Triple Oral Antithrombotic Therapy in Atrial Fibrillation and Coronary Artery Stenting: Searching for the Best Combination

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Abstract

Patients with atrial fibrillation (AF) who are treated with oral anticoagulants often have concurrent coronary artery disease. Triple oral antithrombotic therapy (TOAT) is often necessity to prevent stent thrombosis or myocardial infarction associated with percutaneous coronary intervention or acute coronary syndrome in patients with comorbid coronary artery disease and AF. Although the use of TOAT (aspirin, clopidogrel, and warfarin) has excellent efficacy against thrombotic complications, this comes on the expense of increased bleeding risk. This review discusses potential strategies to improve TOAT benefit–risk ratio evidence from the literature. These strategies include: (1) dropping aspirin; (2) reducing the duration of TOAT; (3) switching warfarin to a direct oral anticoagulant (DOAC); (4) the use of DOAC in combination with a single antiplatelet agent; and (5) switching clopidogrel to a novel antiplatelet agent. Although dropping aspirin and reducing TOAT duration should be considered in selected AF patients at low risk of thrombosis, the role of DOACs and novel antiplatelets in TOAT has not been thoroughly studied, and there is limited evidence to support their use currently. Ongoing studies will provide safety and efficacy data to guide clinicians who frequently face the challenge of determining the best TOAT combination for their patients.

Keywords
► antithrombotic
► antiplatelet
► warfarin
► atrial fibrillation
► acute coronary syndrome

Stroke Prevention in Atrial Fibrillation Using Oral Anticoagulants

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias, with 10% prevalence in patients ≥ 80 years of age.[1–3] AF is an independent risk factor for stroke with an annual risk ranging from 2 to 18% based on the presence of other risk factors. Among different oral antithrombotic therapy studied, warfarin was shown to reduce stroke risk by 64% when compared with placebo and by 39% when compared with aspirin in AF patients.[4] Furthermore, it has been shown to be more effective than dual antiplatelets (DAP) when tested as an alternative antithrombotic regimen.[5] Although the effectiveness of warfarin was evident, the safety and complexity of managing warfarin therapy left patients and practitioners searching for alternative treatment options. Since 2010, four direct oral anticoagulants (DOACs) have been introduced into the market as an alternative to warfarin. DOACs act by directly and selectively inhibiting key coagulation factors such as thrombin (i.e., dabigatran) or factor Xa (i.e., rivaroxaban, apixaban, and edoxaban).[6–8] For many nonvalvular AF patients, DOACs are now recommended as first-line therapy for stroke prevention due to a favorable side effect profile and a lower risk of intracerebral hemorrhage.[9,10] In addition, these agents do not usually require strict routine monitoring or dose adjustments and have fewer drug–drug and drug–food interactions.

Ischemic Risk Prevention in Patients with Acute Coronary Syndromes and/or Undergoing Percutaneous Coronary Intervention Using DAP Treatment

Since 2001, DAP treatment with aspirin and clopidogrel has been the treatment of choice in patients with acute coronary syndromes (ACS) and in patients undergoing percutaneous coronary intervention (PCI) to prevent complications such as stent thrombosis, recurrent myocardial infarction (MI), and stroke.[11,12] Although aspirin is known to significantly reduce cardiovascular events after ACS, the addition of clopidogrel as a second antiplatelet was found to improve ACS outcomes significantly compared with aspirin alone.[13,14] Not long ago, novel antiplatelet agents (prasugrel and ticagrelor) were introduced as alternatives to clopidogrel in the setting of ACS. Prasugrel and ticagrelor generally achieve higher degrees of platelet inhibition than clopidogrel and do not appear to be affected by *CYP2C19* polymorphism.[15,16] As compared with clopidogrel, both agents were shown to improve clinical outcomes among patients with ACS but with an increase in bleeding risk, particularly in those undergoing PCI.[17,18] Current guidelines recommend the use of DAP for at least 4 weeks after bare-metal stent and for at least 6 months after drug-eluting stent (DES).[19,20] However, the exact duration of DAP therapy in patients receiving DES placement remains a controversial issue.[21–23]

