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JACC FOCUS SEMINAR: PHARMACOLOGICAL AGENTS FOR CV CARE

JACC STATE-OF-THE-ART REVIEW

Antithrombotic Agents

From Aspirin to DOACs in Coronary Artery Disease and in Atrial Fibrillation (Part I)

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ABSTRACT

For secondary prevention of coronary artery disease (CAD), oral antiplatelet therapy is essential. In case of coronary intervention, temporary dual antiplatelet therapy is mandatory as well. Recently, low-dose oral anticoagulation has entered the CAD arena. Atrial fibrillation (AF) is often seen in CAD and vice versa. In most patients stroke prevention in AF consists of oral anticoagulation. In many cases of CAD in patients with AF, anticoagulation has to be combined with antiplatelet agents (so called, dual pathway antithrombotic therapy). Excess bleeding in these conditions is a rapidly rising problem. This review addresses the antithrombotic options in CAD alone, in AF alone, and in their combination, when either an invasive or a noninvasive approach has been chosen. (J Am Coll Cardiol 2019;■:■–■) © 2019 by the American College of Cardiology Foundation.

Although coronary atheromatosis may be silent for many years, it may result in symptomatic ischemic heart disease, either in stable slowly progressive conditions such as angina pectoris or in acute complications on the basis of plaque rupture or erosion leading to acute myocardial infarction or even sudden cardiac death.

More than 170 years ago the German pathologist Rudolf Virchow suggested that thrombosis in a blood vessel may be caused by an interaction between a blood vessel abnormality, blood flow disturbance, and blood constituents (1). About 130 years later this was confirmed by another pathologist, Michael Davies, who related plaque rupture to the clinical conditions described earlier here (2,3). These concepts introduced antithrombotic therapy as secondary prevention for patients either with stable ischemic heart disease or after acute coronary syndromes (ACS) (**Figure 1**) (4). Options include therapies that directly inhibit platelet function (antiplatelet therapy) and those that interfere with the coagulation cascade (oral anticoagulant therapy).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ADP = adenosine diphosphate

AF = atrial fibrillation

CAD = coronary artery disease

COX = cyclooxygenase

CYP = cytochrome P

DAPT = dual antiplatelet therapy

DOAC = direct oral anticoagulant agent

ICH = intracranial hemorrhage

MI = myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

VKA = vitamin K antagonist

Both have been extensively tested in the secondary prevention of coronary artery disease (CAD) with regard to both efficacy and safety.

Another thrombotic condition in the heart is the formation of thrombi in the left atrium and left atrial appendage, which may lead to systemic embolization including ischemic stroke. These thrombi exclusively develop in atrial fibrillation (AF). To prevent stroke in AF, oral anticoagulant agents have been studied. Sometimes CAD and AF coexist, and both antiplatelet and oral anticoagulant therapies are combined in an individual patient. Because both strategies are accompanied by excess bleeding, combination therapy is challenging and requires balancing of the benefits and risks in each individual patient.

This review addresses the current standard of care in secondary prevention of CAD (stable CAD and ACS) with antithrombic therapies in patients both with and without AF. Four approaches are discussed: 1) antiplatelet therapy; 2) vitamin K antagonists (VKAs); 3) direct oral anticoagulant agents (DOACs) alone; and 4) DOACs plus antiplatelet therapy. Six clinical conditions are presented with their accompanying antithrombotic strategies: 1) stable CAD managed noninvasively; 2) ACS managed noninvasively; 3) stable CAD and AF managed noninvasively; 4) stable CAD managed invasively; 5) ACS managed invasively; and 6) ACS and AF managed invasively.

HIGHLIGHTS

- Approximately 30% of AF patients have coexisting CAD, wherein most patients need oral anticoagulant agents combined with antiplatelet drugs leading to excess bleeding complications.
- Both ACS and PCI make more intensified antiplatelet strategies necessary, and these regimens further increase bleeding risk, especially in patients with coexisting AF.
- Future options for these patients include low-dose oral anticoagulation in stable CAD or after DAPT cessation. Dropping aspirin after PCI in AF may also be a future approach.

