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Triple therapy in patients with atrial fibrillation and acute coronary syndrome or percutaneous coronary intervention/stenting

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Abstract

Patients with atrial fibrillation (AF) and acute coronary syndrome (ACS) are at high risk of stroke, recurrent coronary ischemic events, and cardiovascular mortality. The composition of antithrombotic therapy including an oral anticoagulant and antiplatelet drug(s) should be tailored according to the individual patient's risk profile, to reduce the bleeding risk and maintain antithrombotic effect. There is no single antithrombotic treatment regimen that would fit to all patients with AF and ACS. However, available data promote the use of full-dose direct oral anticoagulants (DOACs) (dabigatran 150 mg twice daily or apixaban 5 mg twice daily) or rivaroxaban 15 mg once daily in patients with AF and ACS or percutaneous coronary intervention (PCI). For many patients, a DOAC plus $P2Y_{12}$ inhibitor early after ACS and/or PCI would be optimal, whereas a longer course of triple therapy should be used in patients at high thrombotic risk.

KEYWORDS

acute coronary syndrome, antiplatelets, atrial fibrillation, oral anticoagulation, percutaneous coronary intervention, triple therapy

Essentials

- Atrial fibrillation (AF) is common among patients with vascular disease.
- Studies on antithrombotic management in patients with AF and acute coronary syndrome (ACS) were assessed.
- Balancing the risk of ischemia and stroke and bleeding in patients with AF and ACS remains challenging.
- Direct oral anticoagulant–based management strategies are preferred.

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults, coexisting with vascular disease in about 30% of patients. Over 80% of patients with AF have ≥1 stroke risk factor(s), thus requiring stroke prevention therapy, most commonly using oral anticoagulants (OACs).[1] Given that the estimated global prevalence of AF is 1% to 3% and around 20% of patients with AF would need a percutaneous coronary intervention (PCI), about 1 to 3 million Europeans with AF taking OACs may require PCI.[2–5]

Patients with AF and acute coronary syndrome (ACS) (ie, unstable angina, non–ST-segment elevation myocardial infarction [MI] or ST-segment elevation MI) have particularly high risk of recurrent coronary events (ie, MI or stent thrombosis), stroke, and cardiovascular mortality.[6]

Preventing stroke, recurrent cardiac ischemia, and stent thrombosis using a combined antithrombotic therapy needs to be balanced against the risk of major bleeding (including intracranial hemorrhage ICH; Figure 1).[1,7] The use of dual antiplatelet therapy (DAPT) alone would not sufficiently protect patients against stroke, whereas OAC monotherapy, either a direct oral anticoagulant (DOAC) or vitamin K antagonist (VKA), would not protect patients against new coronary events.[8,9] Triple therapy (TT) using DAPT in combination with an OAC effectively prevents vascular ischemic events but is associated with considerably increased risk of bleeding.[10]

2 | OVERVIEW OF PUBLISHED DATA

Various studies have addressed the challenging management of patients with AF and ACS. Observational studies have shown that in AF patients after MI/PCI, dual antithrombotic therapy (clopidogrel and OAC) was equal to or better than TT in terms of benefit (MI or coronary death, fatal or nonfatal ischemic stroke, and all-cause mortality) and safety outcomes (fatal or nonfatal bleeding).[11] In the Management of Patients With Atrial Fibrillation Undergoing Coronary Artery Stenting (AFCAS) registry,[12] TT, DAPT, and dual antithrombotic therapy (VKA with clopidogrel) had similar 1-year efficacy (stroke/transient ischemic events, peripheral embolism, MI, revascularization, definite/probable stent thrombosis) and safety (minor and major bleedings), but the study was limited by a low rate of adverse events and relatively small size of the group taking VKA with clopidogrel.