Triple Oral Antithrombotic Therapy

Triple oral antithrombotic therapy (TOAT) is commonly used for patients with AF on oral anticoagulant therapy who experience an ACS or undergo elective PCI. It is estimated that coronary artery disease coexists in 20 to 30% of AF patients who also qualify for oral anticoagulant therapy.[24,25] Aspirin, clopidogrel, and warfarin have long been the mainstay TOAT combination. Despite its adequate efficacy, suboptimal safety remains a topic of much concern, especially given the morbidity and mortality associated with antithrombotic-related bleeding.[26–30] Potential strategies to improve TOAT (aspirin, clopidogrel, and warfarin) benefit–risk ratio include: (1) dropping aspirin; (2) reducing the duration of TOAT; (3) switching warfarin to a DOAC; (4) the use of DOAC in combination with a single antiplatelet agent; and (5) switching clopidogrel to a novel antiplatelet agent (►**Table 1**). In this review, we will discuss evidence from the literature on the efficacy, safety, and usefulness of these different strategies (►**Table 2**).

Dropping Aspirin

The reported efficacy of the TOAT (aspirin, clopidogrel and warfarin) comes at the expense of increased risk of bleeding. Several observational studies reported two- to threefold increase in bleeding with the use of TOAT when compared with DAP or to the use of warfarin and a single antiplatelet agent.[27,29,31,32] Since warfarin was deemed necessary for stroke prevention and the omission of clopidogrel could

Table 1 Potential strategies to improve TOAT (aspirin, clopidogrel, and warfarin) benefit–risk ratio

1. Dropping aspirin
2. Reducing the duration of TOAT
3. Switching warfarin to a DOAC
4. The use of DOAC in combination with a single antiplatelet agent
5. Switching clopidogrel to a novel antiplatelet agent

Abbreviations: DOAC, direct oral anticoagulant therapy; TOAT, triple oral anticoagulant therapy.

lead to an increased risk of stent thrombosis, the combination of warfarin and clopidogrel was chosen by The WOEST (The What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) study investigators to be tested for its safety and efficacy against TOAT.[30] This randomized controlled trial of 573 patients with ACS or elective PCI and a concurrent need for long-term warfarin therapy demonstrated that patients randomized to warfarin plus clopidogrel (omitting aspirin) had significantly reduced risk of major bleeding compared with patients randomized to TOAT therapy (19.4 vs. 44.4%; hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.26–0.40; $p < 0.001$). In addition, the use of clopidogrel with warfarin alone (omitting aspirin) was associated with a lower risk of combine thromboembolic endpoint that included death, MI, stroke, target-vessel revascularization, and stent thrombosis (11.1 vs. 17.6%; HR, 0.60; 95% CI, 0.38–0.94; $p = 0.025$). However, as the trial was powered to detect a difference in major bleeding and not in thromboembolic events, there were no statistically significant differences seen between the two study groups for MI, target-vessel revascularization, stroke, or stent thrombosis. All-cause mortality rate was lower in the clopidogrel/warfarin group compared with the TOAT group, which could be mediated by the lower number of bleeding in the clopidogrel/warfarin group. Similar findings were also reported in recently published large datasets highlighting the increased risk of bleeding and lack of clinical benefit associated with TOAT compared with warfarin/single antiplatelet.[33–35]

Reducing the Duration of Triple Oral Antithrombotic Therapy

In patients receiving a stent post-ACS/PCI without an indication for oral anticoagulant, shortening the duration of DAP therapy has been studied extensively. These trials yielded mixed results regarding the net clinical efficacy but reached agreement on the increased risk of bleeding with prolonged DAP therapy.[23,36,37] Similarly, longer duration of TOAT has long been recognized to increase the risk of bleeding complications. Recently, the ISAR-TRIPLE (Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation) study investigated TOAT after stenting and its duration.[38] Its aim was to evaluate

Table 2 Summary of clinical studies that investigated efficacy and/or safety of potential strategies to improve TOAT

