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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Antithrombotic Therapy for Patients Undergoing Cardiac Electrophysiological and Interventional Procedures

JACC State-of-the-Art Review

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ABSTRACT

Electrophysiological and interventional procedures have been increasingly used to reduce morbidity and mortality in patients experiencing cardiovascular diseases. Although antithrombotic therapies are critical to reduce the risk of stroke or other thromboembolic events, they can nonetheless increase the bleeding hazard. This is even more true in an aging population undergoing cardiac procedures in which the combination of oral anticoagulants and antiplatelet therapies would further increase the hemorrhagic risk. Hence, the timing, dose, and combination of antithrombotic therapies should be carefully chosen in each case. However, the maze of society guidelines and consensus documents published so far have progressively led to a hazier scenario in this setting. Aim of this review is to provide—in a single document—a quick, evidenced-based practical summary of the antithrombotic approaches used in different cardiac electrophysiology and interventional procedures to guide the busy clinician and the cardiac proceduralist in their everyday practice.
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HIGHLIGHTS

- Cardiac electrophysiological and other interventional procedures can usually be performed safely without interrupting (or only briefly interrupting) oral anticoagulants.
- OAC can be combined with a single antiplatelet agent and is feasible in patients with AF undergoing PCI.
- The long-term antithrombotic strategy should be individualized based on the balance of thromboembolic and hemorrhagic risks.

Cardiac electrophysiology and interventional procedures are performed in a progressively aging population. These include catheter ablation of cardiac arrhythmias, implantation of cardiac devices (cardiac implantable electronic devices [CIEDs]), electrical/pharmacological cardioversion, percutaneous closure of the left atrial appendage (LAA) (left atrial appendage occlusion [LAAO]), transcatheter aortic valve replacement (TAVR), transcatheter mitral valve repair (TMVR) and transcatheter mitral valve implantation (TMVI), and percutaneous coronary intervention (PCI). As catheter manipulation in the heart can be thrombogenic per se and patients frequently present with comorbidities that require the use of oral anticoagulation (OAC), clinicians should balance the thromboembolism (TE) against the bleeding risk in each case. On the behalf of the American College of Cardiology and Electrophysiology and Interventional Council, the aim of this review is to provide an evidenced-based practical perspective on the perioperative use of different antithrombotic strategies during cardiac interventions. For this purpose, an evidence-based description of the antithrombotic strategies utilized for specific cardiac interventions is provided for each section followed by bullet-point paragraphs summarizing practical suggestions supported by the corresponding class of recommendations and level of evidence (Table 1). In case of specific antithrombotic strategies not addressed or mentioned by society documents, the writing group provided practical suggestions based on the available evidence in each field.

PHARMACOLOGIC CONSIDERATIONS ON OAC

Major characteristics of direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) are displayed in Table 2. Over the years, DOACs have been increasingly used for their superiority or noninferiority over VKAs.[1-8] When DOACS are used, the following pharmacokinetic aspects should be considered.

ABSORPTION. For absorption, periprocedural heparin bridging is no longer required because DOACs achieve peak plasma levels within 2 to 4 hours after oral administration.[9] Rivaroxaban should be administered after meals due to enhanced absorption by food intake (Table 2). Capsule fracture should be avoided in case of dabigatran administration due to its low bioavailability.[9]

HALF-LIFE. DOACs display shorter half-life than VKAs (ie, 5-17 hours),[9] with faster effects due to rapid steady-state plasma concentrations. Despite overlapping half-lives between DOACs (Table 2), rivaroxaban and edoxaban are the unique DOACs recommended for once daily administration for TE prophylaxis for atrial fibrillation (AF) and venous thromboembolism.[3,4,9]

EXCRETION. For excretion, differently from VKAs, DOAC dose adjustment is needed for renal impairment.[9] Dabigatran is excreted mostly in its active form in the urine and should be avoided for creatinine clearance (CrCl) <30 mL/min and used with great caution when CrCl is 30 to 50 mL/min.[9] Likewise, due to the lack of data, factor Xa inhibitors are not recommended in patients with a CrCl <15 mL/min.[9]

CATHETER ABLATION OF AF

Pulmonary vein isolation—the cornerstone of catheter ablation of AF—is associated with a nontrivial incidence of hemorrhagic complications (3%) and TE events (1%)[10,11] with magnetic resonance imaging-detected silent cerebral lesions occurring in up to 2% to 40% of cases.[12] Although their clinical impact is still under debate,[13] the energy source used during ablation seems to lead to these cerebral lesions through different mechanisms. Clot formation and embolism may ensue from prolonged catheter dwelling in the left atrium (LA), longer time to therapeutic activated clotted time, extensive LA substrate ablation, and finally, need for periprocedural electrical cardioversions during the procedure.[14] On the other hand, cryoballoon ablation may cause air embolism due to catheter exchanging through the same transseptal sheath.[15] Therefore, adequate antithrombotic strategies and proper catheter handling are

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CIED = cardiac implantable electronic device
DAPT = dual antiplatelet therapy
DOAC = direct oral anticoagulant
LAAEI = left atrial appendage electrical isolation
LAAO = left atrial appendage occlusion
OAC = oral anticoagulation
PCI = percutaneous coronary intervention
SAPT = single antiplatelet therapy
TAVR = transcatheter aortic valve replacement
TMVI = transcatheter mitral valve implantation
TMVR = transcatheter mitral valve repair
VKA = vitamin K antagonist

TABLE 1 Summary of Definitions of Level of Confidence and Class of Recommendations Used in Guidelines and Consensus Documents

	Definition	Suggested Wording to Use
Class		
I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	—
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.	Should be considered
IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended
Level of Evidence		
A	Data derived from multiple randomized clinical trials or meta-analyses.	
B	Data derived from a single randomized clinical trial or large nonrandomized studies.	
C	Consensus of opinion of the experts and/or small studies, retrospective studies, and registries.	

paramount before, during, and postprocedure to prevent TE events in this setting.

PERIPROCEDURAL ANTICOAGULATION FOR CATHETER ABLATION OF AF. Historically, periprocedural OAC management in patients undergoing AF ablation entailed VKA discontinuation with heparin bridging. Over the years, a body of evidence proved the superiority of uninterrupted vs interrupted VKA strategy for periprocedural TE events[12,16] without increasing the risk of major bleeding or pericardial effusion.[16-18] In this regard, multiple randomized controlled trials (RCTs)[13,18-23] investigated the role of strategies based on uninterrupted DOACs vs VKAs in AF patients undergoing pulmonary vein isolation and found that uninterrupted DOACs were noninferior to uninterrupted VKAs regarding the evaluated hemorrhagic and ischemic hazards (Table 3). Likewise, a meta-analysis of these trials demonstrated a significantly reduced risk of major bleeding for patients on uninterrupted DOACs vs uninterrupted VKAs, with no difference in minor bleeding and silent cerebral lesions.[24] Different DOAC strategies during pulmonary vein isolation were investigated as well. Although RCTs comparing truly and minimally interrupted DOACs (ie, <12 hours) are not available, a descriptive meta-analysis assessing the pooled weighted mean incidence of overall bleeding for different periprocedural DOAC approaches (eg, uninterrupted, mildly interrupted and interrupted DOACS strategies) showed a slight increase of the bleeding risk for a strategy based on minimally interrupted (8.62%; 95% CI: 5.16-12.86) vs uninterrupted (6.33%; 95% CI: 3.65-9.68), and fully interrupted DOACs (3.53%; 95% CI: 2.11-5.29) in 8,362 patients undergoing AF ablation.[25] Regarding the TE risk, another meta-analysis including 18 studies accounting for 6,203 patients showed no difference for the risk of symptomatic TE events between groups.[26] However, an uninterrupted DOAC strategy was associated with a significant reduction in the rate of silent cerebral lesions detected on brain magnetic resonance imaging when compared with minimally interrupted DOACs (OR: 0.44; 95% CI: 0.23-0.83; $P = 0.01$).[26] Taken together, uninterrupted DOAC therapy should likely be the preferred OAC in patients undergoing AF ablation.[9,17] More studies are needed to assess the safety and efficacy of minimally interrupted DOACs vs fully uninterrupted DOACs in this setting.

Evidence-based practical approach at a glance.

- For patients undergoing AF ablation and therapeutically anticoagulated with VKAs or DOACs, catheter ablation should be performed without OAC interruption (Class I, Level of Evidence: A).[27]
- Uninterrupted DOACs should be the preferred strategy in eligible patients (eg, patients without mechanical heart valves, thrombophilia, or other clear indications for VKAs) (Class I, Level of Evidence: A).[27,28]

INTRAPROCEDURAL ANTICOAGULATION FOR CATHETER ABLATION OF AF. Unfractionated heparin should be administered before or immediately after transseptal puncture to achieve and maintain an activated clotting time of 300 to 400 seconds.[9,17] Although the amount of heparin required to achieve such target may be higher in patients on factor Xa inhibitors,[29] it may be reasonable to use the same value in all patients on an uninterrupted OAC strategy.[9] Furthermore, heparin should be preferably administered right before transseptal puncture because the incidence of cerebral lesions seems even lower in this setting.[12] Finally, administration of protamine to reverse heparin effect is reasonable after AF ablation, recognizing that adverse reactions such as significant hypotension can happen in 1% of patients.[30]

Evidence-based practical approach at a glance.

- Unfractionated heparin should be administered after femoral venous access and before transseptal puncture to reduce the risk of TE events. After transseptal access, additional boluses of unfractionated heparin are required to maintain an activated clotting time of 300 to 400 seconds (Class I, Level of Evidence: B).[17]
- Administration of protamine is reasonable before sheath removal to facilitate adequate hemostasis (Class IIa, Level of Evidence: B).[17]

TABLE 2 Characteristics of Most Commonly Used Anticoagulation Agents

	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Mechanism of action	VKORC1 inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Bioavailability	~100%	7%	~50%	66% fasting, 80% with food	~62%
Time to peak effect	72-96 h	1 h, 2 h with food	3-4 h	2-4 h	1-2 h
Half-life	7 d	12-17 h	5-9 h	8-15 h	10-14 h
Protein binding	97%	35%	~87%	92%-95%	55%
Excretion	92% renal	80% renal	27% renal	66% liver, 33% renal	50% renal
Dosing	Target to desired international normalized ratio	150 mg twice daily: dose reduction to 75 mg orally twice daily if the CrCl (estimated using actual body weight) is 15-30 mL/min. Dose reduction is not recommended for patients with ESRD in the 2019 ACC/AHA/HRS AF guideline focused update.[60] 110 mg twice daily The FDA has not approved this dose for use in AF in the United States. In the European label, a twice daily dose of 110 mg is suggested for patients >80 years of age and "for consideration" for those 75-80 years of age.	5 mg twice daily: dose reduction to 2.5 mg orally twice daily if the patient meets at least 2 of the following 3 characteristics: age >80 y, actual body weight <60 kg, and/or serum creatinine >1.5 mg/dL. Patients with ESRD receiving hemodialysis were not enrolled in clinical trials. However, the prescribing information suggests no dosing adjustment for patients with ESRD unless they have additional dose reduction characteristics.	20 mg once a day: dose reduction to 15 mg orally once daily with the evening meal for patients with CrCl (estimated using actual body weight) <50 mL/min. Patients with ESRD were not enrolled in clinical trials. Dose reduction not recommended for patients with ESRD in the 2019 ACC/AHA/HRS AF guideline focused update.[60]	60 mg once a day recommended for patients with a CrCl (estimated using actual body weight) of 51-95 mL/min (not recommended for patients with a CrCl >95 mL/min). Dose reduction to 30 mg orally once daily if the CrCl is 15-50 mL/min. No dosing recommendations in ESRD.

ACC = American College of Cardiology; AF = atrial fibrillation; AHA = American Heart Association; CrCl = creatinine clearance; ESRD = end-stage renal disease; FDA = Food and Drug Administration; HRS = Heart Rhythm Society.

POSTPROCEDURAL ANTICOAGULATION FOLLOWING CATHETER ABLATION OF AF. Because there are no RCTs evaluating the optimal OAC strategy after AF ablation, the decision on whether to continue OAC depends on the individual patient TE/hemorrhagic risk. Although recurrent and asymptomatic AF post-ablation would justify the benefit of long-term OAC (**Table 4**),[31-34] it would expose low-risk patients (CHA_2DS_2-VASc score <2) to an increased risk of minor and major bleeding (**Table 5**).[35-40] However, observational studies showed that discontinuation of OAC can be associated with an increased risk of stroke in a population at high risk for TE events (CHA_2DS_2-VASc score ≥2).[33] Similar results were also reported in a recently published meta-analysis.[41] Therefore, patients with a high risk of TE based on CHA_2DS_2-VASc score should be continued indefinitely on OAC until new evidence becomes available. Two ongoing trials, the OAT (Safety of Oral Anticoagulation Therapy Withdrawal After Successful Cardiac Ablation in Patients with AF and Associated High Risk Factors for Embolic Events; NCT01959425) trial and the OCEAN (Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for AF; NCT02168829) trial, will help clarify whether OAC discontinuation after AF ablation is safe. **Figure 1** summarizes the current evidence on the periprocedural management of anticoagulation for patients undergoing AF ablation.

Evidence-based practical approach at a glance.