In the warfarin era, the What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) trial assessed the use of antiplatelet therapy in patients on a VKA.[13] The use of dual antithrombotic therapy (clopidogrel and a VKA) was compared to triple therapy (VKA and clopidogrel plus aspirin). Dual antithrombotic therapy was associated with significantly lower risk of Thrombolysis in Myocardial Infarction (TIMI) minor and major bleeding in comparison to TT (of note, there was no significant difference in major bleeds). However, the trial was small; not all patients were taking OACs for AF-related stroke prevention (69% of patients had AF) and 25% to 30% of participants had an ACS; radial access was chosen in only 25% to 27% of patients; and TT was continued for 12 months. Notably, the WOEST trial also showed that patients taking TT had a higher risk of mortality compared with those on dual antithrombotic therapy (ie, clopidogrel and a VKA).

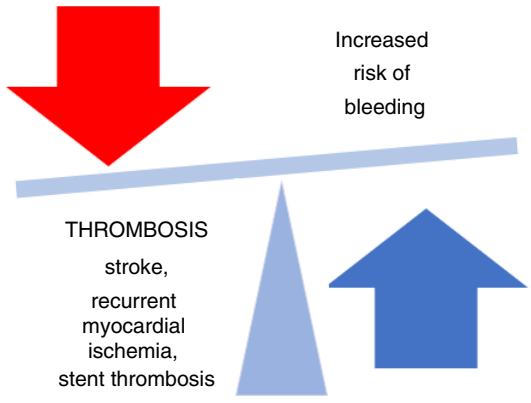

FIGURE 1 Balancing the risks in the patients with atrial fibrillation who present with an acute coronary syndrome and/or undergo percutaneous coronary intervention/stenting

In the contemporary era of DOACs, post hoc analyses of the landmark DOACs trials for stroke prevention in AF showed consistent efficacy and safety of the respective DOAC versus warfarin irrespective of the concomitant aspirin use or nonuse.[14–17] Although patients concomitantly using an antiplatelet drug (mostly aspirin) and OAC (either a DOAC or warfarin) were at higher risk of both ischemic and bleeding events compared with those on OAC monotherapy, the rates of hemorrhagic stroke or ICH were consistently lower with DOACs in comparison to warfarin.[14–17]

Contemporary observational studies consistently reported findings similar to those substudies. The Danish nationwide registry–based study, for example, reported that among patients with AF and MI and/or PCI, those taking a DOAC plus DAPT had a significantly lower risk of bleeding than patients taking a VKA plus DAPT, with no significant differences in all-cause mortality, ischemic stroke, or MI between the 2 treatment regimens.[18] The study was limited by lack of significant parameters (International Normalized Ratio [INR], blood pressure, creatinine clearance, estimated glomerular filtration rate, and alanine amino transferase). There was also no possibility to compare safety and efficacy of particular DOACs because of the limited number of patients.

Four recent open-label, randomized, controlled clinical trials investigated the use of DOACs in patients with AF with a recent ACS and/or undergoing a PCI[19–22] see Table 1. The PIONEER AF-PCI (an open-label, randomized, controlled, multicenter study exploring 2 treatment strategies of rivaroxaban and dose-adjusted oral VKA treatment strategy in subjects with AF undergoing PCI)[19] was an exploratory study comparing bleeding rates across 3 strategies (low-dose rivaroxaban [2.5 mg twice daily] plus DAPT vs. rivaroxaban 15 mg once daily, or 10 mg once daily in patients with a creatinine clearance of <50 mL/min, plus clopidogrel [dual antithrombotic therapy with DOAC or TT with DOAC] vs. TT with VKA plus DAPT) in patients with AF after a PCI with stent placement. The primary safety end point was defined as the percentage of patients with either TIMI major bleeding, minor bleeding, or bleeding requiring medical attention events by the end of 12 months of randomized therapy. Secondary safety end points were defined as the incidence of each component of the bleeding composite (TIMI major bleeding, minor bleeding, and bleeding requiring medical attention), the composite of adverse cardiovascular events (cardiovascular death, stroke, and MI), as well as cardiovascular death, MI, stroke, and stent thrombosis. The treatment regimens with rivaroxaban 15 mg once daily plus clopidogrel for 12 months or rivaroxaban 2.5 mg twice daily plus DAPT for 1, 6, or 12 months were associated with lower rates

TABLE 1 Randomized clinical trials of combined antithrombotic therapies in patients with AF with ACS or PCI/Stenting

