifically reverse dabigatran-associated anticoagulation, with normalization of ecarin clotting and dilute thrombin times within minutes, an effect that is sustained to 24 hours.<sup>63</sup> These initial findings were confirmed in the subsequent full cohort analysis (N = 503 patients), where idarucizumab rapidly and effectively reversed the anticoagulation effect of dabigatran, while demonstrating rates of thrombosis that were lower than those reported in studies of prothrombin complex concentrates for the reversal of VKAs.<sup>64</sup> For other anticoagulants, clinical trials with andexanet alfa (for the reversal of Factor Xa inhibitors) and ciraparantag, a broad spectrum agent to reverse the effects of factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban, the direct thrombin inhibitor dabigatran, and low molecular weight and UFH, are currently underway.<sup>65,66</sup>

### CONCLUSIONS

Emerging data suggest that DOACs have similar safety and efficacy outcomes as VKAs when administered in the setting of electrophysiological procedures such as cardioversion, AF ablation, and CIED. Advantages with the DOACs for these procedures include convenience, rapid, and predictable onset of action, elimination of periprocedural parenteral anticoagulation, and patient satisfaction. Therapeutic anticoagulation with DOACs during cardioversion does not increase risk for major thromboembolic or bleeding events as compared with VKAs. Shorter times to cardioversion have been reported with the use of DOACs, rather than traditional VKA which typically requires a 3-week delay and verification of therapeutic INR, unless bridging with heparin is utilized when no existing thromboembolism is found on TEE. Existing studies of DOAC therapy during cardiac ablation for AF have employed protocols with uninterrupted,<sup>16–25</sup> and minimally interrupted DOAC therapies,<sup>11–15</sup> which reported outcomes similar to those with protocols relying on VKA. The recent Heart Rhythm Society guidelines recommend that heparin should be administered before, or immediately after transseptal puncture during AF catheter ablation, with ongoing monitoring to achieve and maintain an ACT of at least 300 seconds.<sup>34</sup> Consensus guidelines suggest that most cardiac procedures carry a low risk for bleeding and therefore ongoing anticoagulation can be continuous throughout most procedures. However, minimal interruption may still be prudent for patients at highest risk for bleeding, including those with renal impairment and/or having significant drug–drug interactions that are likely to lead to anticoagulant accumulation. In most situations when therapy is interrupted, reinitiation of the DOAC after AF ablation can occur within hours after vascular hemostasis is achieved, limiting the time frame when a patient is unprotected from thromboembolic events. At present, the use of DOACs during CIED procedures is the area with the greatest need for additional data from randomized and controlled trials.

### REFERENCES

1. January CT, Wann LS, Alpert JS, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1–76.
2. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
3. Huisman MV, Rothman KJ, Paquette M, et al; GLORIA-AF Investigators. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF Registry Phase 2. *J Am Coll Cardiol*. 2017;69:777–785.
4. Healey JS, Eikelboom J, Douketis J, et al; RE-LY Investigators. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation*. 2012;126:343–348.
5. Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation*. 2011;123:131–136.