Study	Design	Population	Treatment	Efficacy outcomes	Safety outcomes
Dropping aspirin					
Karjalainen et al (2007)[27]	Retrospective cohort (n = 478)	ACS/PCI + indication for OAC	TOAT vs. DAP vs. warfarin + single AP	At 12 mo, the rate of primary end point (death, MI, TVR, or stent thrombosis) was higher in the warfarin group (21.9 vs. 11%; OR, 2.3; 95% CI, 1.3–3.8). This was mainly driven by a significant difference (8.7 vs. 1.8%, p = 0.003) in mortality	Warfarin use + DAP or single AP associated with in-creased bleeding risk as compared with DAP use without warfarin (adjusted OR, 3.4; 95% CI, 1.2–9.3)
Sørensen et al (2009)[29]	Retrospective cohort (n = 40,812)	First time MI	TOAT vs. DAP vs. warfarin + single AP vs. monotherapy with ASA, clop or warfarin		• The risk of hospital admission for bleeding increased with the number of ATs used with the least incidence with warfarin monotherapy • The yearly incidence of bleeding was highest with clop + warfarin (12.3%) and TOAT (12%) • With ASA as reference, adjusted HRs for bleeding were 1.33 (95% CI, 1.11–1.59) for clop, 1.23 (0.94–1.61) for warfarin, 1.47 (1.28–1.69) for ASA + clop, 1.84 (1.51–2.23) for ASA + warfarin, 3.52 (2.42–5.11) for clop + warfarin, and 4.05 (3.08–5.33) for TOAT
Hansen et al (2010)[31]	Retrospective cohort (n = 82,854)	AF	TOAT vs. DAP vs. warfarin + single AP vs. monotherapy with ASA, clop or warfarin	Cox proportional hazards analysis of nonfatal and fatal ischemic stroke showed no benefit of combination therapy	• Using warfarin monotherapy as a reference, HR (95% CI) for the combined end point was 0.93 (0.88–0.98) for ASA, 1.06 (0.89–1.29) for clopid, 1.66 (1.34–2.04) for DAP, 1.83 (1.72–1.96) for warfarin + ASA, 3.08 (2.32–3.91) for warfarin + clop, and 3.7 (2.89–4.76) for TOAT • Crude incidence rate for bleeding increases with the number of antithrombotics
Lamberts et al (2012)[32]	Retrospective cohort (n = 11,480)	AF + ACS	TOAT vs. DAP vs. warfarin + single AP	No significant difference in thrombo-embolic risk was observed for TOAT vs. warfarin + single AP, HR= 1.15 (95% CI, 0.95–1.4)	• TOAT significantly increased the risk of bleeding compared with warfarin + single AP at 1 y (HR, 1.41; 95% CI, 1.10–1.81) • Crude incidence rate for bleeding increases with the number of antithrombotics
Dewilde et al (2013)[30] WOEST trial	RCT (n = 573)	ACS/PCI + indication for long-term OAC	Warfarin + clop vs. TOAT	Omitting aspirin reduced the risk of combined thromboembolic endpoint (death, MI, stroke, TVR, and ST) (11.1 vs. 17.6%; HR, 0.60; 95% CI, 0.38–0.94)	Warfarin + clop had less major bleeding compared with TOAT (19.4 vs. 44.4%; HR, 0.36; 95% CI, 0.26–0.40) which influenced a reduction in all-cause mortality (HR, 0.39; 95% CI, 0.16–0.93) after 1 y of treatment
Goto et al (2014)[33]	Retrospective cohort (n = 1,057)	AF with first time PCI	OAC vs. no OAC (1-yDAPT use was 47.6% in OAC group and 40.1% in no OAC group)	The cumulative 5-y incidence of stroke was not significantly different between the OAC and no-OAC groups (13.8 and 11.8%; HR, 1.20; 95% CI, 0.83–1.73)	
Reducing the duration TOAT					
Palmerini et al (2015)[23]	Meta-analysis of 10 RCTs (n = 31,666)	PCI (DES)	Shorter vs. longer DAP (vari-able definitions for length of DAP)	• Shorter DAP increased MI risk (HR, 1.51; 95% CI, 1.28–1.77) and ST risk (HR, 2.04; 95% CI, 1.48–2.80) • Shorter DAP was associated with sig-nificantly lower all-cause mortality (HR, 0.82; 95% CI, 0.69–0.98), which was attributable to lower noncardiac	Shorter DAP was associated with a lower risk of major bleeding (HR, 0.58; 95% CI, 0.47–0.72)

Table 2 (Continued)