	PIONEER-AF PCI [23]	RE-DUAL PCI [20]	ENTRUST-AF PCI [22]	AUGUSTUS [24]
Objective	Rivaroxaban + $P2Y_{12}$ inhibitor or DAPT versus VKA + DAPT in patients with NVAF undergoing PCI	Dabigatran + $P2Y_{12}$ inhibitor versus VKA + DAPT in patients with NVAF undergoing PCI	Edoxaban + P2Y12 inhibitor versus VKA + DAPT in patients with NVAF undergoing PCI	Apixaban + ASA/placebo versus VKA + ASA/placebo in patients with NVAF and ACS or PCI
Population size	2124	2725	1506	4600
Treatments	Rivaroxaban 15 mg once daily + $P2Y_{12}$ inhibitor, rivaroxaban 2.5 mg once daily + $P2Y_{12}$ inhibitor + ASA, then rivaroxaban 15 mg once daily + ASA, VKA + $P2Y_{12}$ inhibitor + ASA, then VKA + ASA	Dabigatran 120 mg or 110 mg twice daily + $P2Y_{12}$ inhibitor, VKA + $P2Y_{12}$ inhibitor + ASA	Edoxaban 60 mg once daily or 30 mg once daily + $P2Y_{12}$ inhibitor, VKA + $P2Y_{12}$ inhibitor + aspirin	Apixaban 5 mg or 2.5 mg twice daily + ASA/placebo VKA + ASA/placebo
Duration	12 mo	6-30 mo	12 mo	6 mo
Primary outcome	Clinically significant bleeding	Major or clinically relevant nonmajor bleeding event	Major or clinically relevant nonmajor bleeding	Major or clinically relevant nonmajor bleeding
Main secondary composite end point	The composite of death from cardiovascular causes, myocardial infarction, or stroke	The composite of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization (PCI or coronary artery bypass grafting).	The composite of cardiovascular death, stroke, systemic embolic events, myocardial infarction, and definite stent thrombosis	The composite of death or hospitalization; the composite of death or ischemic events (stroke, myocardial infarction, stent thrombosis [definite or probable], or urgent revascularization)
Analysis period	Treatment-emergent period	Time to first event	Day 1 to 12 mo	Time to first event

Abbreviations: ACS, acute coronary syndrome; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; NVAF, nonvalvular atrial fibrillation; PCI, percutaneous coronary intervention; TTR, time in therapeutic range; VKA, vitamin K antagonists.

of the composite end point of bleeding than TT with VKA plus DAPT for 1, 6, or 12 months.[23] All 3 strategies were associated with similar rates of composite outcome of cardiovascular mortality, MI, or stroke; however, the trial was underpowered to establish superiority or noninferiority of evaluated strategies regarding these outcomes.

The aim of the Evaluation of Dual Therapy with Dabigatran Versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting (REDUAL-PCI)[20] was to compare dual antithrombotic therapy with dabigatran (dabigatran 150 mg or 110 mg twice daily plus clopidogrel or ticagrelor) to TT (warfarin plus clopidogrel or ticagrelor plus aspirin) in patients with AF after PCI. The primary end point was defined as a major or clinically relevant nonmajor (CRNM) bleeding event. The secondary end points were defined as a composite efficacy end point of MI, stroke, or systemic embolism; death or unplanned revascularization; or a combined end point of thromboembolic events or death as well as the individual thromboembolic events and definite stent thrombosis. Compared with TT, both dual antithrombotic therapy regimens (ie, dabigatran 110 mg twice daily or 150 mg twice daily plus a $P2Y_{12}$ inhibitor) were associated with significantly lower risk of major bleeding and CRNM bleeding. Dual antithrombotic therapy with dabigatran (both dabigatran doses taken together) was noninferior to TT regarding the rates of MI, stroke, or systemic embolism. The study was underpowered to evaluate efficacy according to dabigatran dose. Moreover, with respect to the results for the safety and efficacy end points, it is only possible to speculate on the relative contributions of the omission of aspirin and the type of OAC in the dual antithrombotic therapy groups and the triple-therapy group.