6. Piccini JP, Stevens SR, Likhnygina Y, et al; ROCKET AF Steering Committee & Investigators. Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. *J Am Coll Cardiol*. 2013;61:1998–2006.
7. Flaker G, Lopes RD, Al-Khatib SM, et al; ARISTOTLE Committees and Investigators. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *J Am Coll Cardiol*. 2014;63:1082–1087.
8. Plitt A, Ezekowitz MD, De Caterina R, et al; ENGAGE AF-TIMI 48 Investigators. Cardioversion of atrial fibrillation in ENGAGE AF-TIMI 48. *Clin Cardiol*. 2016;39:345–346.
9. Cappato R, Ezekowitz MD, Klein AL, et al; X-Vert Investigators. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J*. 2014;35:3346–3355.
10. Goette A, Merino JL, Ezekowitz MD, et al; ENSURE-AF investigators. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet*. 2016;388:1995–2003.
11. Lakkireddy D, Reddy YM, Di Biase L, et al. Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. *J Am Coll Cardiol*. 2012;59:1168–1174.
12. Bassiouny M, Saliba W, Rickard J, et al. Use of dabigatran for periprocedural anticoagulation in patients undergoing catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2013;6:460–466.
13. Kim JS, She F, Jongnarangsin K, et al. Dabigatran vs warfarin for radiofrequency catheter ablation of atrial fibrillation. *Heart Rhythm*. 2013;10:483–489.
14. Nin T, Sairaku A, Yoshida Y, et al. A randomized controlled trial of dabigatran versus warfarin for periblation anticoagulation in patients undergoing ablation of atrial fibrillation. *Pacing Clin Electrophysiol*. 2013;36:172–179.
15. Imamura K, Yoshida A, Takei A, et al. Dabigatran in the peri-procedural period for radiofrequency ablation of atrial fibrillation: efficacy, safety, and impact on duration of hospital stay. *J Interv Card Electrophysiol*. 2013;37:223–231.
16. Arshad A, Johnson CK, Mittal S, et al. Comparative safety of periblation anticoagulation strategies for atrial fibrillation: data from a large multicenter study. *Pacing Clin Electrophysiol*. 2014;37:665–673.
17. Nagao T, Inden Y, Shimano M, et al. Feasibility and safety of uninterrupted dabigatran therapy in patients undergoing ablation for atrial fibrillation. *Intern Med*. 2015;54:1167–1173.
18. Maddox W, Kay GN, Yamada T, et al. Dabigatran versus warfarin therapy for uninterrupted oral anticoagulation during atrial fibrillation ablation. *J Cardiovasc Electrophysiol*. 2013;24:861–865.
19. Dillier R, Ammar S, Hessling G, et al. Safety of continuous periprocedural rivaroxaban for patients undergoing left atrial catheter ablation procedures. *Circ Arrhythm Electrophysiol*. 2014;7:576–582.
20. Cappato R, Marchlinski FE, Hohnloser SH, et al; VENTURE-AF Investigators. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. *Eur Heart J*. 2015;36:1805–1811.
21. Lakkireddy D, Reddy YM, Di Biase L, et al. 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.
22. Nagao T, Inden Y, Shimano M, et al. Efficacy and safety of apixaban in the patients undergoing the ablation of atrial fibrillation. *Pacing Clin Electrophysiol*. 2015;38:155–163.
23. Di Biase L, Lakkireddy D, Trivedi C, et al. 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.
24. Kaess BM, Ammar S, Reents T, et al. 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.
25. Calkins H, Willems S, Gerstenfeld EP, et al; RE-CIRCUIT Investigators. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. *N Engl J Med*. 2017;376:1627–1636.
26. Kosiuk J, Koutalas E, Doering M, et al. Treatment with novel oral anticoagulants in a real-world cohort of patients undergoing cardiac rhythm device implantations. *Europace*. 2014;16:1028–1032.
27. Kosiuk J, Koutalas E, Doering M, et al. Comparison of dabigatran and uninterrupted warfarin in patients with atrial fibrillation undergoing cardiac rhythm device implantations. Case-control study. *Circ J*. 2014;78:2402–2407.
28. Jennings JM, Robichaux R, McElderry HT, et al. Cardiovascular implantable electronic device implantation with uninterrupted dabigatran: comparison to uninterrupted warfarin. *J Cardiovasc Electrophysiol*. 2013;24:1125–1129.
29. Arnold AZ, Mick MJ, Mazurek RP, et al. Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. *J Am Coll Cardiol*. 1992;19:851–855.
30. Moreyra E, Finkelhor RS, Cebul RD. Limitations of transesophageal echocardiography in the risk assessment of patients before nonanticoagulated cardioversion from atrial fibrillation and flutter: an analysis of pooled trials. *Am Heart J*. 1995;129:71–75.
31. Gallagher MM, Hennessy BJ, Edvardsson N, et al. Embolic complications of direct current cardioversion of atrial arrhythmias: association with low intensity of anticoagulation at the time of cardioversion. *J Am Coll Cardiol*. 2002;40:926–933.
32. Berger M, Schweitzer P. Timing of thromboembolic events after electrical cardioversion of atrial fibrillation or flutter: a retrospective analysis. *Am J Cardiol*. 1998;82:1545–7, A8.
33. Manning WJ, Leeman DE, Gotch PJ, et al. Pulsed Doppler evaluation of atrial mechanical function after electrical cardioversion of atrial fibrillation. *J Am Coll Cardiol*. 1989;13:617–623.
34. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017;14:e275–e444.
35. Klein AL, Grimm RA, Murray RD, et al; Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med*. 2001;344:1411–1420.
36. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
37. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
38. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
39. Schulman S, Angerås U, Bergqvist D, et al; 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 antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8:202–204.
40. Hohnloser SH, Cappato R, Ezekowitz MD, et al; X-Vert Steering Committee and Investigators. Patient-reported treatment satisfaction and budget impact with rivaroxaban vs. standard therapy in elective cardioversion of atrial fibrillation: a post hoc analysis of the X-Vert trial. *Europace*. 2016;18:184–190.
41. Heidbuechel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;17:1467–1507.
42. Pallisgaard JL, Lindhardt TB, Hansen ML, et al. Cardioversion and risk of adverse events with dabigatran versus warfarin—a nationwide cohort study. *PLoS One*. 2015;10:e0141377.
43. Link MS, Haïssaguerre M, Natale A. Ablation of atrial fibrillation: patient selection, periprocedural anticoagulation, techniques, and preventive measures after ablation. *Circulation*. 2016;134:339–352.
44. Zak M, Castiblanco SA, Garg J, et al. Periprocedural management of new oral anticoagulants in atrial fibrillation ablation. *J Cardiovasc Pharmacol Ther*. 2015;20:457–464.
45. Abed HS, Chen V, Kilborn MJ, et al. periprocedural management of novel oral anticoagulants during atrial fibrillation ablation: controversies and review of the current evidence. *Heart Lung Circ*. 2016;25:1164–1176.
46. Di Biase L, Burkhardt JD, Santangeli P, et al. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. *Circulation*. 2014;129:2638–2644.
47. Nagao T, Inden Y, Yanagisawa S, et al. Differences in activated clotting time among uninterrupted anticoagulants during the periprocedural period of atrial fibrillation ablation. *Heart Rhythm*. 2015;12:1972–1978.
48. Rillig A, Lin T, Plesman J, et al. Apixaban, rivaroxaban, and dabigatran in patients undergoing atrial fibrillation ablation. *J Cardiovasc Electrophysiol*. 2016;27:147–153.