Study	Design	Population	Treatment	Efficacy outcomes	Safety outcomes
Elmariah et al (2015)[37]	Meta-analysis of 14 RCTs (n = 69,644)	Patients on DAP for any indication	Longer (> 6 mo) vs. shorter (≤ 6 mo) DAP or ASA alone	mortality (HR, 0.67; 95% CI, 0.51–0.89), with similar cardiac mortality (HR, 0.93; 95% CI 0.73–1.17) Compared with ASA alone or shorter DAP, longer DAP was not associated with a difference in all-cause (HR, 1.04; 95% CI, 0.96–1.18) or cardiovascular mortality (HR, 1.01; 95% CI, 0.93–1.12)	
Fiedler et al (2015)[38] ISAR-TRIPLE	RCT (n = 614)	PCI (DES) + AF on long-term OAC	6 wk vs. 6 mo of TOAT	No significant difference in the combined end point of death, MI, definite ST, and stroke (9.8 vs. 8.8%; HR = 1.14; 95% CI, 0.68–1.91) at 9 mo	TIMI major bleeding at 9 mo was slightly higher in the 6-mo TOAT group when compared with the 6-wk group (5.3 vs. 4.0%; HR, 1.35; 95% CI, 0.64–2.84)
Switching warfarin to a DOAC					
Miller et al (2012)[39]	Meta-analysis of 3 RCTs (n = 44,563)	Nonvalvular AF	DOACs (dabigatran, rivaroxaban, or apixaban) vs. warfarin	DOACs were more efficacious than warfarin in reducing the risk of all-cause stroke and systemic embolism (RR, 0.78; 95% CI, 0.67–0.92), ischemic and un-identified stroke (RR, 0.87; 95% CI, 0.77–0.99), hemorrhagic stroke (RR, 0.45; 95% CI, 0.31–0.68), all-cause mortality (RR, 0.88; 95% CI, 0.82–0.95), and vascular mortality (RR, 0.87; 95% CI, 0.77–0.98)	• DOACs were associated with a lower risk of intracranial bleeding (RR, 0.49; 95% CI, 0.36–0.66). • No increased risk for major bleeding (RR, 0.88; 95% CI, 0.71–1.09) or GI bleeding (RR, 1.25; 95% CI, 0.91–1.72) with DOACs vs. warfarin
Alexander et al (2009)[41] APPRAISE	RCT (n = 1,715)	ACS	Placebo vs. four doses of apixaban: 2.5 mg twice daily, 10 mg once daily, 10 mg twice daily, or 20 mg once daily (nearly all patients received ASA and > 75% on DAP)	Addition of apixaban to AP resulted in tendency to lower rates of ischemic events (HR, 0.73; 95% CI, 0.44–1.19) with apixaban 2.5 mg twice daily and (HR, 0.61; 95% CI, 0.35–1.04) with 10 mg once daily compared with placebo	A dose-dependent increase in major or clinically relevant nonmajor bleeding was observed (HR, 1.78; 95% CI, 0.91–3.48) with apixaban 2.5 mg twice daily and (HR, 2.45; 95% CI, 1.31–4.61) with 10 mg once daily compared with placebo
Mega et al (2012)[42] ATLAS ACS	RCT (n = 15,526)	ACS	Rivaroxaban 2.5 mg or 5 mg twice daily or placebo (nearly all patients were on DAP)	Rivaroxaban significantly reduced the primary efficacy end point (composite of death from cardiovascular causes, MI, or stroke) compared with placebo (8.9 vs. 10.7%; HR, 0.84; 95% CI, 0.74–0.96)	• Rivaroxaban increased the rates of non-CABG major bleeding (2.1 vs. 0.6%) and intracranial hemorrhage (0.6 vs. 0.2%) without a significant increase in fatal bleeding (0.3 vs. 0.2%) or other adverse events • The twice daily 2.5 mg dose resulted in fewer fatal bleeding events than the twice daily 5 mg dose (0.1 vs. 0.4%)
Oldgren et al (2011)[43] RE-DEEM	RCT (n = 1,861)	ACS	Dabigatran (50, 75, 110, and 150 mg twice daily) + DAP vs. placebo + DAP	Incidence of death, MI, or stroke was 3.8% in the placebo group vs. 4.6% in 50 mg, 4.9% in 75 mg, 3.0% in 110 mg, and 3.5% in the 150 mg dabigatran groups	A composite of major or clinically relevant minor bleeding during the 6-mo treatment period showed a dose-dependent increase with dabigatran as compared with placebo (HR, 1.77; 95% CI, 0.70–4.50 for 50 mg; HR, 2.17; 95% CI, 0.88–5.31 for 75 mg; HR, 3.92; 95% CI, 1.72–8.95 for 110 mg; and HR, 4.27; 95% CI, 1.86–9.81 for 150 mg)
Oldgren et al (2013)[44]	Meta-analysis of 7 RCTs (n = 30,866)	ACS	ASA alone ± DOAC and DAP ± DOAC	• When compared with ASA alone, the combination of DOAC + ASA reduced the incidence of MACE (HR, 0.7; 95% CI, 0.59–0.84)	• DOAC + ASA increased clinically significant bleeding (HR, 1.79; 95% CI, 1.54–2.09) • DOAC + DAPT more than doubled the bleeding (HR, 2.34; 95% CI, 2.06–2.66)