Both the PIONEER AF-PCI and RE-DUAL PCI trial clearly showed that dual therapy including the respective DOAC plus a $P2Y_{12}$ inhibitor (mostly clopidogrel) was associated with significantly less major bleeding in comparison to TT with VKA plus dual antiplatelet therapy. However, these trials could not distinguish whether the bleeding risk reduction was driven by the use of a DOAC or nonuse of aspirin, or both.

Apixaban was tested in an open-label, 2 × 2 factorial, randomized controlled trial evaluating the safety of apixaban versus VKA and aspirin versus placebo in patients with AF and ACS and/or PCI (the AUGUSTUS trial).[21] Patients with AF and an ACS and/or PCI within the preceding 14 days were randomized to apixaban 5 mg twice daily (or apixaban 2.5 mg twice daily in patients fulfilling dose reduction criteria) versus VKA and to aspirin versus aspirin-placebo. The primary outcome was major bleeding defined by

the ISTH or CRNM bleeding. Secondary outcomes included the composite end point of death, stroke, MI, stent thrombosis, or urgent hospitalization and the composite of death, hospitalization, and first hospitalization for any cause. Dual antithrombotic therapy (apixaban plus $P2Y_{12}$ inhibitor without aspirin) was associated with significantly lower incidence of bleeding when compared to regimen with VKA, aspirin, or both. Apixaban without aspirin was also correlated with significantly lower incidence of hospitalizations than VKA, aspirin, or both. There were no significant differences in ischemic events, although the rates of stent thrombosis and cardiovascular events were numerically higher in the placebo-treated patients compared to those on aspirin, while the rate of stroke was lower in patients on apixaban than in those on VKA.[24] One of the major study limitations is the poor quality of anticoagulation with VKA (time in therapeutic range [TTR] in patients on VKA was lower than in previous randomized trials).

In the Safety and Efficacy of an Edoxaban-Based Antithrombotic Regimen in Patients With AF Following Successful PCI With Stent Placement (the ENTRUST-AF PCI) trial,[22] AF patients undergoing PCI for stable coronary artery disease or ACS were randomized to dual antithrombotic therapy with a DOAC (edoxaban [60 mg once daily or 30 mg once daily where dose reduction criteria were fulfilled] with a $P2Y_{12}$ inhibitor for 12 months) or TT with VKA plus $P2Y_{12}$ inhibitor and aspirin (100 mg once daily for 1-12 months). The primary end point was defined as the composite of major or CRNM bleeding defined by the ISTH. The composite of cardiovascular death, stroke, systemic embolic events, MI, and definite stent thrombosis was defined as the main efficacy outcome. Edoxaban 60 mg once daily plus a $P2Y_{12}$ inhibitor was noninferior to TT with VKA regarding major or CRNM bleeding events at 12 months. The main efficacy outcome (composite of cardiovascular death, stroke, systemic embolic events, MI, or definite stent thrombosis) were similar in both treatment arms. The study was limited by its open-label design. It was also underpowered and limited by a small proportion of patients medicated with a more potent $P2Y_{12}$ inhibitor than clopidogrel.

In a network meta-analysis that included the WOEST, PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials and 4 different treatment strategies (ie, DOAC or VKA plus a $P2Y_{12}$ inhibitor dual regimens and DOAC or VKA plus a $P2Y_{12}$ and aspirin TT regimens),[25] DOAC-based dual treatments were associated with fewer TIMI major bleedings and less ICH compared with VKA with DAPT, and there was no statistically significant difference in the rates of major adverse cardiac events, all-cause death, and cardiovascular mortality among the 4 treatment regimens. No statistically significant differences were revealed with respect to stroke, MI, and stent thrombosis among the treatment regimens (see Table 2).

In another meta-analysis,[26] data from the PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials were evaluated. The use of DOACs was associated with significantly lower rates of bleeding and similar rates of ischemic events (stroke, MI, and stent thrombosis) and all-cause death/cardiovascular mortality than VKA-based treatments (Table 3). Dual antithrombotic therapy was associated with a significantly lower incidence of bleeding; similar rates of stroke, MI, and all-cause/cardiovascular death; and a significantly greater risk of stent thrombosis when compared with TT (Table 3).