- The decision on OAC continuation after the blanking period postablation (ie, 2-3 months) should be primarily based on the CHA_2DS_2-VASc score and not on ablation success/failure (Class I, Level of Evidence: C).[17,27]
- In patients with a high TE risk (eg, CHA_2DS_2-VASc score ≥2 in males and CHA_2DS_2-VASc score ≥3 in females), continuation of OAC is recommended (Class I, Level of Evidence: C),[17,27] and DOACs should be preferred over VKAs.[1-4,24]
- In patients at high risk of bleeding (eg, previous bleeding from an unidentified or uncontrollable source, known bleeding disorder) and TE events (eg, CHA_2DS_2-VASc score ≥2), LAAO can be considered as an alternative to OAC (Class IIb, Level of Evidence: B).[28]

SPECIAL CONSIDERATIONS OF OAC IN PATIENTS UNDERGOING AF ABLATION. Elderly Patients. Because comorbidities may expose elderly people (>75 years of age) to an exceedingly high risk of TE and hemorrhagic complications postablation,[42] a patient-tailored approach is required. Small-sized studies suggest that—compared with younger patients—uninterrupted OAC may be associated with a higher bleeding risk with overlapping TE hazard in elderly patients undergoing AF ablation.[43,44] However, lower

TABLE 3 Major Trials of Preprocedural Anticoagulation for Catheter Ablation of AF

	COMPARE[18] (N = 1,584)	VENTURE-AF[19] (N = 248)	ASCERTAIN[20] (N = 132)	RE-CIRCUIT[21] (N = 704)	AXAFA-AFNET5[13] (N = 674)	Kuwahara et al[22] (N = 200)	ELIMINATE-AF[23] (N = 632)
Trial design	Open label, randomized	Open label, randomized	Open label, randomized	Open label, randomized	Open label, randomized	Open label, randomized	Open label, randomized
Type of AF	Paroxysmal 27% Nonparoxysmal 63%	Paroxysmal 74% Nonparoxysmal 26%	Paroxysmal 61% Nonparoxysmal 39%	Paroxysmal 67% Nonparoxysmal 33%	Paroxysmal 58% Nonparoxysmal 42%	Paroxysmal 60% Nonparoxysmal 40%	Paroxysmal 67.6% Nonparoxysmal 32.4%
Treatment arms	Uninterrupted VKA vs VKA with LMWH bridge	Uninterrupted rivaroxaban vs Uninterrupted VKA	Uninterrupted rivaroxaban vs uninterrupted VKA	Uninterrupted dabigatran vs uninterrupted VKA	Uninterrupted apixaban vs uninterrupted VKA	Uninterrupted apixaban vs uninterrupted VKA	Uninterrupted edoxaban vs uninterrupted VKA
Thromboembolic events	RR: 0.051 (95% CI: 0.012-0.211)	0% vs 0.8% (P = NS)	Silent cerebral lesions 15.6% vs 15.9% (P = 1.00)	0% vs 0.003% (P = NS)	Stroke/TIA 0.6% vs 0% (P = NS) Silent cerebral lesions 31.2% vs 24.8% (P = NS)	Silent cerebral lesions 2% vs 3% (P = NS)	Silent cerebral lesions 13.8% vs 9.6% (P = NS)
Bleeding events	Major 0.76% vs 0.38 (P = 0.31) Minor 22% vs 4.1% (P < 0.001)	All events: 0% vs 0.4% (P = NS)	Major 3.1% vs 1.6% (P = NS) Minor 18.8% vs 19% (P = NS)	Major 1.6% vs 6.9% P < 0.001 Minor 18.6% vs 17% (P = NS)	Major 6.2% vs 7.9% (P = NS)	Major 1% vs 0% (P = NS) Minor 3% vs 4% (P = NS)	Major 0.3% vs 2% (P = NS)

AF = atrial fibrillation; ASCERTAIN = Asymptomatic Cerebral Infarction During Catheter Ablation for Atrial Fibrillation: Comparing Uninterrupted Rivaroxaban and Warfarin; AXAFA-AFNET5 = Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation; COMPARE = 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 Patients Undergoing Catheter Ablation randomized trial; ELIMINATE-AF = Uninterrupted edoxaban vs. vitamin K antagonists for ablation of atrial fibrillation; LMWH = low-molecular-weight heparin; RE-CIRCUIT = Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation; VENTURE-AF = Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation; VKA = vitamin K antagonist.

TE/bleeding events were observed in elderly patients on uninterrupted DOACs,[45] especially in those on apixaban.[46] Despite this evidence, there are no RCTs comparing different antithrombotic strategies in this frail population.

Evidence-based practical approach at a glance.

- In elderly patients undergoing AF ablation, uninterrupted OAC should be considered to reduce the risk of TE events (authors' suggestions based on current evidence in the field).[43,44]
- DOACs, particularly apixaban, should be considered the preferred treatment choice in elderly patients (>75 years) without a clear indication for the use of VKA such as mechanical heart valves (authors' suggestions based on current evidence in the field).[45,46]
- LAAO might be considered in elderly patients at increased TE risk and high bleeding hazard on long-term OAC (Class IIb, Level of Evidence: B).[28]

Chronic kidney disease. Although Yanagisawa et al[47] showed that chronic kidney disease (CKD) is associated with a significantly higher incidence of bleeding than TE risk, data on patients undergoing AF ablation are scarce. Therefore, data on patients with CKD on OAC should be extrapolated from studies investigating the general CKD population with AF. In this regard, the safety profile of DOACs seems to be at least noninferior or even superior to VKA in patients with CrCl <50 mL/min.[48-50] Although Coleman et al showed that rivaroxaban was associated with a relative risk reduction in bleeding of 32% with an overlapping risk of stroke or systemic embolism compared with VKA treatment in patients in hemodialysis,[28,51] in a recently published network meta-analysis, apixaban was the only DOAC not to be associated with an increased bleeding hazard in end-stage renal disease.[52] However, no significant impact on the risk of stroke has been demonstrated for apixaban 5 mg BID in observational studies conducted on this population.[53]

Evidence-based practical approach at a glance.

- OAC should be considered during the first 2 to 3 months after AF ablation to reduce the risk of periprocedural stroke even in CKD patients. The decision to continue OAC after 2 months should be based on the TE/hemorrhagic risk (Class I, Level of Evidence: C).[17,27]
- For patients with AF and CHA_2DS_2-VASc score ≥2 in men or ≥3 in women and with end-stage CKD (CrCl <15 mL/min) or on dialysis, it might be reasonable to prescribe apixaban (Class IIb, Level of Evidence: B).[28]

Left atrial appendage electrical isolation. Beyond pulmonary vein isolation, catheter ablation of non-pulmonary vein triggers including left atrial appendage electrical isolation (LAAEI)[54,55] has progressively emerged as a treatment option to improve outcomes in patients with persistent and long-standing persistent AF undergoing ablation.[54] Although a body of evidence has reported the

TABLE 4 Studies Against Stopping Anticoagulation After Catheter Ablation of AF

First Author	Year	Design	AF Type	Sample Size	Outcomes
Hindricks et al[31]	2005	Prospective cohort	Paroxysmal persistent	114	Asymptomatic recurrences increased from 5% preablation to 37% postablation.
Verma et al[32]	2013	Prospective multicenter cohort	Symptomatic	50	The ratio of asymptomatic to symptomatic AF episodes increased postablation from 1.1 before to 3.7 after ablation.
Noseworthy et al[33]	2015	Retrospective	Paroxysmal Persistent	6,886	The risk of cardioembolism beyond 3 mo was increased in high-risk patients (CHA_2DS_2-VASc score ≥2) off anticoagulation (HR: 2.48; 95% CI: 1.11-5.52; $P < 0.05$) but not in low-risk patients.
Takigawa et al[34]	2014	Prospective observational	Paroxysmal	1,156	Late (>6 mo) incidence of thromboembolism postablation of AF was low (0.78%), and all patients with recurrence of AF were asymptomatic. A $CHADS_2$ score ≥2 was independently associated with thromboembolism.

AF = atrial fibrillation.

benefit of LAAEI on top of pulmonary vein isolation to improve maintenance of sinus rhythm in these patients,[56,57] LAAEI entails the electrical disconnection of the left atrial appendage (LAA) from the LA, thus leading to the potential impairment of LAA mechanical function and the ensuing increased TE hazard, especially in patients without adequate anticoagulation regimens.[58] Therefore, OAC or LAAO devices are mandatory in this setting.[59-61] Because the temporary suspension of OAC due to surgical, endoscopic, or dental procedures may increase the TE hazard in these patients,[62] LAAO seems even more appealing in this scenario. **Figure 2** displays a proposed algorithm for the management of patients undergoing LAAEI.

Evidence-based practical approach at a glance.

- Patients undergoing LAAEI should remain on lifelong therapeutic OAC regardless of the CHA_2DS_2-VASc score (authors' suggestions based on current evidence in the field).[60]
- In patients undergoing LAAEI and not deemed suitable for lifelong OAC (eg, high bleeding risk), LAAO is considered a reasonable alternative to prevent TE events (authors' suggestions based on current evidence in the field).[60]

PERIPROCEDURAL ANTICOAGULATION IN LAA CLOSURE

The burden of comorbidities[63] and nonadherence to therapy[64] may expose patients on OAC to an exceedingly high risk of TE and hemorrhagic complications, especially in an elderly population.[63] For this reason, LAAO has been developed for stroke prevention as an alternative to OAC in AF. Percutaneous LAAO can be performed by the Amulet (Abbott), WATCHMAN (Boston Scientific), and LARIAT (SentreHEART) devices, whereas LAA clipping (AtriClip, AtriCure) is a surgical alternative to percutaneous LAAO. The best antithrombotic regimen is yet to be established in these patients and WATCHMAN device has been mostly investigated. Current therapies are based on large clinical studies[65-67] and summarized in a recently published expert consensus document.[68] They commonly entail 6-month dual antiplatelet therapy (DAPT) post-LAAO[69] or postprocedural treatment with OAC plus aspirin.[66,67] When this latter strategy is adopted, OAC is discontinued 45 days post-LAAO if transesophageal echocardiography (TEE) proves adequate LAA closure. Then, 6-month DAPT with aspirin plus clopidogrel is instituted followed by long-term aspirin.[66,67] However, the role of antiplatelet therapy seems unclear due to evidence of enhanced coagulation cascade without platelet activation after LAAO.[69] In fact, the ADRIFT (Assessment of DAPT Versus Rivaroxaban in AF Patients Treated with Left Atrial Appendage Closure) trial proved that, similarly to DAPT, rivaroxaban was not associated with device-related thromboses after 3 months of follow-up.[70] Likewise, in a vast multicenter prospective study, Della Rocca et al[71] showed that, after successful WATCHMAN implantation, long-term half-dose DOACs significantly reduced the risk of the composite endpoint of device-related thrombosis and major bleeding events compared with standard antiplatelet-based therapy. Therefore, not only is a short-term DOAC regimen feasible after LAAO,[68,72] but long-term, low-dose DOACs seem even safer than the standard full-dose DOAC regimens.[71] **Figure 3** shows potential antithrombotic strategies in patients undergoing LAAO with a WATCHMAN device. As for the other percutaneous devices, LARIAT devices do not require postprocedural OAC due to LAA ligation through pericardial access that would limit the risk for device-related thrombosis.[73]

TABLE 5 Studies in Favor of Stopping Anticoagulation After Catheter Ablation of AF

First Author	Year	Design	AF Type	Sample Size	Outcomes
Nademanee et al[35]	2008	Prospective cohort, single center Catheter substrate ablation of AF guided by CFAE	Paroxysmal, persistent, LSPAF	674	VKA therapy was discontinued in 434 (84%) of 517 patients in sinus rhythm postablation. The annual stroke rate was 0.4% off VKA compared with 2% on VKA treatment ($P = 0.004$).
Themistoclakis et al[36]	2010	Multicenter retrospective	Paroxysmal, persistent LSPAF	2,692	Patients discontinued anticoagulation from 3 to 6 mo after successful ablation of AF. A total of 2 (0.07%) patients off anticoagulation and 3 (0.45%) patients on anticoagulation had an ischemic stroke ($P = 0.06$). The major bleeding rate was 0.04% off anticoagulation and 2% on anticoagulation ($P < 0.0001$).
Bunch et al[37]	2013	Case-control study	Paroxysmal, persistent, LSPAF	4,212 post-AF ablation 16,848 AF control subjects without ablation 16,848 healthy control subjects with no AF	AF patients postablation had a lower stroke risk compared with AF patients without ablation (4.5% vs 6.3%). AF ablation patients had similar stroke risk compared with control subjects without AF (4.5% vs 4.4%).
Winkle et al[38]	2013	Prospective cohort	Paroxysmal, persistent, LSPAF	108	At a median of 2.3 years of follow-up, no post-AF ablation patients without recurrence had a stroke. Bleeding risk was increased with anticoagulation (8.3% vs 0%; $P = 0.027$).
Karasoy et al[39]	2015	Retrospective study with an age- and gender-matched cohort	Not specified	4,050	Thromboembolic risk after ablation was relatively low compared with a matched nonablated AF cohort. The adjusted incidence rate ratio of thromboembolic events after adjusting for anticoagulation, antiplatelets and CHA_2DS_2-VASc score was 0.53 (95% CI: 0.43-0.65) in favor of the ablation cohort.
Liang et al[40]	2018	Retrospective cohort	Persistent, LSPAF	400	A low rate of clinical stroke was observed in patients that discontinued anticoagulation after successful ablation of nonparoxysmal AF (incidence: 0.49 per 100 patient-years).