(Continued)

Table 2 (*Continued*)

Study	Design	Population	Treatment	Efficacy outcomes	Safety outcomes
				• Compared with DAP, adding DOAC decreased the incidence of MACE modestly (HR, 0.87; 95% CI, 0.80–0.95)	
Dans et al (2013)[46]	RCT subgroup analysis (n = 18,113)	AF + ACS	Dabigatran 110 mg or 150 mg BID vs. warfarin with or without AP	Dabigatran 110 mg BID was noninferior to warfarin in reducing stroke and systemic embolism in patients receiving AP (HR = 0.93; 95% CI, 0.70–1.25)	• Fewer major bleeds occurred with dabigatran than warfarin in both subgroups (HR, 0.82; 95% CI, 0.67–1.00 for those on AP; HR, 0.79; 0.64–0.96 for those not on AP) • Concomitant use of a single AP (HR, 1.60; 95% CI, 1.42–1.82) and DAP (HR, 2.31; 95% CI, 1.79–2.98) increased the risk of major bleeding
Alexander et al (2011)[47] APPRAISE 2	RCT (n = 7,392)	ACS + ≥ two risk factors for recurrent ischemic events	Apixaban 5 mg BID vs. placebo, in addition to standard AP	No significant difference in the composite end point of cardiovascular death, MI, or ischemic stroke between apixaban and placebo (HR, 0.95; 95% CI, 0.80–1.11)	• The trial was terminated prematurely because of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events • TIMI major bleeding occurred more in the apixaban group vs. placebo (HR, 2.59; 95% CI, 1.50–4.46) • A greater number of intracranial and fatal bleeding events occurred with apixaban than with placebo
Clopidogrel vs. a novel antiplatelet agent					
Sarafoff et al (2013)[49]	Prospective cohort (n = 377)	ACS (DES) + indication for OAC	TOAT with prasugrel + ASA + warfarin vs. TOAT with clop + ASA + warfarin	There was no significant difference in the composite ischemic end point of death, MI, ischemic stroke, or definite ST (9.5 vs. 7.0%; HR, 1.4; 95% CI, 0.3–6.1)	Composite of TIMI major and minor bleeding at 6 mo occurred significantly more often in the prasugrel compared with the clop group (28.6 vs. 6.7%; HR, 4.6; 95% CI, 1.9–11.4)

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; AP, antiplatelet; ASA, aspirin; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; Clop, clopidogrel; CrI, credible interval; CVD, cardiovascular disease; DES, drug-eluting stent; DOAC, direct oral anticoagulant; HR, hazard ratio; MI, myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative Risk; ST, stent thrombosis; TIMI, thrombolysis in myocardial infarction; TOAT, triple oral antithrombotic therapy; TVR, target vessel revascularization.