Overall, available data support the use of full-dose DOAC (dabigatran 150 mg twice daily or apixaban 5 mg twice daily) or rivaroxaban 15 mg once daily in patients with AF and ACS or PCI. An initial course of first months after ACS or PCI may be prudent, particularly in patients at high risk of recurrent ischemia.

TABLE 2 Summarized outcomes of trials assessing treatment regimens in patients with AF with ACS or PCI/stenting[25]

	VKA + DAPT (reference)					
	VKA + $P2Y_{12}$ inhibitor		DOAC + DAPT		DOAC + $P2Y_{12}$ inhibitor	
Outcomes	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
TIMI major bleeding	0.58	0.31-1.08	0.70	0.38-1.23	0.49	0.30-0.82
TIMI major and minor bleeding	0.49	0.26-0.92	0.63	0.33-1.17	0.43	0.25-0.76
Primary safety outcome (trial defined)	0.45	0.21-0.92	0.64	0.31-1.31	0.47	0.25-0.85
ICH	1.44	0.40-5.22	0.54	0.15-1.92	0.26	0.08-0.79
All-cause death	0.84	0.40-1.56	1.04	0.54-1.98	1.02	0.59-1.74
Cardiovascular death	0.82	0.42-1.49	0.94	0.53-1.63	1.11	0.70-1.75
Primary MACE (trial defined)	0.96	0.60-1.46	0.94	0.60-1.15	1.02	0.71-1.97
MI	1.25	0.77-1.99	1.13	0.72-1.78	1.18	0.81-1.72
Stroke	1.02	0.36-2.65	0.91	0.35-2.32	0.77	0.34-1.67
Stent thrombosis	1.08	0.46-2.31	0.93	0.40-2.17	1.41	0.71-2.76
Hospitalization	0.86	0.57-1.23	0.80	0.55-1.13	0.80	0.59-1.08

Note: Odds ratio < 1 favors nonreference strategy; odds ratio > 1 favors reference strategy.

Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulants; ICH, intracranial hemorrhage; MACE, major adverse cardiac event; MI, myocardial infarction; OR, odds ratio; TIMI, Thrombolysis in Myocardial Infarction; VKA, vitamin K antagonist.

TABLE 3 Summarized outcomes of PIONEER-PCI, RE-DUAL PCI, and AUGUSTUS trials[26]

	Dual antithrombotic therapy versus triple antithrombotic therapy		DOAC-based antithrombotic treatment regimen versus VKA-based antithrombotic treatment regimen	
Outcomes	**OR**	**95% CI**	**OR**	**95% CI**
ISTH major bleeding	0.60	0.49-0.73	0.58	0.48-0.70
Stroke	1.01	0.68-1.51	0.84	0.56-1.28
Myocardial infarction	1.21	0.96-1.54	0.98	0.78-1.25
Stent thrombosis	1.67	1.02-2.73	1.10	0.68-1.77
All-cause death	1.05	0.83-1.34	1.02	0.80-1.30
CV death	1.13	0.81-1.56	1.11	0.80-1.55

Abbreviations: CI, confidence interval; CV; cardiovascular; DOAC, direct oral anticoagulant; OR, odds ratio; VKA, vitamin K antagonist.

3 | TT IN PATIENTS WITH AF AND ACS FROM DISCHARGE TO 12 MONTHS AFTER ACS

Owing to increased stroke risk in patients with ACS and AF, such patients should be considered for concomitant OAC use.[27] There is no single strategy of TT use that would be suitable for all patients with AF and ACS. The composition and duration of TT should be individualized based on the estimated bleeding and cardioembolic and atherothrombotic risks in each patient.[28–32] Stroke risk should be evaluated using the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category) score, while the risk of ischemic events risk can be determined using the Global Registry of Acute Coronary Events (GRACE) score.[29] The risk of bleeding risk is dynamic and should be regularly reassessed using the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR) score. Modifiable bleeding risk factors should be identified and actively managed.[28,33,34] Of note, the use of a formal bleeding risk score has been shown to be superior to relying only on an approach based on modifiable bleeding risk factors.[35]