CFAE = complex fractionated atrial electrogram; LSPAF = long-standing, persistent atrial fibrillation; other abbreviations as in Tables 3 and 4.

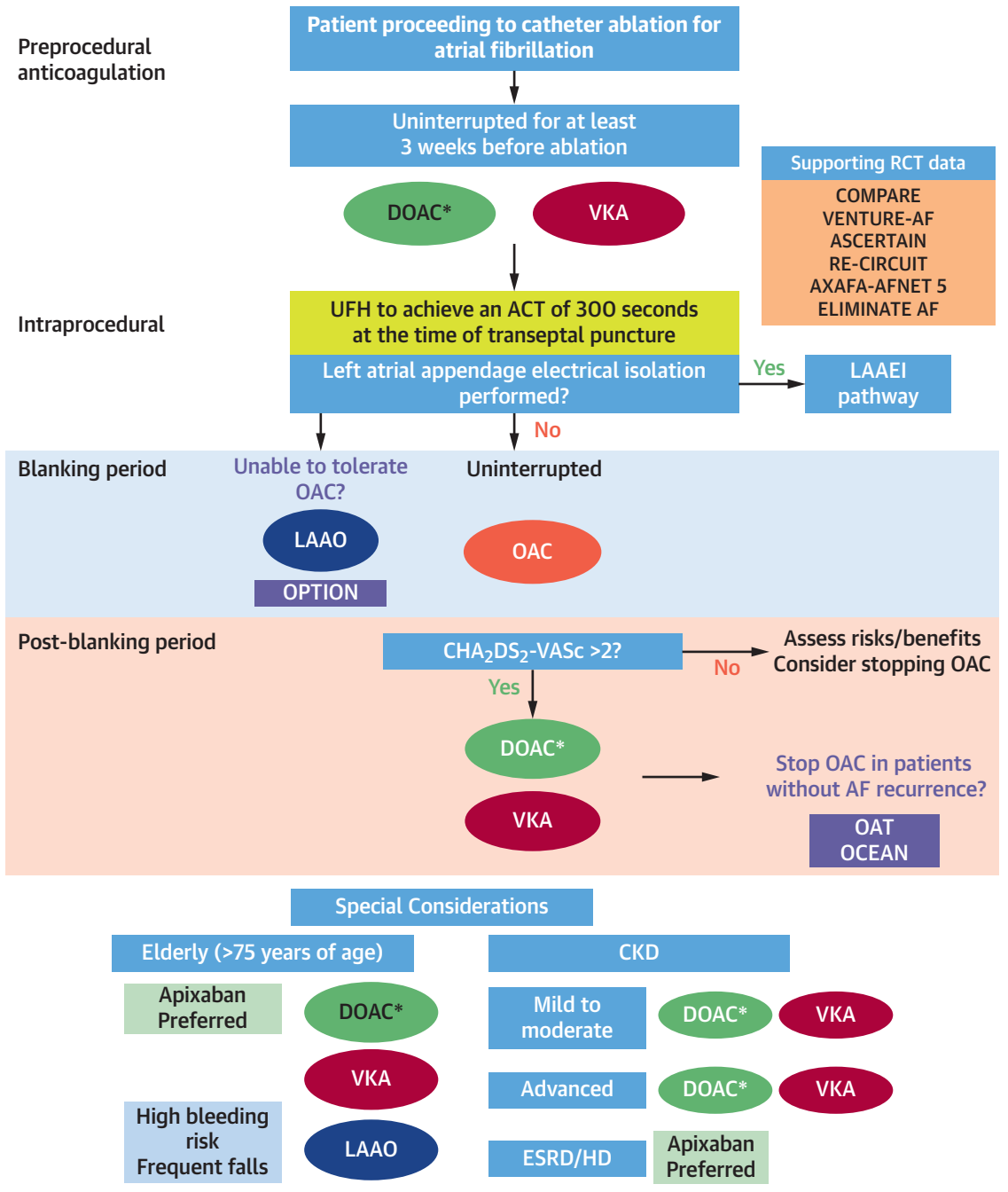
Conversely, a DAPT regimen is generally recommended for Amulet.[74]

Finally, although the experience with LAAO immediately after pulmonary vein isolation is limited,[59] the OPTION (Comparison of Anticoagulation with Left Atrial Appendage Closure After AF Ablation) and the aMAZE (LAA Ligation Adjunctive to pulmonary vein isolation for Persistent or Long-standing Persistent Atrial Fibrillation) trials are currently investigating the role of WATCHMAN and LARIAT systems after AF ablation.

EVIDENCE-BASED PRACTICAL APPROACH AT A GLANCE.

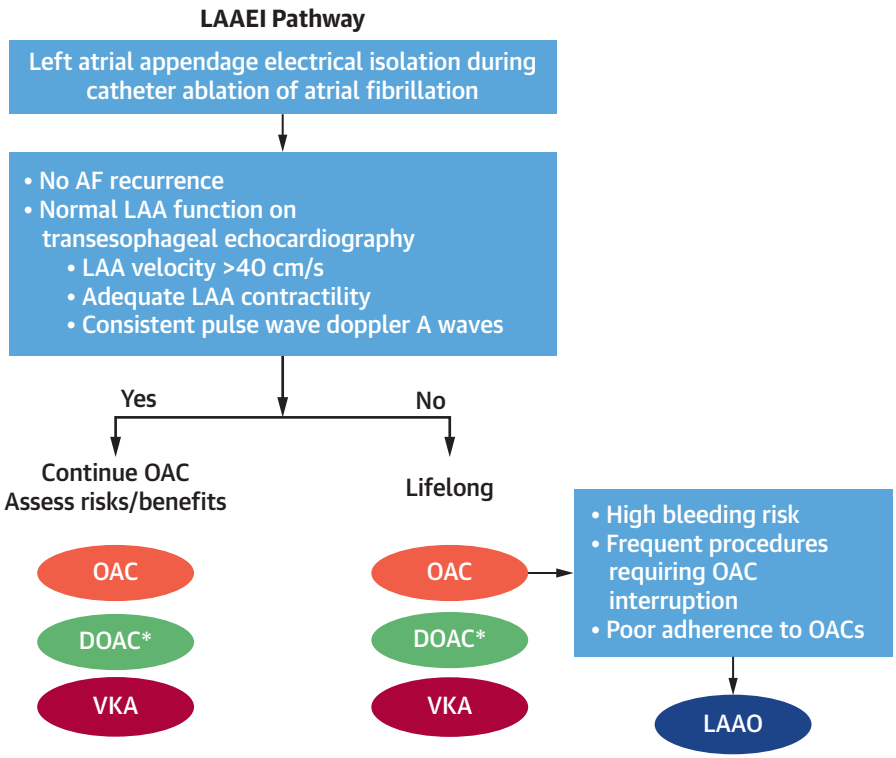
- Administration of unfractionated heparin achieving an activated clotting time of 300 seconds is recommended in patients undergoing LAAO with endocardial devices (expert opinion or Level of Evidence: C).[68]
- In patients undergoing LAAO, the TE vs bleeding risk should be addressed. Treatment alternatives include 6-month DAPT or OAC plus aspirin for 45 days post-LAAO for WATCHMAN devices. For the latter strategy, if LAA closure is confirmed by TEE or computed tomography scanning, OAC therapy should be held and followed by 6-month DAPT and then by long-term aspirin (expert opinion or Level of Evidence: C).[68] Alternatively, recent evidence supports the use of short-term, half-dose DOACs postsuccessful LAAO (authors' suggestions based on current evidence in the field).[71]
- LARIAT devices do not require postprocedural OAC. DAPT is generally recommended after LAAO with Amulet devices (expert opinion or Level of Evidence: C).[68]

FIGURE 1 Periprocedural Anticoagulation for Catheter Ablation of AF



Flowchart indicating oral anticoagulation (OAC) approaches for patient undergoing atrial fibrillation (AF) ablation. *Preferred If nonvalvular AF and no mechanical valve. ACT = activated clotting time; ASCERTAIN = Asymptomatic Cerebral Infarction During Catheter Ablation for Atrial Fibrillation: Comparing Uninterrupted Rivaroxaban and Warfarin; AXAFA-AFNET5 = Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation; CKD = chronic kidney disease; COMPARE = 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 Patients Undergoing Catheter Ablation randomized trial; DOAC = direct oral anticoagulant; ELIMINATE AF = Uninterrupted edoxaban vs. vitamin K antagonists for ablation of atrial fibrillation; ESRD = end-stage renal disease; HD = hemodialysis; LAAEI = left atrial appendage electrical isolation; LAAO = left atrial appendage occlusion; OAT = Safety of Oral Anticoagulation Therapy Withdrawal After Successful Cardiac Ablation in Patients with AF and Associated High Risk Factors for Embolic Events; OCEAN = Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for AF; RCT = randomized controlled trial; RE-CIRCUIT = Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation; UFH = unfractionated heparin; VENTURE-AF = Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation; VKA = vitamin K antagonist.

FIGURE 2 Periprocedural Anticoagulation for Electrical Isolation of LAA



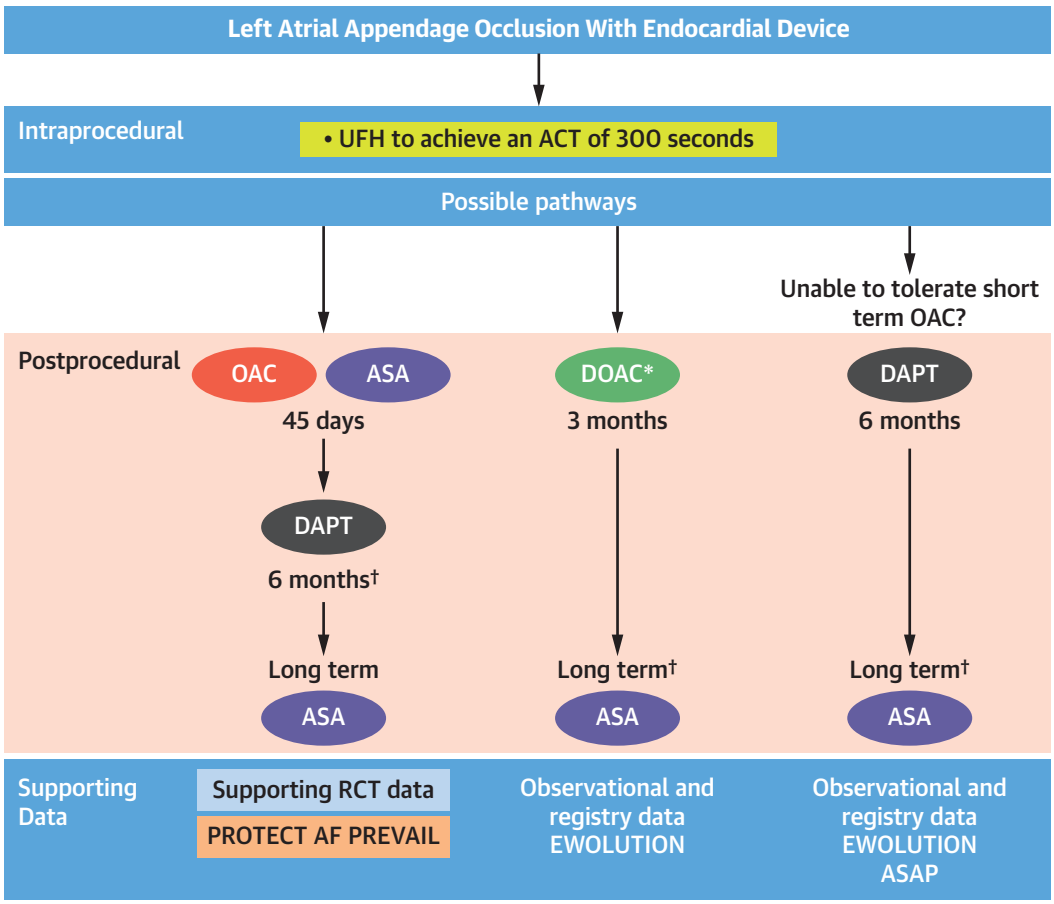
Flowchart indicating OAC approaches for patient undergoing left atrial appendage (LAA) isolation. *Preferred if nonvalvular AF and no mechanical valve. Abbreviations as in Figure 1.