whether shortening the duration of clopidogrel therapy from 6 months to 6 weeks after DES implantation was associated with a superior net clinical outcome in patients receiving concomitant aspirin and oral anticoagulant therapy. This study demonstrated that among 614 patients on long-term oral anticoagulation who are receiving DES for stable angina or ACS, a 6-week TOAT course was not superior to a 6-month triple therapy. Specifically, there was no significant difference in the primary combined end point of death, MI, definite stent thrombosis, and stroke (9.8 vs. 8.8%; HR = 1.14; 95% CI, 0.68–1.91; $p = 0.63$), or the secondary bleeding end point of thrombolysis in MI (TIMI) major bleeding (5.3 vs. 4.0%; HR, 1.35; 95% CI, 0.64–2.84; $p = 0.44$) in the 6-month group when compared with the 6-week group at 9 months. Individual components of the primary end point were similar, with the exception of a higher incidence of MI in the 6-week compared with the 6-month therapy group (2 vs. 0%; $p = 0.03$). However, results of this trial should be interpreted in light of several limitations. First, the difference in the incidence of MI is likely due to imbalance in the ischemic events between groups at 6 weeks when both arms were still on TOAT. Only one MI event occurred after 6 weeks (on day 212 post-PCI) while the patient was receiving oral anticoagulation and aspirin. This imbalance is likely due to the early randomization of patients' post-PCI and not at 6 weeks when prior event exposure might have been balanced by randomization.[38] Second, the study was only powered to detect a fairly large reduction (60%) in events, leaving the subgroups underpowered for further analyses. Apart from the ISAR-TRIPLE trial, shortening the duration of clopidogrel in TOAT-treated patients has not been studied prospectively. A retrospective nationwide registry found no clinical benefit and possible harm with the prolonged use of TOAT beyond 4 months.[33]

Switching Warfarin to a Direct Oral Anticoagulant

DOACs have repeatedly reduced the risk of intracerebral bleeding when compared with warfarin in several phase III studies.[39] Therefore, replacement of warfarin with a DOAC in TOAT is a logical strategy to reduce the risk of bleeding in patients requiring combined anticoagulant and antiplatelet therapy. Unlike warfarin, DOACs have fast onset of action and do not have fluctuating levels of anticoagulant effect except in patients with sudden deterioration of kidney and/or renal function, as well as in those receiving antibiotic therapy.[40] Despite these benefits, the exact role of DOACs in patients with ACS and AF is not fully elucidated. AF patients requiring oral anticoagulant therapy were systematically excluded from recent ACS trials testing DOACs, and patients with recent ACS were excluded from most phase III stroke prevention trials in AF patients.[41–45] So far, there have been no published head-to-head comparisons of any DOACs and warfarin in AF patients with ACS except for a subanalysis of the RE-LY study.[46] This substudy showed that dabigatran 110 mg BID was noninferior to warfarin in reducing stroke and systemic embolism and was associated with fewer major bleeds regardless of the use of DAP. However, the effect of dabigatran 150 mg BID on stroke and systemic embolism reduction was less prominent among patients using DAP. In addition, dabigatran 150 mg had similar rate of major bleeding to warfarin regardless of the use of DAP. In the time-dependent analysis, there was an additive effect on major bleeding risk with the number of antiplatelets used regardless of the oral anticoagulant dose used (HR, 1.60; 95% CI, 1.42–1.82 for a single vs. no antiplatelet and HR, 2.31; 95% CI, 1.79–2.98 for DAP vs. no antiplatelet). It is important to remember that this post hoc analysis was not part of the primary randomization and therefore must be interpreted as an observational (nonrandomized) finding.