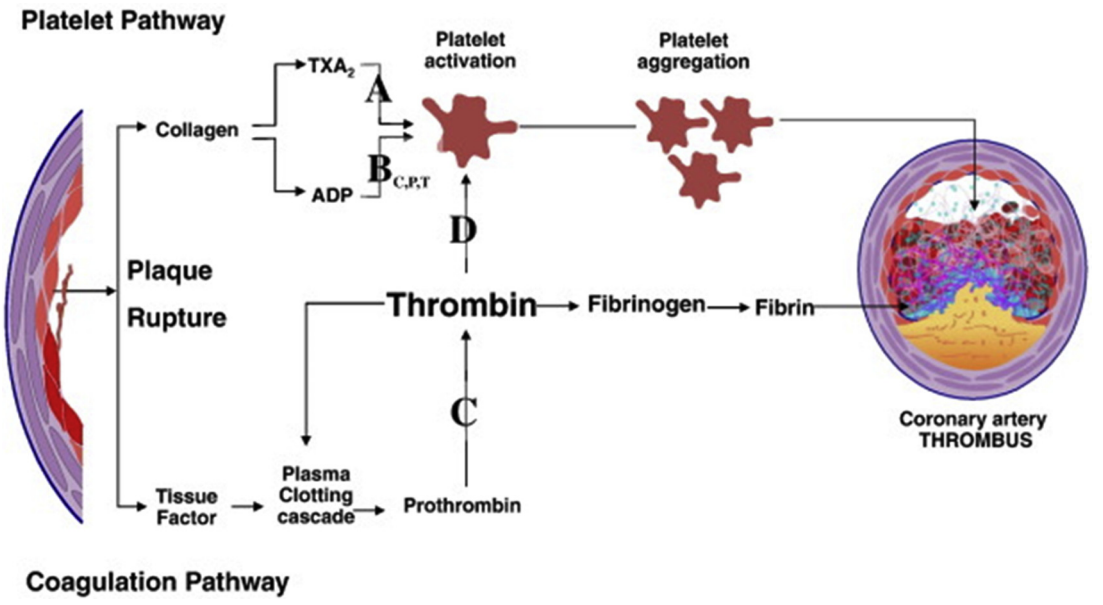
PHARMACOLOGY OF ANTIPLATELET THERAPY

Release of thromboxane A_2 from platelets and subsequent activation of platelets by the TPα (platelet thromboxane A2) receptor is an important amplification pathway contributing to platelet aggregation and, consequently, thrombosis (**Figure 2**) (5). In addition, thromboxane A_2 is a vasoconstrictor, thus promoting increased resistance to blood flow. Binding of platelet glycoprotein VI receptors to collagen, exposed following endothelial disruption, is a particularly potent stimulus of platelet thromboxane A_2 release by inducing the cytosolic release of arachidonic acid, which is converted rapidly to thromboxane A_2 by cyclooxygenase 1 (COX-1) and thromboxane synthase. This is the foundation for the clinical efficacy of aspirin (acetylsalicylic acid), which is an irreversible inhibitor of platelet COX-1 even at very low doses. For example, daily dosing with aspirin 25 mg led to 95% inhibition of platelet thromboxane synthesis (6). Standard once-daily dosing with aspirin 75 to 100 mg provides a consistent and very high level of COX-1 inhibition in adherent patients (7). Avoidance of enteric-coated formulations and/or higher or more frequent doses of aspirin may be required in patients with moderate or severe obesity (8).

Adenosine diphosphate (ADP) is stored at high concentration in platelet dense granules and is released on platelet activation in response to numerous platelet activators, including thromboxane A_2, thrombin and collagen, as well as ADP itself (7). ADP, acting through $P2Y_{12}$ receptors, is one of many platelet agonists to initiate platelet activation but plays a unique and central role in amplification of platelet activation through $P2Y_{12}$ receptors. Platelet $P2Y_{12}$ receptor activation not only amplifies platelet aggregation responses but also markedly amplifies platelet granule release and platelet procoagulant activity. These characteristics have made the platelet $P2Y_{12}$ receptor a key target for treating and preventing arterial thrombosis.