49. Phan K, Wang N, Pison L, et al. Meta-analysis of dabigatran vs warfarin in patients undergoing catheter ablation for atrial fibrillation. *Int J Cardiol*. 2015;189:199–203.
50. Providência R, Albenque JP, Combes S, et al. Safety and efficacy of dabigatran versus warfarin in patients undergoing catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Heart*. 2014;100:324–335.
51. Aryal MR, Ukaigwe A, Pandit A, et al. Meta-analysis of efficacy and safety of rivaroxaban compared with warfarin or dabigatran in patients undergoing catheter ablation for atrial fibrillation. *Am J Cardiol*. 2014;114:577–582.
52. Phan K, Wang N, Pison L, et al. Rivaroxaban versus warfarin or dabigatran in patients undergoing catheter ablation for atrial fibrillation: a meta-analysis. *Int J Cardiol*. 2015;185:209–213.
53. Kuwahara T, Abe M, Yamaki M, et al. Apixaban versus warfarin for the prevention of periprocedural cerebral thromboembolism in atrial fibrillation ablation: multicenter prospective randomized study. *J Cardiovasc Electrophysiol*. 2016;27:549–554.
54. Di Biase L, Callans D, Hæusler KG, et al. Rationale and design of AXAFA-AFNET 5: an investigator-initiated, randomized, open, blinded outcome assessment, multicentre trial to comparing continuous apixaban to vitamin K antagonists in patients undergoing atrial fibrillation catheter ablation. *Europace*. 2017;19:132–138.
55. Robinson M, Healey JS, Eikelboom J, et al. Postoperative low-molecular-weight heparin bridging is associated with an increase in wound hematoma following surgery for pacemakers and implantable defibrillators. *Pacing Clin Electrophysiol*. 2009;32:378–382.
56. Birnie DH, Healey JS, Wells GA, et al; BRUISE CONTROL Investigators. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med*. 2013;368:2084–2093.
57. Finks SW, Trujillo TC, Dobesh PP. Management of venous thromboembolism: recent advances in oral anticoagulation therapy. *Ann Pharmacother*. 2016;50:486–501.
58. Boehringer Ingelheim Pharmaceuticals Inc. Prescribing information (07/2017) Pradaxa® (dabigatran etexilate mesylate) capsules, for oral use. Available at: <http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf>. Accessed October 25, 2017.
59. Daiichi Sankyo Inc. Prescribing information (09/2017) Savaysa® (edoxaban) tablets, for oral use. Available at: <http://dsi.com/prescribing-information-portlet/getPIContent?productName=Savaysa&inline=true>. Accessed October 25, 2017.
60. Bristol-Myers Squibb Company. Prescribing information (04/2017) Eliquis® (apixaban) tablets, for oral use. Available at: [http://packageinserts.bms.com/pi/pi\\_eliquis.pdf](http://packageinserts.bms.com/pi/pi_eliquis.pdf). Accessed July 6, 2017.
61. Janssen Pharmaceuticals Inc. Prescribing information (03/2017) Xarelto® (rivaroxaban) tablets, for oral use. Available at: <https://www.xarelto-us.com/shared/product/xarelto/prescribing-information.pdf>. Accessed July 6, 2017.
62. Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. *J Am Coll Cardiol*. 2017;69:871–898.
63. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511–520.
64. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377:431–441.
65. Rogers KC, Shelton MP, Finks SW. Reversal agents for direct oral anticoagulants: understanding new and upcoming options. *Cardiol Rev*. 2016;24:310–315.
66. Finks SW, Rogers KC. Idarucizumab (Praxbind): the first reversal agent for a direct oral anticoagulant. *Am J Med*. 2017;130:e195–e197.