4 | BLEEDING PREVENTION AND BLEEDING REDUCTION STRATEGIES

TT is associated with increased rates of major bleeding ranging from 5% to 15% at 1 year.[36–40] Unfortunately, major bleeding may result in a 2- to 8-fold increase in the risk of mortality and nonfatal cardiovascular events.[41–45]

The risk of bleeding varies with different antithrombotic treatment regimens. The risk of bleeding with aspirin together with clopidogrel is higher during the early months after initiation. Bleeding on warfarin is also highest in the early period after the drug initiation (initial 3 months).[46] Clinical risk scores may facilitate decision making regarding the most suitable treatment strategy, but their predictive ability is generally modest, and interscore variability is present.[47] Another hurdle is that bleeding risk is closely related to the stroke risk and some thromboembolic risk factors such as older age, uncontrolled hypertension, or history of stroke have also been identified as bleeding risk factors.[48] Thus, patients with high bleeding risk also have a high risk of stroke.

To minimize bleeding risk, while maintaining antithrombotic effect,[49] VKA therapy should be well managed, with a high TTR (>65%-70%),[50] and the lowest effective dose of aspirin should be chosen. Regarding DOACs, the doses approved for stroke prevention should be used. Data on concomitant use of prasugrel or ticagrelor in patients taking OACs are scarce, and the risk of bleeding with either of these drugs may be excessive in combination with aspirin in anticoagulated patients.[31,51,52] Hence, clopidogrel is the preferred antiplatelet agent regarding PCI in patients with indications for OACs.[9,28,53] Importantly, new-generation drug-eluting stents and radial approach should be used to minimize bleeding risk, while proton pump inhibitors should be considered in all patients receiving TT to minimize gastrointestinal bleeding.[51] Concomitant use of nonsteroidal anti-inflammatory drugs should be avoided in patients with AF and ACS (Figure 2).[49]

5 | CHALLENGES IN COMBINED ANTITHROMBOTIC AND ANTIPLATELET THERAPY

One of the most challenging patients among AF population are those with AF and end-stage renal disease on hemodialysis. Severe chronic kidney disease (CKD) elevates the risk of major and intracranial bleeding, and this risk may be greater by the use of OAC or/and antiplatelet therapy. The evidence for antithrombotic therapy declines with the renal function.[54] There are no randomized trials dedicated to OACs in patients undergoing hemodialysis. Of note, there are currently 3

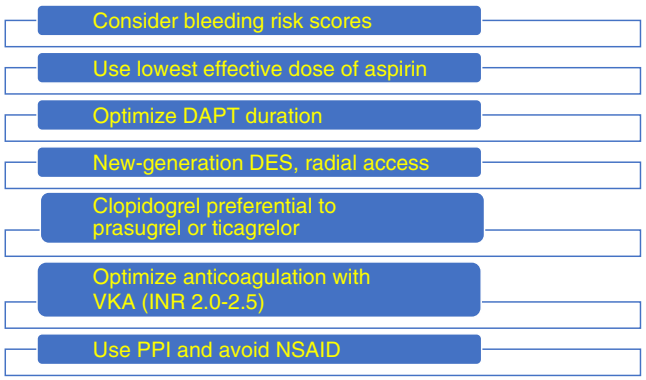

FIGURE 2 Strategies to reduce bleeding risk. DAPT, dual antiplatelet therapy; DES, drug-eluting stent; INR, International Normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; VKA, vitamin K antagonist

ongoing randomized trials of stroke prevention in patients with AF on hemodialysis: the AXADIA trial,[55] comparing apixaban 2.5 mg twice daily to phenprocoumon; the AVKDIAL trial (Oral Anticoagulation in Hemodialysis Patients), comparing VKA to no antithrombotic treatment; and the RENAL-AF (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation) trial, comparing apixaban 5 mg twice daily to warfarin. In one systematic review and meta-analysis[56] of 14 observational studies, the use of warfarin in patients with AF on hemodialysis was not associated with ischemic stroke or ICH. The use of warfarin in the above-mentioned population of patients was not associated with a clear benefit or harm. In individuals with CKD who start an OAC, concomitant antiplatelet therapy including low-dose aspirin may substantially make bleeding risk higher and should be used judiciously. In dialysis-dependent patients, individualized decision making may be appropriate.