Clopidogrel is a thienopyridine prodrug that undergoes hepatic metabolism through cytochrome P (CYP) P450 enzymes to produce an active metabolite that binds irreversibly to $P2Y_{12}$ receptors to inhibit the binding of ADP. The pharmacodynamic and clinical efficacy of clopidogrel are limited in some individuals as a result of insufficient active metabolite generation, partly related to loss-of-function variants of CYP2C19 and/or drug interactions but also because of many other factors, thus making the individual response unpredictable even with genetic

FIGURE 1 Mechanism of Coronary Thrombosis and Its Inhibition With Antithrombotic Therapy



Reprinted with permission from Welsh et al. (4). A = platelet inhibition by aspirin; ADP = adenosine diphosphate; B = platelet inhibition by $P2Y_{12}$ inhibitors; C = inhibition by oral anticoagulation; D = indirect platelet inhibition by platelet thrombin receptor antagonists (not reported here); TXA_2 = thromboxane A_2.

information (9). Clopidogrel also has weak off-target anti-inflammatory effects in ACS patients, the clinical implications of which are poorly understood at present (10). Prasugrel, like clopidogrel, is a thienopyridine prodrug but is much more efficiently converted to its active metabolite, without relevant effects of genetic variation in CYP activity or drug interactions (11). This results in more rapid and predictable platelet inhibition compared with clopidogrel and, consequently, more effective prevention of arterial thrombosis, particularly stent thrombosis (**Figure 3**).

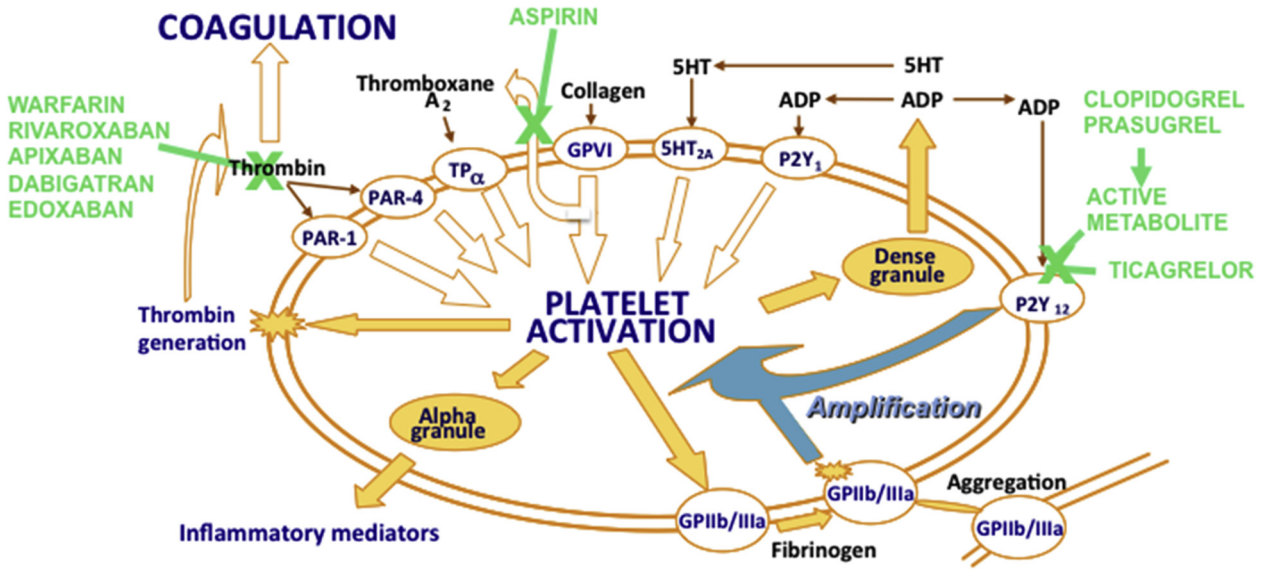
Ticagrelor represents a more recent class of platelet $P2Y_{12}$ inhibitor, binding reversibly to the receptor and not requiring metabolism for its activity (although it has an active metabolite that contributes about 20% to 30% of the inhibitory effects) (11). Ticagrelor also has more rapid and predictable platelet inhibition compared with clopidogrel and, additionally, has more rapid and predictable offset of effect following cessation of therapy (12,13). Ticagrelor is associated with the most consistently high and least variable levels of platelet inhibition during long-term maintenance therapy compared with clopidogrel and prasugrel (14). Ticagrelor 60 mg twice daily and 90 mg twice daily achieve similarly high levels of platelet $P2Y_{12}$ inhibition (15,16). Ticagrelor is associated with dyspnea that is usually mild and well tolerated, often transient, but it sometimes may be intolerable and require alternative therapy (17).