PERIPROCEDURAL MANAGEMENT OF CARDIOVERSION

Electrical or pharmacological cardioversion is an effective method to restore normal sinus rhythm. However, if AF duration is more than 48 to 72 hours, the postcardioversion TE hazard can be as high as 5% to 7% in patients without adequate OAC.[75,76] This risk is related to the migration of dislodged thrombi or to their embolization postcardioversion through mechanisms of LA stunning.[77] Although LA stunning generally subsides within 1-week postcardioversion, it may take up to a month in some patient categories.[78,79] Therefore, current guidelines recommend OAC for 3 weeks before cardioversion if AF onset >48 hours, or, alternatively, TEE can be performed to rule out LAA thrombi.[9,80,81] The TEE approach also proved to yield even lower bleeding hazards than the conventional strategy thanks to a shorter OAC duration.[80] On the other hand, guidelines agree that OAC may not be required before cardioversion in patients with AF ≤48 hours and deemed to be at low TE risk.[9,81] However, this evidence is based on the results of a small retrospective study[82] and the risk of TE events is non-negligible even in patients with AF ≤48 hours.[83] In this regard, a subanalysis of the retrospective Finnish CardioVersion study showed that a delay to cardioversion ≥12 hours from symptom onset was an independent predictor of TE complications in patients undergoing successful cardioversion for AF, especially in elderly patients experiencing heart failure and/or diabetes.[84] Based on this evidence, the Canadian Cardiovascular Society Guidelines only limited immediate cardioversion to patients with brief AF duration (<12 hours) without recent stroke history (within 6 months) or in cases with low TE risk ($CHADS_2$ score <2) and AF onset within 12 to 48 hours.[85] In all the other cases, cardioversion might be postponed after 3 weeks of OAC or TEE carried out as an alternative strategy.[85]

Regarding the best antithrombotic strategy postcardioversion, short-term (4 weeks) OAC is generally recommended regardless of CHA_2DS_2-VASc

FIGURE 3 Periprocedural Anticoagulation for LAAO With WATCHMAN Device



Flowchart indicating OAC approaches for patient undergoing LAAO. *Consider half-dose DOAC plus aspirin (ASA); see text for further details. †If no evidence of peridevice leak. ASAP = Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology study; DAPT = dual antiplatelet therapy; EWOLUTION = Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology; PREVAIL = Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy; PROTECT AF = Percutaneous Left Atrial Appendage Closure vs Warfarin for Atrial Fibrillation; other abbreviations as in Figure 1.

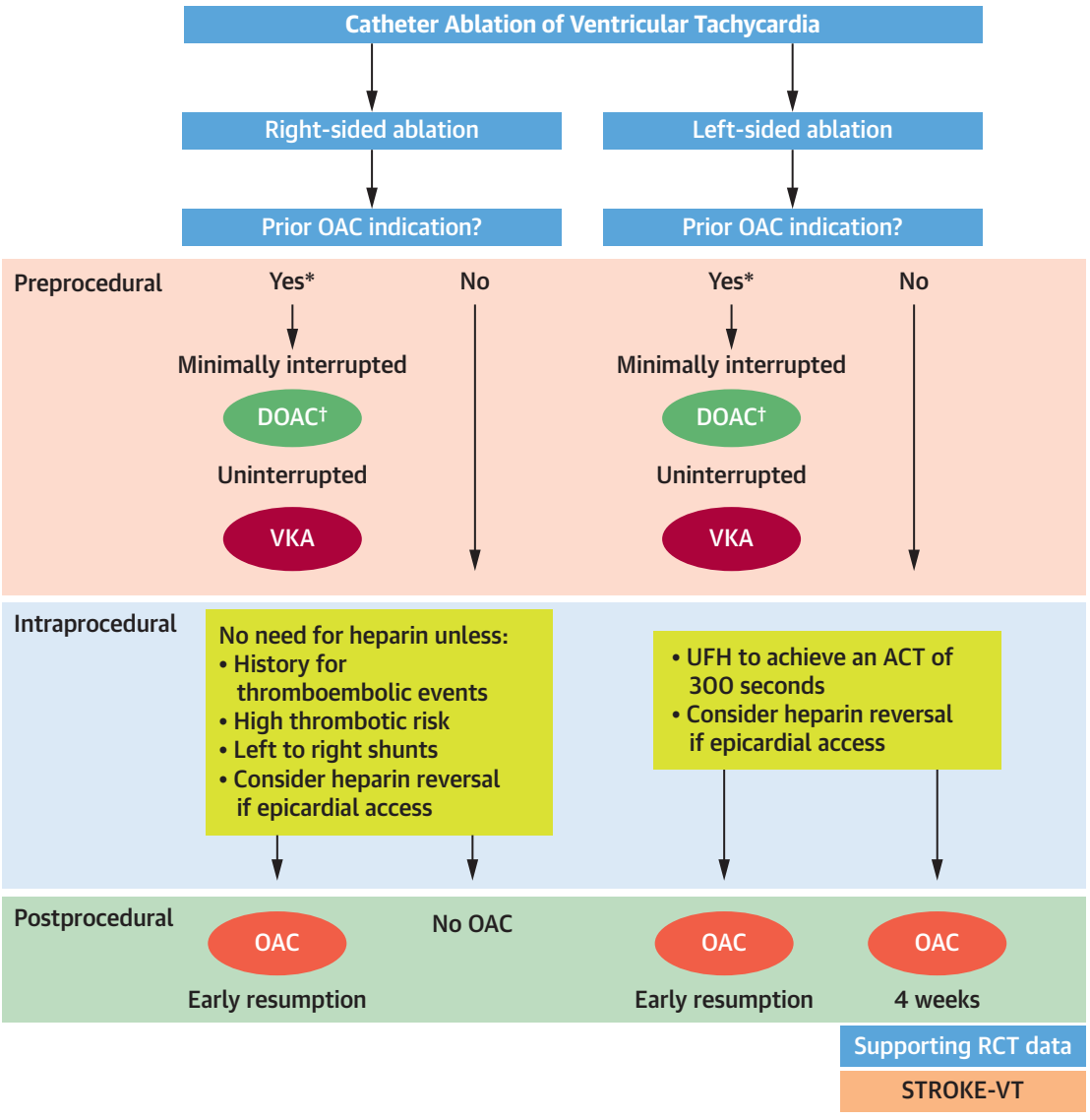
score,[27,28] with the only exception of patients with AF episodes ≤24 hours and very low TE risk (CHA_2DS_2-VASc score = 0 and CHA_2DS_2-VASc score = 1 for men and women, respectively). Then, the decision about long-term OAC should be based on the TE/bleeding risk profile[27,28] and considered for a CHA_2DS_2-VASc score value as low as 1 in men and 2 in women.[27]

Regarding the best OAC strategy, phase 3 RCTs comparing VKA vs DOACs in patients undergoing cardioversion[86-89] showed the noninferiority of DOACs to VKAs, and as assessed in real-world data, all DOAC agents display a low incidence of TE events (0.3% of event rate).[90]

EVIDENCE-BASED PRACTICAL APPROACH AT A GLANCE.

- In patients with AF onset >48 hours, OAC therapy for at least 3 weeks should be considered before cardioversion (Class I, Level of Evidence: B).[27,28] Alternatively, TEE should be performed before cardioversion to exclude atrial thrombus (Class I, Level of Evidence: B) (Class IIa, Level of Evidence: B).[34,35]
- In patients with AF onset ≤48 hours, cardioversion can be performed with a low risk of TE events (Class IIa, Level of Evidence: B).[27] However, in patients with early onset AF deemed at high risk of TE events (ie, AF duration <12 hours and history of recent stroke/transient ischemic attack or AF

FIGURE 4 Periprocedural Anticoagulation for Catheter Ablation of VT



Flowchart indicating OAC approaches for patient undergoing ventricular tachycardia (VT) ablation. *If epicardial access is planned: consider holding DOAC for 48 hours or VKA for 1-5 days with or without bridging. †Preferred If nonvalvular AF and no mechanical valve. STROKE-VT = safety and efficacy of DOACs vs aspirin for reduction of risk of cerebrovascular events in patients undergoing VT ablation; other abbreviations as in Figure 1.

duration within 12-48 hours in patients with $CHADS_2$ score >1), cardioversion might be delayed after 3 weeks of adequate OAC or TEE performed to rule out LAA thrombi (weak recommendation, low-quality evidence).[85]

- In AF patients undergoing cardioversion, DOACs are recommended with at least similar efficacy and safety to warfarin (Class I, Level of Evidence: A).[27]
- After cardioversion, short-term OAC (4 weeks) should be administered in all patients regardless of CHA_2DS_2-VASc score and AF duration (Class I, Level of Evidence: B).[35] However, in patients with a definite duration of AF ≤24 hours and a very low TE risk (CHA_2DS_2-VASc = 0 in men or 1 in women), postcardioversion OAC for 4 weeks might be omitted (Class IIb, Level of Evidence: B or Level of Evidence: C).[27,28]

- Following these 4 weeks, the decision to continue OAC should be based on the CHA_2DS_2-VASc score (Class I, Level of Evidence: B or Level of Evidence: C).[27,28] Lifelong OAC should be considered if CHA_2DS_2-VASc score ≥1 in men and CHA_2DS_2-VASc score ≥2 in women (Class IIa, Level of Evidence: B)[27] and definitely recommended for CHA_2DS_2-VASc score ≥2 in men and CHA_2DS_2-VASc score ≥3 in women (Class I, Level of Evidence: A).[27,28]

PERIPROCEDURAL ANTICOAGULATION DURING VENTRICULAR TACHYCARDIA ABLATION

During ventricular tachycardia (VT) ablation, emboli may ensue from clot and char formation at the catheter tip or endothelial site of ablation or from air microemboli during manipulation of catheters and sheaths.[91] The ablation modality, including epicardial access, may further expose these patients to TE/hemorrhagic complications.[92,93] Therefore, the optimal OAC strategy in patients undergoing VT ablation is unclear. Although right-sided VT would not mandate periprocedural anticoagulation therapy except for patients on chronic OAC or in the rarer cases with left-to-right shunts or thrombophilia,[94] in case of left-sided VT, intraprocedural heparin administration is required before or immediately after transseptal puncture to maintain and activated clotting time longer than 250 to 300 seconds.[94] Although no heparin administration is needed when catheter ablation is uniquely performed in the pericardial space, heparin reversal with protamine can be considered before epicardial access in case of a combined endoepicardial approach.[94] However, no specific postprocedural antithrombotic regimens have been hitherto suggested for catheter ablation of left-sided VT.

The STROKE-VT (Safety and Efficacy of DOACs vs Aspirin for Reduction of Risk of Cerebrovascular Events in Patients Undergoing VT Ablation) trial helped clarify their management. Despite similar procedure-related complications and in-hospital mortality, the study showed that postprocedural DOAC administration was associated with a significantly reduced TE risk compared with aspirin (DOACs: 0% vs 6.5%; $P < 0.001$; aspirin: 4.9% vs 18.0%; $P < 0.001$). Of note, retrograde aortic approach, prolonged radiofrequency time, low ejection fraction, and finally, use of aspirin instead of DOACs were identified as independent predictors of cerebral ischemic lesions on the multivariate analysis.[95] For patients undergoing VT ablation and already on OAC, the evidence seems to be heading toward uninterrupted anticoagulation[94,96] and OAC should then be resumed 4 to 6 hours after the procedure if no contraindications arise.[97]

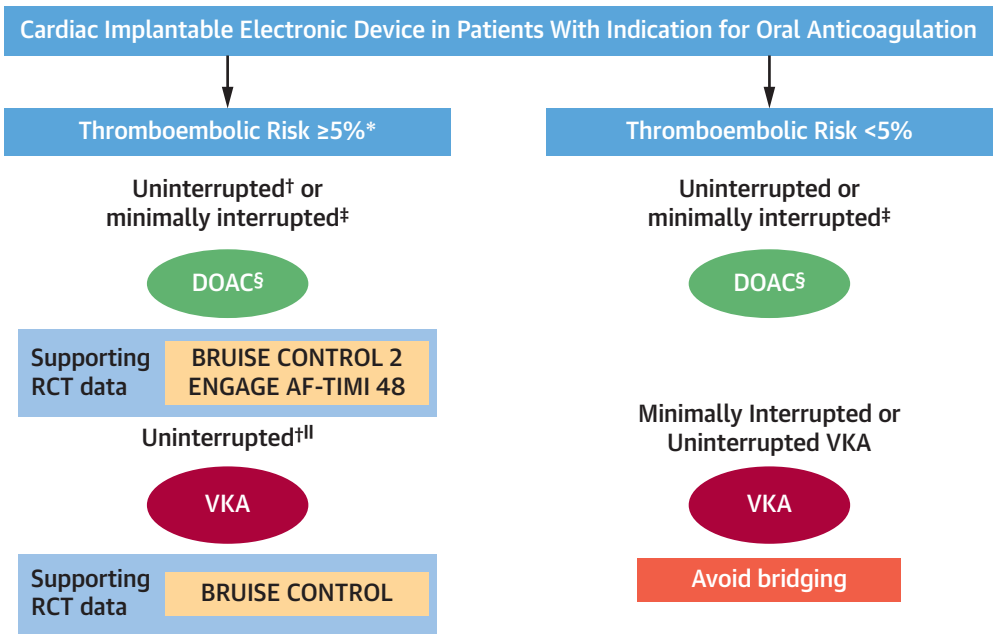
As for postprocedural management of access sites, differently from other electrophysiology procedures,[98] no RCTs comparing manual compression with temporary figure-of-eight suture closures or vascular closure devices are available for VT ablation. However, temporary suture techniques and vascular closure devices may yield faster hemostasis and ambulation times and reduce hemostasis-related pain compared with manual compression.[94]

Figure 4 summarizes a proposed algorithm for patients undergoing VT ablation while waiting for sounder evidence in the field.

EVIDENCE-BASED PRACTICAL APPROACH AT A GLANCE.