The use of DOACs in combination with aspirin and clopidogrel was more commonly studied in patients with ACS (but not AF). For instance, in the Re-DEEM study, the addition of different doses of dabigatran or placebo to DAP treatment post-ACS was assessed in 1,861 patients.[43] This phase II study showed that dabigatran was associated with a dose-dependent increase in bleeding events when compared with placebo for 50 mg (HR, 1.77; 95% CI, 0.70–4.50); for 75 mg (HR, 2.17; 95% CI, 0.88–5.31); for 110 mg (HR, 3.92; 95% CI, 1.72–8.95); and for 150 mg (HR, 4.27; 95% CI, 1.86–9.81), with no significant difference in the cardiovascular efficacy outcomes. On the contrary, low-dose rivaroxaban (2.5 or 5 mg BID) were compared with placebo in 15,526 ACS patients receiving DAP treatment in ATLAS ACS 2–TIMI 51 study.[42] Both rivaroxaban doses were shown to significantly improve the primary cardiovascular efficacy outcomes (9.1 vs. 10.7%; HR, 0.84; 95% CI, 0.72–0.97 for 2.5 mg and 8.8 vs. 10.7%; HR, 0.85; 95% CI, 0.73–0.98 for 5 mg). A reduction in cardiovascular and all-cause mortality was also shown in the rivaroxaban 2.5 mg arm (2.7 vs. 4.1%; HR, 0.66; 95% CI, 0.51–0.86 for cardiovascular mortality and 2.9 vs. 4.5%; HR, 0.83; 95% CI, 0.72–0.97 for all-cause mortality). However, major bleeding and intracranial hemorrhage were significantly higher in the rivaroxaban group (2.1 vs. 0.6%; HR, 3.96; 95% CI, 2.46–6.38 for major TIMI bleeding and 0.6 vs. 0.2%; HR, 3.28; 95% CI, 1.28–8.42 for intracranial hemorrhage), without a significant increase in fatal bleeding. Finally, a range of apixaban doses compared with placebo in ACS patients receiving DAP treatment were investigated in the APPRAISE trial.[41] In this study, apixaban 10 mg BID and apixaban 20 mg once daily were discontinued because of excess total bleeding. The two other doses of apixaban (2.5mg BID and 10 mg once daily) still showed a dose-related increase in bleeding and a trend toward improvement in cardiovascular ischemic events. Apixaban 5 mg BID was then explored further in the APPRAISE-2 study.[47] The study was prematurely stopped due to excessive TIMI major bleeding in the apixaban group (1.3 vs. 0.5%; HR, 2.59; 95% CI, 1.50–4.46; $p = 0.001$) without a significant improvement in the efficacy outcomes.

A recent meta-analysis, including seven randomized, placebo-controlled phase II and III studies of DOACs in 30,866 patients with recent ACS, showed that the addition of DOACs to aspirin alone led to a 30% reduction in major adverse cardiovascular events (MACE) (HR, 0.70; 95% CI, 0.59–0.84), but a substantial increase in bleeding (HR, 1.79; 95% CI, 1.54–2.09). The reduction in MACE events was attenuated

(HR, 0.87; 95% CI, 0.80–0.95) and the risk of major bleeding was more pronounced (HR, 2.34; 95% CI, 2.06–2.66) when DOACs were used in combination with DAP therapy including aspirin and clopidogrel.[44]

Use of Direct Oral Anticoagulant in Combination with a Single Antiplatelet Agent

To explore the outcomes associated with DOAC therapy as a part of the antithrombotic therapy in AF patients who experience an ACS, two trials are ongoing or planned. The first trial, PIONEER AF-PCI (NCT01830543), is an open-label, randomized, controlled, multicenter study exploring rivaroxaban or dose-adjusted warfarin in subjects with AF who undergo PCI and require DAP therapy.[48] This trial is designed to explore safety outcomes, primarily related to clinically significant bleeding. This trial will also study the more potent platelet inhibitors prasugrel and ticagrelor in combination with oral anticoagulant with regard to bleeding safety outcomes. A similar but larger clinical trial with dabigatran is the RE-DUAL PCI (Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting) trial (NCT02164864). The main objective of this study is to compare a dual antithrombotic therapy regimen of dabigatran 110 mg BID plus clopidogrel to a TOAT combination of warfarin plus clopidogrel or ticagrelor plus aspirin in AF patients who undergo a PCI with stenting (elective or due to ACS). The study aims to demonstrate noninferiority of dabigatran when compared with warfarin in efficacy and safety. However, it is important to note that both trials will not evaluate the combination of DOACs with DAP but will evaluate the efficacy and safety of dual therapy of DOAC combined with a single antiplatelet to TOAT with warfarin, aspirin, and clopidogrel.[11]