PHARMACOLOGY OF ORAL ANTICOAGULANT AGENTS

There are now 4 DOACs available for clinical use in stroke prevention of AF (18). VKAs were the only oral anticoagulant agents for decades until 2010, when dabigatran was approved for stroke prevention in AF. Since then, rivaroxaban, apixaban, and edoxaban have also been approved.

VITAMIN K ANTAGONISTS. VKAs, including warfarin and several other coumarins, work by inhibiting the enzyme vitamin K epoxide reductase and thus the recycling (and activity) of vitamin K (19). Without the availability of vitamin K to carboxylate certain glutamic acid residues on coagulation factors II, VII, IX, and X (as well as proteins S and C), activity of these factors is reduced, and their effects on generating thrombin is diminished. This prevents fibrin generation by decreasing the conversion of fibrinogen (**Figure 4**) (18). The full effect of VKAs takes several days because of the half-lives of the coagulation

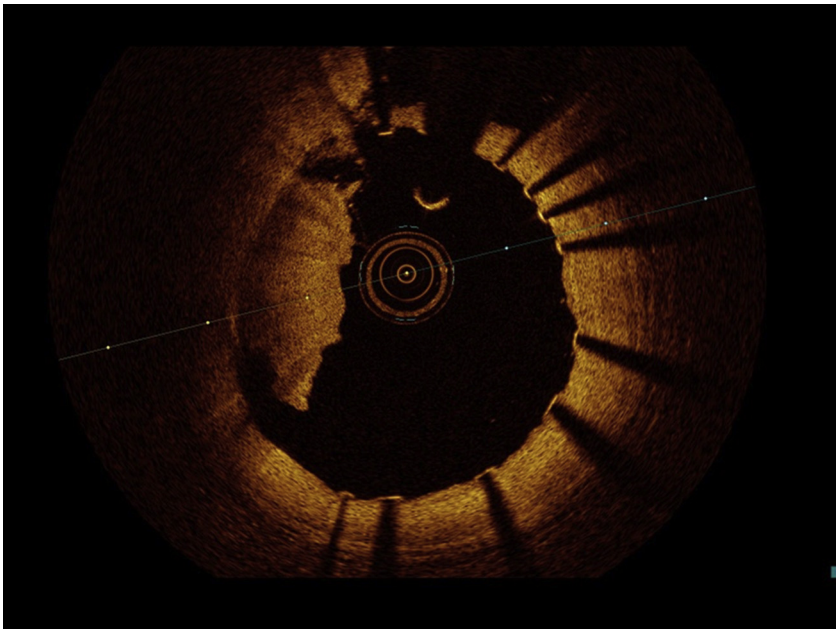
FIGURE 2 Mechanisms of Platelet Activation



5HT = 5-hydroxy tryptamine (serotonin); ADP = adenosine diphosphate; GP = glycoprotein; PAR = protease-activated receptor; TPα = platelet thromboxane A2 receptor. (Reprinted with permission from Storey [5].)