6 | FUTURE DIRECTIONS

Many questions regarding optimal combination(s) of antiplatelet and antithrombotic therapy in patients with AF and ACS or elective PCI remain unanswered, including optimal timing of aspirin cessation and adequate $P2Y_{12}$ inhibitor(s) to be used concomitantly with OACs.[57] The role of aspirin instead of a $P2Y_{12}$ inhibitor in dual therapy in different clinical settings also needs further research, as well as the time trends in recurrent coronary ischemic events with dual therapy versus TT and risk difference with dual therapy versus TT in different clinical settings (ie, ACS vs elective PCI, etc). New large-scale randomized clinical trials investigating these issues are unlikely, but patient-level meta-analyses of available studies could provide additional insights.

Also, the search for efficacious anticoagulant(s) associated with minimal bleeding risk continues. Research on anticoagulant agents targeting factor XI or XII in the coagulation cascade are promising developments.[57–60] Evolutions in antithrombotic therapies for ACS are also apparent.[7]

7 | CONCLUSIONS

Balancing the prevention of stroke and recurrent coronary ischemic events against the risk of bleeding in patients with AF and ACS or elective PCI may be challenging. To mitigate the risk of bleeding in these patients, DOAC-based treatment strategies should be used in preference to VKA in DOAC-eligible patients, and duration of TT should be minimized. For many patients, a DOAC plus $P2Y_{12}$ inhibitor early after ACS and/or PCI would be optimal, whereas a longer course of TT should be used in patients at high thrombotic risk.

8 | ISTH 2019 MELBOURNE REPORT

At the ISTH Congress in Melbourne, there was much focus on AF risk assessment and aspects of its management.

For example, Osman[61] reported that machine learning algorithms had a good performance in predicting stroke outcomes (among others, type of stroke, 1-year survival, and post-stroke depression). Abdulrehman et al[62] evaluated the real-world use and appropriateness of idarucizumab, which appeared to be in concordance to institutional criteria, mostly for trauma-related hemorrhages without knowledge of dabigatran concentration. Costa et al[63] assessed the effect of a patient-oriented educational strategy focused on low-income patients with poor anticoagulation control. Patients with AF on warfarin for at least 6 months and with TTR <60% were enrolled and the intervention group participated in educational sessions based on a patient-oriented care approach, which seem to improve anticoagulation management compared to the control group.

In the Effect of Bleeding Risk and Frailty Status on Anticoagulation Patterns in Octogenarians With Atrial Fibrillation (FRAIL-AF) study, Joosten et al[64] examined whether switching from INR-guided VKA therapy to a DOAC-based management strategy compared to continuing VKA therapy was safe in frail elderly patients with AF.

Foulon et al[65] evaluated the link between plasma dabigatran concentrations and thrombinography/fibrinography parameters measured using the thrombodynamics system in an in vitro study and in 18 subjects aged >80 years receiving dabigatran for AF. They found that thrombodynamics enables a reliable analysis of the concentration-dependent effect of dabigatran on thrombinography and some fibrinography parameters.

Douketis et al[66] reported that in dabigatran and rivaroxaban-medicated patients who interrupted therapy for an elective surgery/procedure, DOAC level cannot be reliably determined by a normal prothrombin time or an activated partial thromboplastin time. In apixaban-medicated patients, an undetectable/minimal DOAC level might be reported based on a normal thrombin time.

Konigsbrugge et al[67] evaluated the risk of major bleeding in hemodialyzed patients associated with antithrombotic treatment (the Vienna Investigation of Atrial fibrillation and Thromboembolism in Hemodialysis Patients [VIVALDI]). The incidence of major bleedings was greater in individuals on hemodialysis and the risk of major bleeding was equally elevated in patients on anticoagulation and antiplatelet drugs.

RELATIONSHIP DISCLOSURE

GYHL has been a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo. He has been a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. TSP has been a consultant for Bayer/Jansen and BMS/Pfizer (no fees). MK declared no conflict of interest.

AUTHOR CONTRIBUTIONS

MK reviewed the literature and drafted the manuscript. TSP and GYHL critically revised the manuscript.

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