Switching Clopidogrel to a Novel Antiplatelet Agent

Although the previously discussed strategies were intended primarily to reduce the risk of bleeding associated with TOAT, switching clopidogrel to a novel antiplatelet agent aims to enhance the net clinical benefit rather than reducing the risk of bleeding. Novel antiplatelet drugs, such as prasugrel and ticagrelor, have been shown to be more effective at reducing recurrent MI, stroke, and death than clopidogrel in patients with ACS, but they were also associated with an increased risk of bleeding.[17,18] The use of prasugrel in TOAT was studied by Sarafoff et al in 2013.[49] When compared with clopidogrel, the treatment with prasugrel in addition to aspirin and warfarin for a 6-month regimen was associated with a significant increase in the rate of bleeding (28.6 vs. 6.7%; HR, 3.2; 95% CI, 1.1–9.1; $p = 0.03$). There was no significant difference in the combined ischemic secondary end points. Similarly, there was a recent report of two cases of fatal bleeding when prasugrel was used as part of TOAT.[50] To that end, use of prasugrel is generally not recommended as a part of a TOAT regimen.[19] Although ticagrelor was not studied to date in TOAT, it is likely to expose patients to a higher risk of bleeding as well given its results in ACS patients when compared with clopidogrel.[17]

Guideline Recommendations

Both the American College of Cardiology/American Heart Association (AHA) and the European Society of Cardiology (ESC) recommend shortening the duration of TOAT as much as possible when indications dictate the use of all three antithrombotic agents.[19,51] They then recommend the use of an oral anticoagulant plus a single antiplatelet agent to reduce bleeding risk. The TOAT regimen recommended by the ESC is aspirin and clopidogrel combined with either warfarin or the lowest dose of DOAC (dabigatran 110 mg BID, rivaroxaban 15 mg daily, and apixaban 2.5 mg BID). The AHA, however, does not recommend the use of DOACs in TOAT since they were not evaluated in AF patients with ACS/PCI. The bleeding risk associated with prasugrel is excessive and was not tested for ticagrelor, hence both the AHA and the ESC recommend against the use of novel antiplatelets in TOAT. Both guidelines also recommend to maintain international normalized ratio levels between 2.0 and 2.5 in AF patients receiving warfarin along with DAP.[52] A summary of both guidelines' recommendations is provided in ►Table 3.

Table 3 ACC/AHA and ESC guideline summary on the use of TOAT

Guideline	Recommendation
ACC/AHA and ESC	Shorten the duration of TOAT as much as possible followed by the use of oral anticoagulant and a single antiplatelet agent
ACC/AHA	Recommended TOAT: warfarin + aspirin + clopidogrel
ESC	Recommended TOAT: warfarin or the lowest dose of DOAC (dabigatran 110 mg BID, rivaroxaban 15 mg daily, apixaban 2.5mg BID) + aspirin + clopidogrel
ACC/AHA and ESC	Control INR levels between 2.0 and 2.5 in AF patients receiving warfarin along with DAP
ACC/AHA and ESC	Recommend against the use of novel antiplatelets in TOAT

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; AF, atrial fibrillation; DAP, dual antiplatelets; DOAC, direct oral anticoagulant; ESC, European Society of Cardiology; INR, international normalized ratio; TOAT, triple oral antithrombotic therapy.

Summary

TOAT (warfarin/aspirin/clopidogrel) increases the risk of bleeding when compared with the use of a combination of warfarin and a single antiplatelet agent. Dual therapy with warfarin and clopidogrel should be considered as an alternative to triple therapy in selected AF patients at low risk of stent thrombosis/recurrent cardiac events. If TOAT (warfarin/aspirin/clopidogrel) therapy is used, clinicians must weigh ischemic and bleeding risks of their patients when deciding on the duration of this combination due to the fact that its optimal duration is not established. The use of prasugrel in combination with warfarin and aspirin leads to a significant increase in bleeding compared with the combination of clopidogrel, aspirin, and warfarin. Therefore, the use of prasugrel (or ticagrelor) as a part of TOAT is not recommended.[19]

Among patients with ACS but no comorbid AF, the addition of a DOAC to antiplatelet therapy led to a modest reduction in cardiovascular events but on the expense of excessive bleeding risk. This was most evident in patients receiving DAP therapy. Notably, the reduction in ischemic events by DOACs was most promising when added to a single antiplatelet therapy. Therefore, studies evaluating the combination of DOACs and a single antiplatelet therapy in AF patients who experience an ACS were initiated and results are still pending.

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