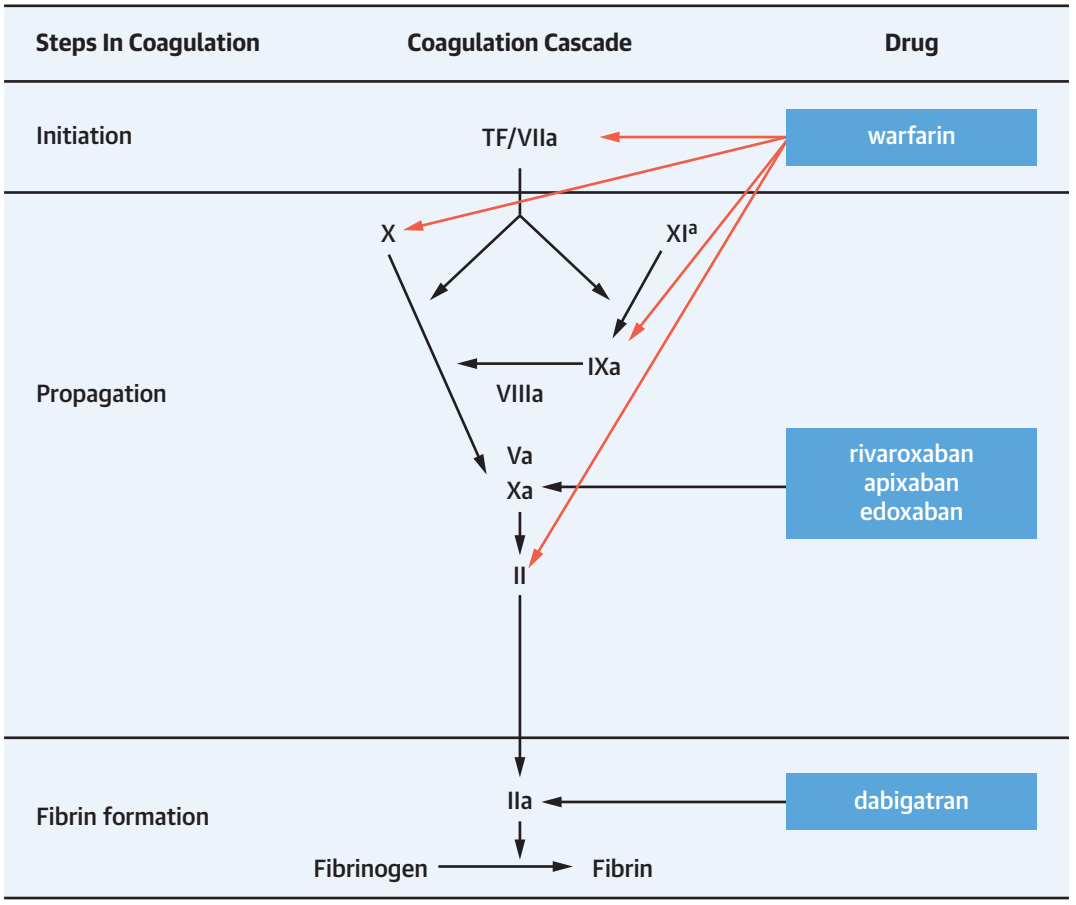
factors, and the effect of these drugs lasts several days related to the time it takes to generate sufficient amounts of new, functional factors. Challenges with the use of VKAs relate to many interactions with food (related to vitamin K content) and drugs, as well as heterogeneity in drug metabolism related to genetics and other patient factors. This makes careful monitoring and frequent dose adjustment necessary.

FIGURE 3 OCT Image of Coronary Stent Thrombosis



OCT = optical coherence tomography. (Courtesy Sint Antonius Ziekenhuis, Nieuwegein, The Netherlands.)

FIGURE 4 Simplified Scheme of the Coagulation Cascade and Its Inhibition by Oral Anticoagulation



TF = tissue factor. (Adapted from Weitz and Bates [18].)

Intensity of VKA therapy varies considerably. For that purpose, monitoring of the international normalized ratio (INR) is used. The optimal range is between 2.0 and 3.0, but time in therapeutic range is generally poor (20).

DIRECT THROMBIN INHIBITOR. Dabigatran is a direct thrombin inhibitor, preventing thrombin from converting fibrinogen to fibrin (21). Dabigatran etexilate is the oral prodrug that is converted to the active dabigatran drug by a serum esterase. It is a competitive and reversible inhibitor of thrombin. It has an oral bioavailability of only about 7%. Because it is better absorbed in an acid environment, it is administered in a capsule with tartaric acid, which may contribute to the gastrointestinal side effects observed in some patients. Dabigatran is approximately 80% renally eliminated. Its action peaks approximately 1 to 2 hours after ingestion. The half-life is on average 12 hours, but it is longer in patients with impaired renal function. It is dosed every 12 hours. It is metabolized by the P-glycoprotein pathway and thus interacts with drugs that affect that pathway.

INHIBITORS OF ACTIVATED FACTOR X. There are 3 approved oral inhibitors of factor Xa: rivaroxaban, apixaban, and edoxaban (21). Each is a competitive and reversible inhibitor of activated factor X and thus inhibits the generation of thrombin and its effects on converting fibrinogen to fibrin (**Figure 4**) (18). Each has a half-life of about 12 hours. For treating AF, edoxaban is dosed once a day and apixaban is dosed twice a day. Rivaroxaban is dosed once a day for AF (21) and twice for treatment of vascular disease. Each indication has different dosing recommendations for each drug. Renal elimination varies among the drugs: edoxaban is about 50% renally eliminated,

rivaroxaban about 35%, and apixaban 25%. Rivaroxaban and apixaban undergo liver metabolism by CYP P4503A4, which is not the case for edoxaban. All 3 factor Xa blockers undergo metabolism by the P-glycoprotein transporter. Rivaroxaban has a significant food effect, with approximately 40% more absorption when taken with a high-calorie meal.