- Intraprocedural anticoagulation is not mandatory in patients undergoing right ventricular catheter ablation unless other TE risk factors are present (Class I, Level of Evidence: C) (see **Figure 4**).[94]
- In patients undergoing left ventricular (LV) ablation, intraprocedural administration of unfractionated heparin to achieve an activated clotting time of 250 to 350 seconds should be considered (Class I, Level of Evidence: B).[94]
- In patients undergoing endoepicardial LV ablation, epicardial access should be obtained before infusion of intraprocedural heparin or heparin reversal with protamine can be considered before epicardial access (Class IIa, Level of Evidence: C).[94]
- Regardless of VT ablation site, in patients with a previous indication for OAC, an uninterrupted or minimally interrupted strategy should be considered and OAC resumed 4 to 6 hours after the procedure if no contraindications arise (expert opinion or Level of Evidence: C).[97]
- In patients with high TE risk and previous indication for OAC undergoing epicardial ablation, epicardial access can be considered with an uninterrupted or a minimally interrupted OAC strategy (expert opinion or Level of Evidence: C).[97]
- In patients undergoing LV ablation without a previous indication for OAC, 4-week OAC (preferably DOACs) postablation can be considered to reduce the TE risk (authors' suggestions based on current evidence in the field).[95]

FIGURE 5 Periprocedural Anticoagulation for Implantation of Cardiac Implantable Electronic Devices



Flowchart indicating OAC approaches for patient undergoing cardiac pacing devices. *High risk defined as: CHA_2DS_2-VASc score of ≥3, CHA_2DS_2-VASc of 2 and recent stroke/TIA within 3 months, mechanical valves, recent thromboembolism in the last 3 months, plan for intraprocedural cardioversion. †Preferred if bleeding risk is low. ‡Interrupt oral anticoagulation preferably 24 hours preprocedure and no longer than 48 hours. Resume anticoagulation 12 to 24 hours postprocedure. §Preferred if no valvular AF and no mechanical valve. ‖Consider bridging therapy in the presence of mechanical valves after weighing in risks and benefits. BRUISE CONTROL = Pacemaker or Defibrillator Surgery without Interruption of Anticoagulation; ENGAGE AF-TIMI 48 = Edoxaban versus Warfarin in Patients with Atrial Fibrillation; other abbreviations as in Figure 1.

ABLATION OF LEFT-SIDED ACCESSORY PATHWAYS AND FOCAL LEFT ATRIAL TACHYCARDIA

Silent cerebral lesions have been demonstrated in young and healthy individuals undergoing catheter ablation of left-sided accessory pathways and focal atrial tachycardias.[99,100] Although prior anticoagulant therapy is not warranted, after transseptal catheterization, 5,000 to 15,000 U (or 90-200 U/kg) of unfractionated heparin is recommended followed by 1,000 U/h during the procedure.[101]

Although there is no clear evidence supporting the postinterventional use of OAC or aspirin,[97] postprocedure antithrombotic management might be considered in the setting of extensive ablation in the left chamber. The final decision should be patient based.

EVIDENCE-BASED PRACTICAL APPROACH AT A GLANCE.

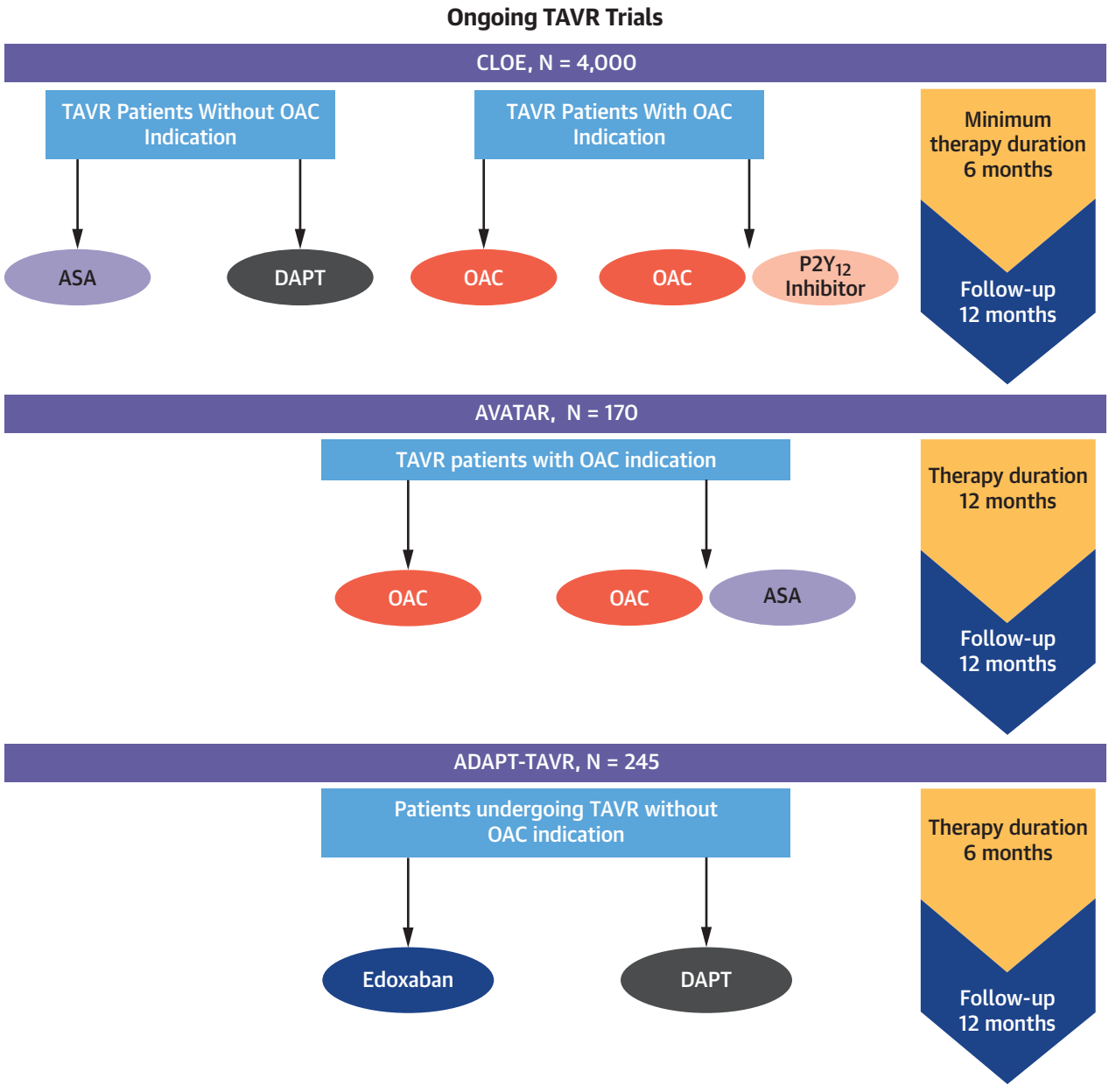
- During the ablation procedure, it is recommended to give unfractionated heparin with a target activated clotting time of 300 seconds (expert opinion or Level of Evidence: C).[97]
- After focal ablation of a left-sided accessory pathway or atrial tachycardia, OAC or the use of aspirin is not recommended unless otherwise indicated (expert opinion or Level of Evidence: C).[97]

PERIPROCEDURAL ANTICOAGULATION DURING CARDIAC DEVICE IMPLANTATION

With the progressive aging of the general population, utilization of CIEDs is on the rise.[102] The high prevalence of AF and need for OAC therapy raise the question on the best periprocedural antithrombotic strategy, recognizing that the TE hazard should be balanced against that of pocket hematoma and CIED infection in these patients.[103]

In the BRUISE CONTROL (Pacemaker or Defibrillator Surgery without Interruption of Anticoagulation) trial, patients undergoing CIED implantation were randomized to uninterrupted VKA

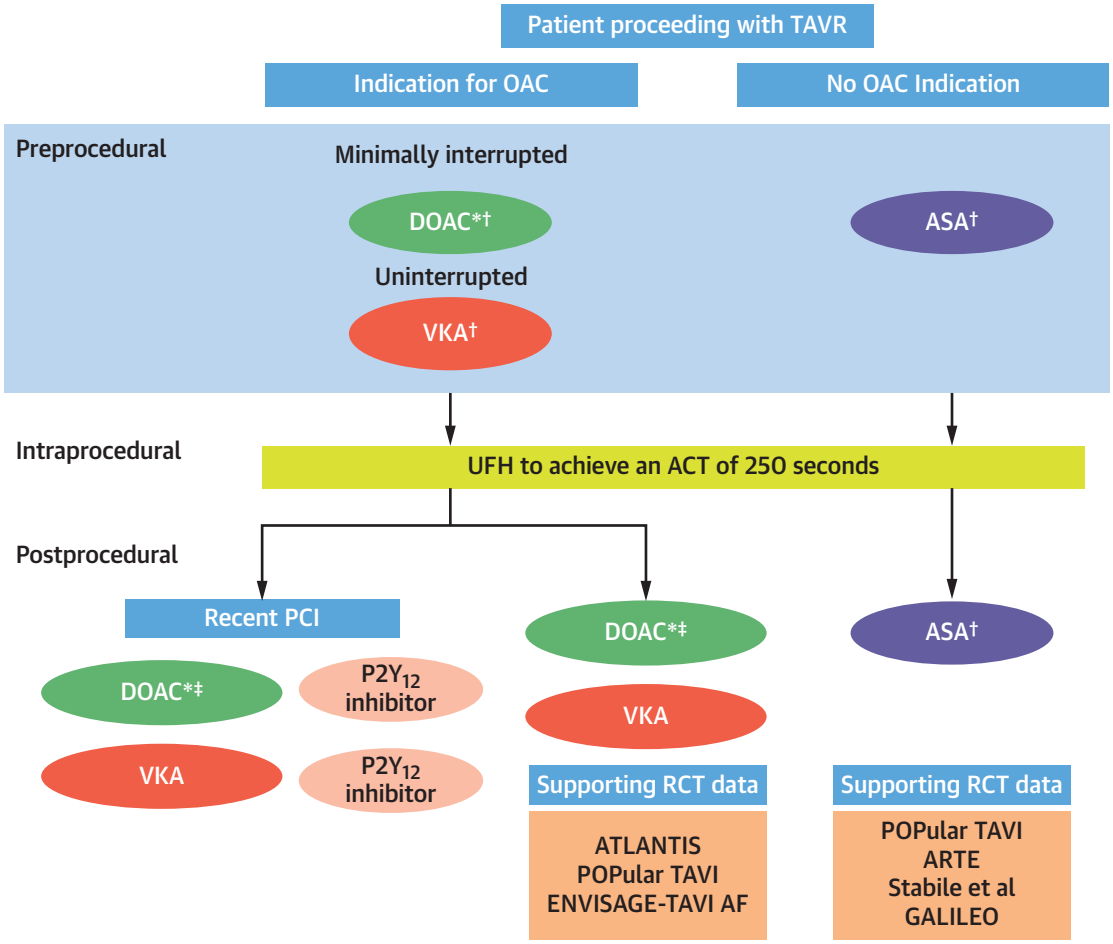
FIGURE 6 Ongoing Trials Evaluating Anticoagulation Strategies for TAVR



Flowchart indicating OAC approaches in ongoing transcatheter aortic valve replacement (TAVR) trials. ADAPT-TAVR = Anticoagulant Versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement; AVATAR = Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions; CLOE = Clopidogrel Omission After Transcatheter Aortic Valve Replacement; other abbreviations as in Figures 1 and 3.

or interrupted VKA with heparin bridging. Although no difference was observed regarding TE events in these 2 groups, a significantly higher risk of pocket hematoma was found in patients with interrupted VKA and heparin bridging,[104] with similar results reported in a vast meta-analysis conducted on 2,321 CIED patients.[105] Following this evidence, the 2015 European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society position paper on the antithrombotic management in patients undergoing electrophysiological procedures recommended uninterrupted VKA in all patient subgroups