INDICATIONS FOR ANTITHROMBOTIC THERAPY IN CAD WITH AND WITHOUT ATRIAL FIBRILLATION

ANTITHROMBOTIC THERAPY IN STABLE CAD MANAGED NONINVASIVELY. Besides lipid lowering, antithrombotic therapy has been the cornerstone of secondary prevention for CAD for the last 70 years. The first randomized trial with warfarin was carried out in New York and published in 1949 (22). This landmark study was followed by many studies underscoring warfarin's benefit. In the 1980s antiplatelet therapy was introduced. Aspirin came as a simple, lifesaving, and very cheap alternative and remains there today. Both myocardial infarction (MI) and stroke were significantly reduced, as shown in 27 controlled studies of aspirin in the secondary prevention of CAD including 39,308 patients (23). Therefore, aspirin is firmly recommended in international guidelines for secondary prevention in CAD (24–26). For patients not tolerating aspirin, clopidogrel is an effective alternative with similar safety (27).

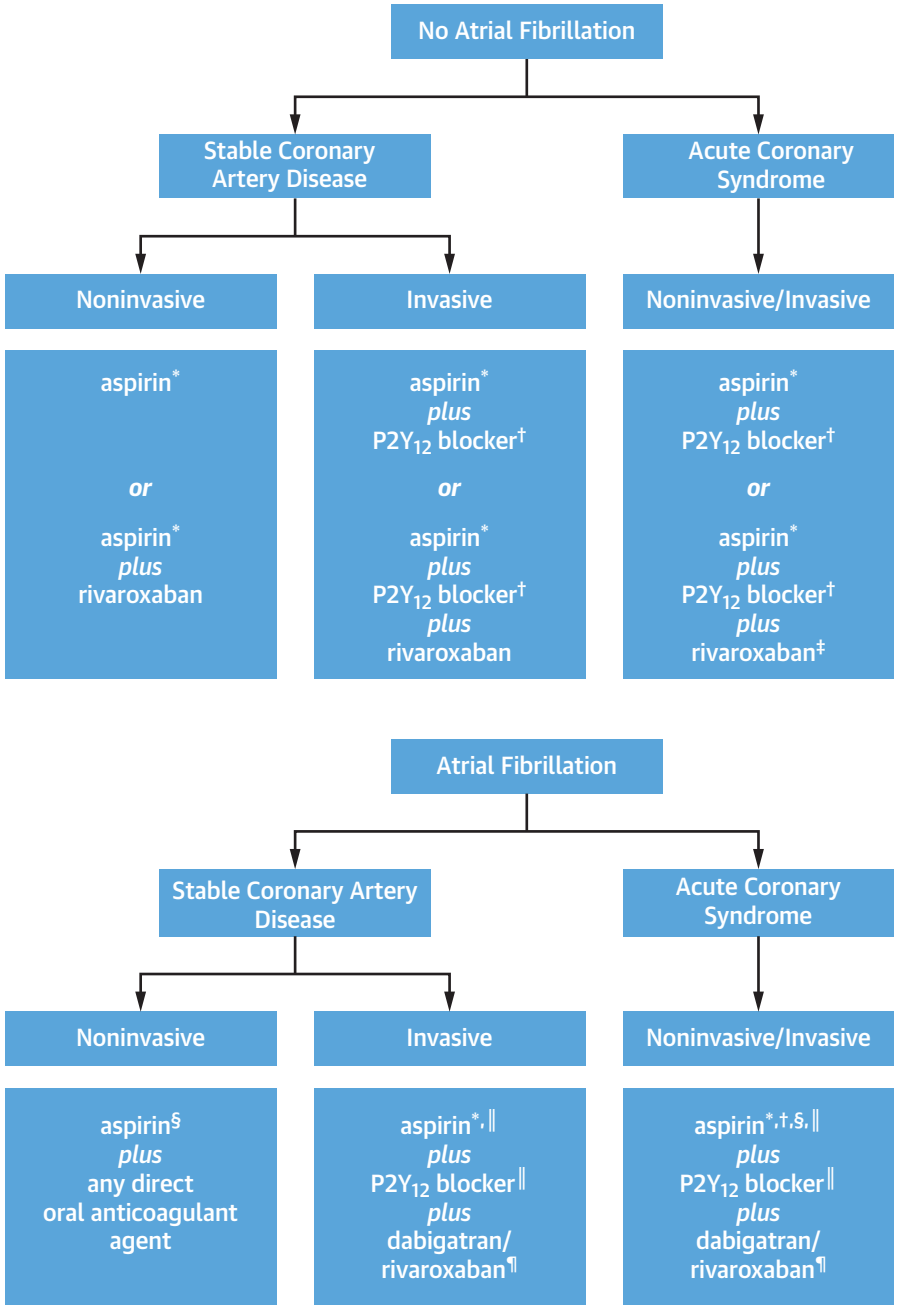
Trialists evaluated the combination of VKA and aspirin in 2 large aspirin-controlled studies on warfarin after MI: WARIS-2 (Warfarin and Aspirin ReInfarction Study-2) and ASPECT-2 (Secondary Prevention of Events in Coronary Thrombosis-2). Both studies showed a benefit of the combination compared with aspirin alone, but at the cost of excess of major bleeding (28,29). Given the complexity and bleeding, this approach has been abandoned. However, given the old beneficial data with warfarin, researchers tried to improve secondary prevention further after MI by adding a DOAC on top of aspirin. In the ESTEEM (Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients With Recent Myocardial Damage) trial, the oral direct thrombin blocker ximelagatran reduced ischemic events compared with placebo in aspirin-treated in patients after MI (30), but the drug was not approved because of liver toxicity. Recently, in the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, very low dose rivaroxaban (2.5 mg twice daily) was evaluated in patients with stable atherosclerosis (CAD and peripheral artery disease). The trial included 27,395 patients at increased risk of atherothrombotic events (previous MI or multivessel CAD, age 65 years or older, or additional risk factor) and without high bleeding risk, but it was terminated prematurely after 23 months for efficacy (31). In the CAD substudy with 24,824 patients, rivaroxaban 2.5 mg twice daily plus aspirin showed a 23% reduction in total mortality, a 44% reduction in stroke, and a 14% nonsignificant reduction in MI in comparison with aspirin alone (32). Rivaroxaban combined with aspirin increased major bleeding significantly by 66% compared to aspirin alone, with the excess mainly related to gastrointestinal bleeding.