FIGURE 7 Periprocedural Anticoagulation for TAVR

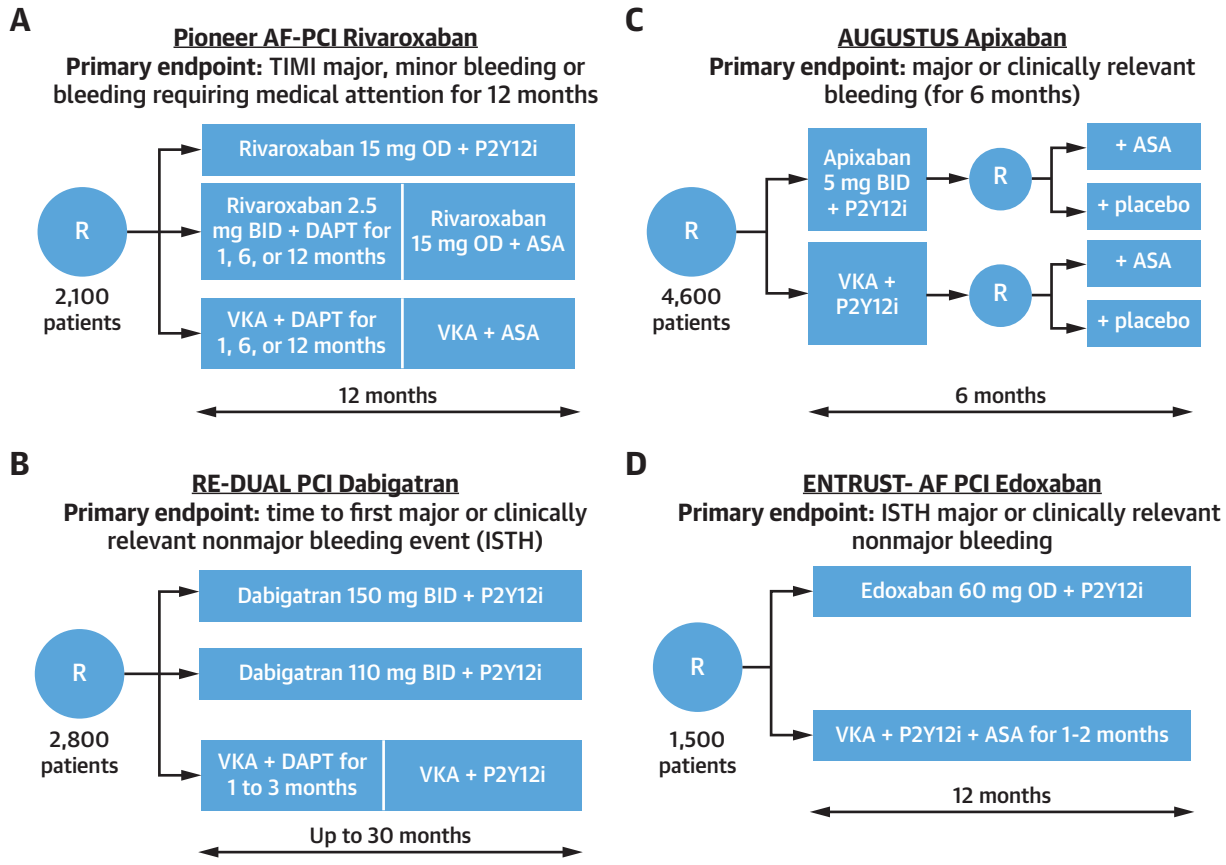


Flowchart indicating OAC approaches for patient undergoing TAVR. *Preferred if nonvalvular AF and no mechanical valve; †Avoid DAPT if possible, use DAPT only when clear indication exists (ie., recent PCI). ‡Apixaban preferred. Avoid Edoxaban as it increases bleeding risk. ARTE = Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement With a Balloon-Expandable Valve: The Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation Randomized Clinical Trial; ATLANTIS = Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis; ENVISAGE-TAVI AF = Edoxaban versus Vitamin K Antagonist for Atrial Fibrillation after TAVR; GALILEO = Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes; POPular TAVI = Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation; other abbreviations as in **Figures 1, 3, and 6**.

undergoing CIED implantation except for CIED patients with low TE risk (ie, <5%), in whom temporary VKA interruption without bridging might be considered.[97,106]

However, the experience with DOACs was limited when this consensus paper was published. In the BRUISE CONTROL-2 trial, the investigators proved the noninferiority of uninterrupted DOACs for both the primary (pocket hematoma) and secondary (incidence of stroke) endpoints when compared with a strategy based on interrupted DOACs.[107] However, in a recently published study investigating an antithrombotic strategy based on minimally interrupted DOACs, the use of DOAC agents with transient interruption proved to be as safe as uninterrupted VKAs in the periprocedural CIED setting.[108] Similar results were also observed for edoxaban in a subanalysis of the ENGAGE AF-TIMI 48 (Edoxaban versus Warfarin in Patients with Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial.[109] Based on these

FIGURE 8 Clinical Trials on AF Patients Undergoing Percutaneous Coronary Interventions



(A) PIONEER AF-PCI, (B) RE-DUAL PCI, (C) AUGUSTUS, and (D) ENTRUST-AF PCI trials. AUGUSTUS = Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation; BID = twice daily; ENTRUST-AF PCI= Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation; ISTH = International Society on Thrombosis and Hemostasis; OD = once daily; P2Y12i = $P2Y_{12}$ inhibitor; PIONEER AF-PCI = Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI; R = randomization; RE-DUAL PCI = Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Figures 1 and 3.

results, it is reasonable to perform CIED implantations with uninterrupted or minimally interrupted OAC (no longer than 24 hours preprocedure and 12-24 hours postprocedure) without heparin bridging to reduce the risk of bleeding complications (Figure 5).

EVIDENCE-BASED PRACTICAL APPROACH AT A GLANCE.

- In patients at high risk of TE events (see Figure 5), uninterrupted OAC should be the preferred treatment strategy in patients undergoing CIED implantation (expert opinion or Level of Evidence: C).[97] In all the other patients, minimally interrupted or interrupted OAC without heparin bridging can be considered an alternative to uninterrupted OAC in patients undergoing CIED implantation (expert opinion or Level of Evidence: C).[97]
- In patients on VKAs, the international normalized ratio on the day of surgery should be under the upper limit of the prescribed therapeutic range for the patient (expert opinion or Level of Evidence: C).[97]
- As for DOACs, a minimally interrupted strategy with intake of the last dose in the morning of the day before the procedure followed by restarting 12 to 24 hours can be as easily safe as an uninterrupted strategy (expert opinion or Level of Evidence: C).[97,107-109]
- In all cases, heparin bridging is associated with an increased risk of periprocedural complications and

TABLE 6 Patients' Demographics and Outcomes in the RCTs Assessing the Feasibility of DOACs in Patients With AF Undergoing Percutaneous Coronary Intervention

	PIONEER AF-PCI (n = 2,124)[124]		RE-DUAL PCI (n = 2,725)[125]			AUGUSTUS AF-PCI (n = 4,614)[126]		ENTRUST-AF PCI (n = 1,506)[127]	
	TAT	DAT	TAT	DAT 1	DAT 2	TAT	DAT	TAT	DAT
Treatment	VKA + $P2Y_{12}$ Inhibitor + ASA	Rivaroxaban 15 mg OD + $P2Y_{12}$ Inhibitor	VKA + $P2Y_{12}$ Inhibitor + ASA	Dabigatran 150 mg BID + $P2Y_{12}$ Inhibitor	Dabigatran 110 mg BID + $P2Y_{12}$ Inhibitor	VKA + $P2Y_{12}$ Inhibitor + ASA	Apixaban 5 or 2.5 mg or $P2Y_{12}$ Inhibitor	VKA + $P2Y_{12}$ Inhibitor + ASA	Edoxaban 60 mg OD + $P2Y_{12}$ Inhibitor
Trial population characteristics									
Age, y	70 ± 9	70 ± 9	72 ± 9	69 ± 8	71 ± 9	71 (64-77)	70 (64-77)	70 (64-77)	69 (63-77)
CrCl, mL/min	81 ± 30	78 ± 31	75 ± 29	84 ± 31	76 ± 29	91% of patient population <1.5 mg/dL	92% of patient population <1.5 mg/dL	72 (54-91)	72 (54-91)
CHA_2DS_2-VASc score	3.8	3.7	3.8 ± 1.5	3.3 ± 1.5	3.7 ± 1.6	4.0 ± 1.6	3.9 ± 1.6	4.0 (3.0-5.0)	4.0 (3.0-5.0)
Diabetes	31%	29%	38%	34%	36%	36%	36%	34%	34%
Hypertension	75%	73%	N/A	N/A	N/A	88%	88%	91%	90%
History of MI	22%	20%	27%	25%	25%	N/A	N/A	23%	25%
History of stroke	Exclusion criteria	Exclusion criteria	10%	7%	8%	13%	14%	12%	13%
Type of $P2Y_{12}$ inhibitor									
Clopidogrel	96%	93%	92%	88%	87%	93%	93%	92%	93%
Ticagrelor	3%	5%	8%	12%	13%	7%	6%	8%	7%
Prasugrel	<1%	2%	0	0	0	1%	1%	<1%	<1%
Outcomes									
Major or minor bleeding (ISTH criteria)	26.7%	16.8% ($P < 0.001$)	27%	20% (noninferiority $P < 0.001$)	15% (noninferiority $P < 0.001$; superiority $P < 0.001$)	18.7%	7.3%	20%	17% (noninferiority $P = 0.0010$; superiority $P = 0.1154$)
Death	1.9%	2.4% ($P = 0.52$)	4.9%	3.9% ($P = 0.44$)	4.9% ($P = 0.56$)	5.7%	6.2%	4.9%	6.1%
Myocardial infarction	3.5%	3.0% ($P = 0.62$)	3.0%	3.4% ($P = 0.61$)	4.0% ($P = 0.09$)	N/A	N/A	3.0%	3.9%
Stroke	1.2%	1.3% ($P = 0.89$)	1.3%	1.2% ($P = 0.85$)	1.5% ($P = 0.48$)	N/A	N/A	1.6%	1.3%
Stent thrombosis	0.7%	0.8% ($P = 0.79$)	0.8%	0.9% ($P = 0.98$)	1.3% ($P = 0.15$)	N/A	N/A	1.3%	1.7%

Values are mean ± SD or median (Q1-Q3), unless otherwise indicated. All RCTs investigating the feasibility of DOACs in patients with AF undergoing PCI proved the superiority or noninferiority of a DAT (ie, OAC plus single antiplatelet therapy) as for the safety endpoints with overlapping efficacy regarding the ischemic outcomes as compared with TAT (ie, OAC plus double antiplatelet therapy). Even though AUGUSTUS used a 2-by-2 factorial design to compare apixaban vs VKA and ASA vs placebo, data were collected and tabulated as TAT vs DAT for all the appraised trials for the sake of clarity. Similar considerations apply to the PIONEER AF-PCI trial. See Figure 8 for the study design of these trials. CrCl was calculated with the use of the Cockcroft-Gault equation.

AUGUSTUS = Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation; ASA = aspirin; BID = twice daily; CrCl = creatinine clearance; DAT = dual antithrombotic therapy; DOAC = direct oral anticoagulant; ENTRUST-AF PCI = Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation; ISTH = International Society on Thrombosis and Hemostasis; MI = myocardial infarction; N/A = not available; OAC = oral anticoagulation; OD = once daily; PCI = percutaneous coronary intervention; PIONEER = Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI; RCT = randomized controlled trial; RE-DUAL = Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation; TAT = triple antithrombotic therapy; VKA = vitamin K antagonist; other abbreviations as in Tables 3 and 4.

therefore should not be considered during CIED implantation (expert opinion or Level of Evidence: C).[97]

ANTICOAGULATION DURING TAVR

TAVR has become an option for the treatment of aortic stenosis in patients with a very high-to-moderate surgical risk[110] and, more recently, in low-risk cases.[111] Different mechanisms may play a role in thrombus formation and embolization in patients undergoing TAVR. The delayed endothelization of the transcatheter heart valve stent frame could be the site for the development of a platelet-rich thrombus.[112] On the other hand, the valve frame or its leaflets may lead to clot formation. Although both antiplatelet and OAC therapies would be justified, the best antithrombotic strategy is yet to be established.

ANTIPLATELET REGIMENS IN PATIENTS UNDERGOING TAVR. Like PCI, DAPT including aspirin and clopidogrel has been widely adopted in patients undergoing TAVR.[113] However, recent observational studies have questioned the safety and efficacy of this

TABLE 7 Regimens of DOACs Approved in Patients With AF Undergoing PCI

Type of Regimen	Rivaroxaban	Dabigatran	Apixaban	Edoxaban
TAT (OAC + clopidogrel + ASA) Peri-PCI or up to 1 mo according to the thromboembolic/ hemorrhagic risk[a]	15 mg rivaroxaban OD[b] + clopidogrel + ASA	150 mg dabigatran BID (or 110 mg dabigatran BID especially in elderly patients ≥80 years of age or high bleeding risk) + clopidogrel + ASA	5 mg apixaban BID (or 2.5 mg BID if 2 or more of the following dose reduction criteria: ≥80 years of age, weight ≤60 kg, or creatinine level ≥1.5 mg/dL) + clopidogrel + ASA	60 mg edoxaban OD (or 30 mg edoxaban OD if any of the following: CrCl 15-50 mL/min, weight ≤60 kg, or concurrent use of specific potent P-glycoprotein inhibitors) + clopidogrel + ASA
DAT 1 (OAC + clopidogrel) Up to 6-12 mo post-PCI according to the thromboembolic/ hemorrhagic risk[a]	15 mg rivaroxaban OD[b] + clopidogrel	150 mg dabigatran BID (or 110 mg dabigatran BID especially in elderly patients ≥80 years of age or high bleeding risk) + clopidogrel	5 mg apixaban BID (or 2.5 mg BID if 2 or more of the following dose reduction criteria: ≥80 years of age, weight <60 kg, or creatinine level ≥1.5 mg/dL) + clopidogrel	60 mg edoxaban OD (or 30 mg edoxaban OD if any of the following: CrCl 15-50 mL/min, weight ≤60 kg, or concurrent use of specific potent P-glycoprotein inhibitors) + clopidogrel
DAT 2 (OAC + ticagrelor) Up to 12 mo post-PCI and to be considered in patients with high thromboembolic risk and acceptable hemorrhagic hazard[a]	15 mg rivaroxaban OD[b] + ticagrelor Roughly 5% ticagrelor use in the 15 mg rivaroxaban arm in the PIONEER AF-PCI trial	150 mg dabigatran BID (or 110 mg dabigatran BID especially in elderly patients ≥80 years of age or high bleeding risk) + ticagrelor Roughly 12% ticagrelor use in each dabigatran arm in the RE-DUAL PCI trial	5 mg apixaban BID (or 2.5 mg BID if 2 or more of the following dose reduction criteria: ≥80 years of age, weight <60 kg, or creatinine level ≥1.5 mg/dL) + ticagrelor Roughly 6% ticagrelor use in addition to apixaban in the AUGUSTUS trial	60 mg edoxaban OD (or 30 mg edoxaban OD if any of the following: CrCl 15-50 mL/min, weight ≤60 kg, or concurrent use of specific potent P-glycoprotein inhibitors) + ticagrelor Roughly 7% ticagrelor use in addition to edoxaban in the ENTRUST-AF PCI trial

The table reports the suggested antithrombotic regimens in patients with AF undergoing PCI. Direct oral anticoagulants doses are tabulated accordingly. As for antiplatelet regimens: after a 325-mg loading dose administration (in ASA-naive patients), the maintenance dose of ASA should be 75 to 100 mg/d. Clopidogrel should be administered as a 600-mg loading dose followed by a 75-mg daily maintenance dose. Ticagrelor should be administered as a 180-mg loading dose and 90-mg BID maintenance dose. When ticagrelor is combined with OAC, ASA use should generally be discontinued after the peri-PCI period. Regarding the combination of ticagrelor with DOACs, the association with 150 mg or 110 mg dabigatran should be preferred.[133] [a]Thromboembolic risk is increased in patients with 1 or more of the following[133]: acute coronary syndrome, history of stent thrombosis while on antiplatelet therapy, PCI complexity (eg, number of vessels treated and stents implanted, bifurcations, left main coronary artery PCI), previous MI, multivessel coronary artery disease, vascular disease, diabetes mellitus, chronic kidney disease, and heart failure. As for hemorrhagic risk, a patient with increased bleeding risk is identified as having 1 major (other than use of OAC) or 2 minor criteria according to Academic Research Consortium definitions.[133] Major criteria were anticipated use of long-term oral anticoagulation; severe or end-stage chronic kidney disease (estimated glomerular filtration rate <30 mL/min); hemoglobin <11 g/dL, spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent; moderate or severe baseline thrombocytopenia before PCI (platelet count $<100 \times 10^9$/L); chronic bleeding diathesis; liver cirrhosis with portal hypertension; active malignancy (excluding nonmelanoma skin cancer) within the past 12 months; previous spontaneous intracranial hemorrhage (at any time); previous traumatic intracranial hemorrhage within the past 12 month; presence of a brain arteriovenous malformation; moderate or severe ischemic stroke within the past 6 months; nondeferrable major surgery on dual antiplatelet therapy; recent major surgery or major trauma within 30 days before PCI. Minor criteria were ≥75 years of age; moderate chronic kidney disease (estimated glomerular filtration rate 30-59 mL/min); hemoglobin 11-12.9 g/dL for men and 11-11.9 g/dL for women; spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion; long-term use of oral nonsteroidal anti-inflammatory drugs or steroids; any ischemic stroke at any time not meeting the major criterion. [b]According to the North American Consensus Document,[133] 15 mg rivaroxaban should be regarded as the preferred regimen in patients with AF undergoing PCI, suggesting that other dosing regimens, particularly triple therapy with rivaroxaban 20 mg plus dual antiplatelet therapy, are known to be associated with unacceptably high rates of bleeding and therefore should be avoided. However, European guidelines[27] take into account a 20 mg rivaroxaban as the default strategy, thus reserving the 15-mg dose regimen to patients with high hemorrhagic risk.

Abbreviations as in Tables 3 and 6.

approach. A retrospective analysis of the OCEAN-TAVR (Optimized transCathEter vAlvular iNtervention-TAVR) registry highlighted that patients on preprocedural DAPT had no clear benefit on the incidence of TE events but displayed a significantly higher rate of access site bleeding requiring transfusion compared with single antiplatelet therapy (SAPT) (32.4% vs 24.7%; $P = 0.048$) or no preprocedural antiplatelet therapy (34.1% vs 25.5%; $P = 0.030$).[113] A prospective observational study found similar results.[114] Moreover, current registry-based evidence suggests that SAPT may be safer than DAPT after TAVR.[111] Therefore, as suggested by a recent European consensus document,[115] preprocedural DAPT is discouraged in patients undergoing TAVR and only limited postprocedurally to those cases at high risk of ischemia (eg, PCI).[115] Further powered studies are needed to investigate which is the best preprocedural management in low-risk patients.

ANTICOAGULATION REGIMENS IN PATIENTS UNDERGOING TAVR. In patients with a clear indication for OAC, a retrospective analysis found that a minimally interrupted DOAC strategy during TAVR (ie, the last dose of DOAC administered the day before and restarted in the morning of the next day after successful TAVR) was associated with the best 30-day early safety endpoint and lowest 30-day cardiovascular and 1-year mortality as compared with interrupted or uninterrupted VKA.[116] Likewise, a recently published subanalysis from the OCEAN-TAVI (Incidence, Predictors, and Clinical Impact of Prosthesis-Patient Mismatch Following Transcatheter Aortic Valve Replacement in Asian Patients: the Optimized transCathEter vAlvular iNtervention) registry

TABLE 8 Ongoing RCTs on Antithrombotic Therapy Management in Patients With AF Undergoing PCI

Scope	Trial	Design	Estimated Patient Enrollment	Investigated Population	Intervention Arm	Control Arm	Endpoint
To investigate antithrombotic regimens with potent $P2Y_{12}$ inhibitors (eg, ticagrelor)	ADONIS-PCI (NCT04695106)	Noninferiority	2,230	NVAF patients undergoing PCI due to ACS	DAT with dabigatran (150 or 110 mg BID) plus ticagrelor (90 mg BID for 1 mo, followed by ticagrelor 60 mg BID up to 12 mo)	TAT with dabigatran (150 mg BID or 110 mg BID) plus clopidogrel plus ASA, followed by DAT depending on the bleeding and ischemic risks	Major or clinically relevant nonmajor bleeding at 2 y (ISTH bleeding definition).
	EPIDAURUS (NCT04981041)	Superiority for efficacy and noninferiority for safety	2,334	NVAF patients undergoing PCI due to ACS	DAT with DOAC plus prasugrel 10 mg OD or ticagrelor 90 mg BID for 1 mo, followed by DAT with DOAC plus clopidogrel	DAT with DOAC plus clopidogrel	Efficacy: composite of death, MI, definite or probable stent thrombosis, ischemic stroke, and systemic thromboembolism at 6 wk. Safety: clinically relevant bleeding at 6 wk (BARC bleeding definition).
	OPTIMA-4 (NCT03234114)	Superiority	1,472	NVAF patients undergoing PCI with new generation DES due to ACS	DAT with dabigatran 110 mg BID plus ticagrelor 90 mg BID for 12 mo	DAT with dabigatran 110 mg BID plus clopidogrel for 12 mo	Efficacy: 1-y composite of cardiovascular death, MI, ischemic stroke, systemic thromboembolism, or unplanned revascularization. Safety: 1-y major or clinically relevant nonmajor bleeding (ISTH bleeding criteria).
To investigate different antithrombotic regimens and their duration in different clinical settings	APPROACH-ACS-AF (NCT02789917)	Superiority	403	NVAF patients undergoing PCI due to ACS	DAT with apixaban 5 mg BID plus clopidogrel for 6 mo	TAT with phenprocoumon, clopidogrel and ASA 6 mo (if HAS-BLED score ≥3, TAT for 1 month, followed by aspirin-free DAT)	Moderate or major bleeding at 6 mo (BARC bleeding definition).
	COACH-AF-PCI (NCT03536611)	Superiority	1,120	NVAF patients undergoing PCI	TAT with dabigatran 110 mg BID plus clopidogrel and ASA for 1 month, followed by aspirin-free DAT for at least 5 mo	TAT with VKA plus clopidogrel and ASA for 1 month, followed by ASA-free DAT for at least 5 mo	Clinically relevant bleeding at 2 y (BARC bleeding definition).
	OPTIMA-AF (jRCTs051190053)	Noninferiority for efficacy and superiority for safety endpoints	1,090	NVAF patients undergoing nonurgent PCI. ACS patients not included	DAT with DOAC plus clopidogrel or prasugrel for up to 1 mo and DOAC monotherapy thereafter permanently	DAT with DOAC plus clopidogrel or prasugrel for up to 12 mo	Efficacy: the cumulative incidence of a composite of death or thromboembolic events at 12 mo. Safety: bleeding at 12 mo (ISTH definition).
	WOEST 3 (NCT04436978)	Superiority	2,000	NVAF patients presenting with ACS and/or undergoing PCI	DAPT for the first month, followed by DAT up to 12 mo	TAT for up to 30 d, followed by DAT up to 12 mo	Major or clinically relevant nonmajor bleeding at 1 mo (BARC bleeding definition).

Continued on the next page

demonstrated that AF patients undergoing TAVR had a lower incidence of all-cause mortality when treated with DOACs vs VKAs (10.3% vs 23.3%; $P = 0.005$).[117] Although apixaban proved superior to VKA in the protection against TE/hemorrhagic events,[118] edoxaban was associated with a non-negligible risk of gastrointestinal bleeding in this setting.[119] The evidence is far less clear in patients undergoing TAVR

TABLE 8 Continued

Scope	Trial	Design	Estimated Patient Enrollment	Investigated Population	Intervention Arm	Control Arm	Endpoint
To investigate long-term DAT vs OAC only	ADAPT-AF (NCT04250116)	Superiority	960	NVAF patients who underwent PCI 12-18 mo before	OAC with apixaban 5 mg BID or rivaroxaban 20 mg OD for 2 y. In case of renal impairment, reduced dose of apixaban (2.5 mg BID) or rivaroxaban (15 mg OD) or warfarin would be considered	DAT with clopidogrel plus apixaban 5 mg BID or rivaroxaban 15 mg OD for 2 y. In case of renal impairment, reduced dose of apixaban (2.5 mg BID) or rivaroxaban (10 mg OD) or warfarin would be considered.	Composite of death, MI, stent thrombosis, stroke, systemic embolism, major or clinically relevant nonmajor bleeding at 2 y.
	AQUATIC (NCT04217447)	Superiority	2,000	High-risk NVAF patients who underwent PCI more than 1 y before	DAT with OAC (either DOAC or VKA) plus ASA	OAC alone (either DOAC or VKA)	Efficacy: composite of cardiovascular death, myocardial infarction, stroke, any revascularization, systemic embolism or acute limb ischemia at 24-48 mo. Safety: major bleeding at 24-48 mo (ISTH bleeding definition).

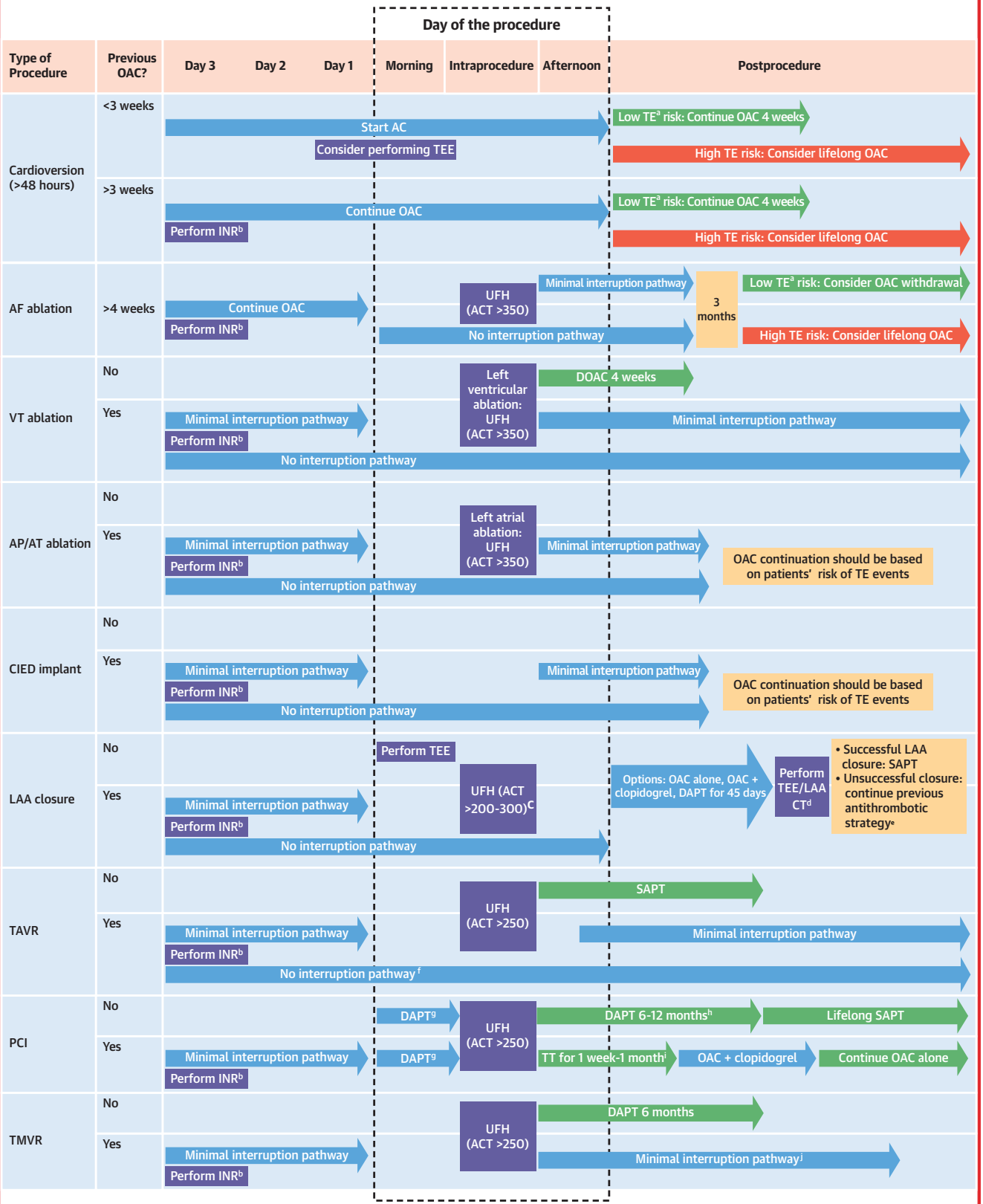
ACS = acute coronary syndrome; ADAPT-AF = Appropriate Duration of Anti-Platelet and Thrombotic Strategy After 12 Months in Patients With Atrial Fibrillation Treated With Drug Eluting Stents; ADONIS-PCI = Dual Antithrombotic Therapy With Dabigatran and Ticagrelor in Patients With Acute Coronary Syndrome and Non-valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; APPROACH-ACS-AF = APixaban vs. PhenpRocoumon in Patients With Acute Coronary Syndrome and Atrial Fibrillation; AQUATIC = Assessment of Quitting Versus Using Aspirin Therapy In Patients Treated With Oral Anticoagulation for Atrial Fibrillation or Other Indication With Stabilized Coronary Artery Disease; BARC = Bleeding Academic Research Consortium; COACH-AF-PCI = Dabigatran Versus Warfarin With Non-Valvular Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; DAPT = dual antiplatelet therapy; EPIDAURUS = Escalated Single Platelet Inhibition for One Month Plus NOAC in Patients With Atrial Fibrillation and Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention; NVAF = nonvalvular atrial fibrillation; OPTIMA-4 = Optimal Antithrombotic Therapy for Acute Coronary Syndrome Patients Concomitant With Atrial Fibrillation and Implanted With New-generation Drug Eluting Stent; OPTIMA-AF = *OPTIMA*l antiplatelet therapy in combination with direct oral anticoagulants in patients with non-valvular *A*trial *F*ibrillation undergoing percutaneous coronary intervention with everolimus-eluting stent; WOEST 3 = What is the Optimal Antithrombotic Strategy in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention?; other abbreviations as in Tables 3 and 6.

and without indications for OAC. Although the ATLANTIS (Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis) trial showed a lower incidence of valve leaflet thrombosis in patients on apixaban undergoing TAVR compared with those on antiplatelet therapy, this observation did not result in better clinical outcomes in the apixaban treated group.[120] A higher death hazard was even observed in the 10 mg rivaroxaban group in the GALILEO (Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) trial.[121] Based on these data, there is no evidence to support VKAs or DOACs post-TAVR in patients without a clear indication for OAC pre-TAVR (eg, AF or venous thromboembolism). Future trials, including CLOE (Clopidogrel Omission After Transcatheter Aortic Valve Replacement), AVATAR (Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions), and ADAPT-TAVR (Anticoagulant Versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement) may clarify the appropriate management post-TAVR (Figure 6). A proposed algorithm for the antithrombotic management of patients undergoing TAVR is displayed in Figure 7.

EVIDENCE-BASED PRACTICAL APPROACH AT A GLANCE.

- In patients undergoing TAVR, pretreatment with DAPT is not recommended unless another indication for DAPT exists (expert opinion or Level of Evidence: C).[115]
- In patients undergoing TAVR and with a prior indication for OAC, a minimally interrupted or an uninterrupted strategy should be considered periprocedurally.[117] OAC with SAPT may be considered for patients at high risk of ischemia or post-PCI (expert opinion or Level of Evidence: C).[115]

CENTRAL ILLUSTRATION Antithrombotic Approaches in Cardiovascular Procedures



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- In patients undergoing TAVR and with a clear indication for OAC, DOACs (particularly apixaban and not edoxaban)[118,119] should be preferred over VKAs (expert opinion or Level of Evidence: C).[117]
- In patients without prior indication for OAC undergoing TAVR and without other indication for DAPT, a SAPT regimen should be used (expert opinion or Level of Evidence: C).[115]
- During TAVR, unfractionated heparin should be administered to achieve an activated clotting time target of 250 to 300 seconds. To prevent cardiovascular access site complications and bleedings, protamine sulfate may be used before closure to reverse anticoagulation (expert opinion or Level of Evidence: C).[115]

ANTICOAGULATION FOR PCI IN PATIENTS WITH AF

OAC management in AF patients undergoing PCI is challenging because DAPT proved to protect from stent thrombosis but it has no role in reducing cardioembolic events in AF patients. Conversely, OAC protects from the opposite risk.[122] Whatever the OAC agent and PCI setting, OAC therapy should be interrupted prior to PCI to reduce the risk of preprocedural bleeding and DAPT administered afterward.[123]

Several RCTs[124-127] have recently underscored a significantly lower hemorrhagic risk for a dual antithrombotic strategy (ie, OAC plus SAPT) compared with the standard-of-care triple therapy (ie, OAC plus DAPT).[128] The design of these trials and their major features are represented in **Figure 8** and **Table 6**. Although the dual strategy with DOACs seems noninferior to the triple therapy with VKA regarding the TE/stent thrombosis risk,[129,130] none of the RCTs with DOACs[124-127] were powered to assess TE outcomes, nor did they include direct comparisons between different DOACs in AF patients undergoing PCI.[131] Hence, a triple antithrombotic therapy—preferably with DOACs—should be considered for up to 30 days in patients with a high atherothrombotic risk, including complex PCI, acute coronary syndromes, or history of stent thrombosis.[13] Alternatively, based on a post hoc analysis of the RE-DUAL PCI (Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation) trial[132] and current guidelines in the field,[9,133] a combination of 150 mg or 110 mg dabigatran with ticagrelor may be considered in patients with an exceedingly high TE risk. The recommended DOAC dosage in conjunction with $P2Y_{12}$ inhibitors is displayed in **Table 7**. As for the best antiplatelet agent of choice, the ongoing RCTs addressing the efficacy and safety of potent $P2Y_{12}$ inhibitors in this setting are reported in **Table 8**.

Finally, data are lacking as to the best long-term antithrombotic regimen after PCI (ie, >12 months). The current recommendation to hold antiplatelet therapy beyond 12 months in patients on OAC is based

CENTRAL ILLUSTRATION Continued

A practical summary of the antithrombotic approaches utilized in interventional and cardiac electrophysiology procedures. See main text for details. Thromboembolic risk is defined by a CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, sex category) score ≥2. [a]Thromboembolic risk is defined by a CHA_2DS_2-VASc score ≥2. [b]In patients receiving VKAs, perform INR measurement 3 days prior to the procedure to allow for sufficient time to adjust treatment accordingly. [c]Use of intraprocedural unfractionated heparin (UFH) in patients undergoing left atrial appendage (LAA) closure should take into consideration individual risks and benefits of anticoagulant treatment, as LAA closure is frequently performed in patients with relative or absolute contraindication to anticoagulant treatment. [d]After LAA closure, 45 days of antithrombotic treatment (consisting of OAC alone, OAC + clopidogrel or dual antiplatelet therapy, DAPT, see text for further details) is recommended to reduce the risk of device related thrombus. Follow-up imaging evaluation with TEE or computed tomography (CT) imaging of the LAA is recommended. [e]In patients with persistent flow into the LAA after 45 days, antithrombotic treatment should be continued and revaluation with imaging studies performed 6 months after the initial procedure. Once successful closure has been confirmed, single antiplatelet therapy (SAPT) may be continued. [f]In patients undergoing transcatheter aortic valve replacement (TAVR) with a previous indication for oral anticoagulation, an uninterrupted strategy with VKAs is feasible with an INR of 2 to 3. [g]In patients undergoing coronary angiography for acute coronary syndromes, dual antiplatelet therapy (DAPT) should be considered prior to the procedure. However, a loading dose of a $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, prasugrel) should only be considered in ST-segment elevation myocardial infarction (STEMI) or in patients with non-ST-segment elevation myocardial infarction once the decision to perform angioplasty has been made. [h]Duration of DAPT therapy should take into consideration the risk of stent thrombosis vs individual bleeding risks. [i]Duration of triple therapy (TT) should be as short as possible (ie, 1 week to 1 month), based on bleeding risk and stent thrombosis risk. Extending TT (ie, DAPT + OAC) beyond 1 month does not provide additional protection against stent thrombosis but increases the risk of bleeding events. [j]Currently, there is not enough evidence supporting the need for SAPT + OAC in patients undergoing TMVR. AC = anticoagulation; AF = atrial fibrillation; ACT = activated clotted time; AP = accessory pathway; AT = atrial tachycardia; CIED = cardiac implantable electronic device; CT = computed tomography; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; INR = international normalized ratio; LAA = left atrial appendage; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; SAPT = single antiplatelet therapy; TAVR = transcatheter aortic valve replacement; TE = thromboembolism; TEE = transesophageal echocardiography; TT = triple therapy; TMVR = transcatheter mitral valve repair; UFH = unfractionated heparin; VT = ventricular tachycardia; VKA = vitamin K antagonists.

on cohort studies[134,135] and on the AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial[136] showing the noninferiority of long-term monotherapy rivaroxaban vs rivaroxaban plus SAPT. Several ongoing RCTs will clarify the best mid-term and long-term antithrombotic strategies in this field (**Table 8**).

EVIDENCE-BASED PRACTICAL APPROACH AT A GLANCE.

- In patients undergoing PCI with an indication for OAC, the combination of OAC with a $P2Y_{12}$ inhibitor (preferably clopidogrel) is recommended. The duration of this therapy should be tailored based on type of coronary intervention and the clinical setting (expert opinion or Level of Evidence: C).[133]
- In patients with an indication for OAC without a clear indication for therapy with a VKA, treatment with a DOAC is preferred over treatment with VKA (expert opinion or Level of Evidence: C).[133]
- A triple antithrombotic therapy, preferably with DOACs, should be considered in patients with high ischemic risk post-PCI (eg, acute coronary syndrome) and for up to 30 days. Alternatively, a combination of DOACs (preferably dabigatran) with ticagrelor might be appropriate (expert opinion or Level of Evidence: C).[133]
- Although clopidogrel should be held after 12 months post-PCI, a combination of OAC plus $P2Y_{12}$ inhibitor could be indefinitely continued in patients with a high risk of TE events (expert opinion or Level of Evidence: C).[133]

ANTICOAGULATION FOR TRANSCATHETER MITRAL AND TRICUSPID VALVE INTERVENTIONS

Transcatheter therapies have been developed to treat patients with mitral valve disease and at prohibitive surgical risk.[137] If percutaneous mitral valve repair (TMVR) is a well-established option for both primary and secondary severe mitral regurgitation, TMVI has also emerged as a treatment option for patients with severe bioprosthetic mitral regurgitation and is under clinical investigation for native valve mitral regurgitation in patients at high risk of surgery.[137] However, these transcatheter valve procedures appear to have different TE risks. Given the low intrinsic thrombogenicity of the device, 1 to 6 months of DAPT (ie, aspirin plus clopidogrel) is generally recommended followed by aspirin alone for 12 months in TMVR patients[137] while long-term OAC seems feasible in those already on OAC (eg, AF).[138] Conversely, the TE risk is higher in patients undergoing TMVI, and they commonly require routine VKA therapy for at least 3 months followed by long-term aspirin.[137,139] DOACs may represent an alternative to VKA, although their role remains largely untested and requires further validation. Similar considerations apply to percutaneous tricuspid valve interventions.[137,139]

EVIDENCE-BASED PRACTICAL APPROACH AT A GLANCE.

- Intraprocedural anticoagulation with unfractionated heparin to achieve an activated clotting time >250 seconds is recommended during percutaneous mitral valve procedures (expert opinion or Level of Evidence: C).[137] Heparin reversal with protamine can considered postprocedure.
- After TMVR, DAPT for 6 months is recommended in patients without a prior indication for OAC (expert opinion or Level of Evidence: C).[137] In patients with clear indication for OAC, long-term OAC only may be considered postprocedure (authors' suggestions based on current evidence in the field).[138]
- In keeping with surgical implantation for biological mitral valve prostheses, the use of OAC with VKA for 3 to 6 months with a target international normalized ratio of 2.5 to mitigate the early risk of TE is recommended after TMVI followed by long-term aspirin (Class IIa, Level of Evidence: B).[139] Similar recommendations to the previous apply to percutaneous tricuspid valve interventions.[139]

CONCLUSIONS

The number of electrophysiological and interventional procedures is increasing worldwide and progressively extended to an aging population with a significant prevalence of comorbidities requiring OAC. The risk of thromboembolic and hemorrhagic complications should be well balanced for each patient in each setting. The **Central Illustration** summarizes the management of peri-, intra-, and postprocedural management of anticoagulation in patients undergoing a variety of electrophysiological and interventional cardiac procedures.

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