Finally, oral anticoagulant therapy with VKA should be added in case of comorbid venous thromboembolism or when a mechanical heart valve has been inserted. However, one should realize that this will increase the risk of major bleeding.

Thus, in stable CAD aspirin is still the gold standard for secondary protection, with clopidogrel monotherapy being an alternative (**Central Illustration**). Yet, adding a very low dose of an oral anticoagulant agent may further improve prognosis in patients at increased risk of atherothrombotic events.

ANTITHROMBOTIC THERAPY IN ACS MANAGED NONINVASIVELY. Given the pathophysiology of ACS, intense antithrombotic therapy is mandated especially in the early days after admission with both dual antiplatelet therapy (DAPT: aspirin loading followed by low-dose aspirin plus a $P2Y_{12}$ inhibitor) and temporary parenteral anticoagulation. After the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial with aspirin plus clopidogrel was published (33), DAPT became the standard of care after MI. Better results with DAPT after ACS were obtained by replacing clopidogrel with the stronger $P2Y_{12}$ blockers prasugrel and ticagrelor (34,35). On top of DAPT, rivaroxaban 2.5 mg twice daily may be given at hospital discharge in stabilized ACS patients. In the ATLAS ACS TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin With or Without Thienopyridine in Subjects With Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 51) trial, this approach resulted in a significant 32% reduction of all-cause mortality, but also in a 4-fold increase in major bleeding including intracranial hemorrhage (ICH) (36). This strategy has been approved in Europe and other regions, but not the United States. Furthermore, many physicians are reluctant to administer 3 antithrombotic agents in a single patient at hospital discharge for ACS. These strategies are now part of the European (37,38) and

CENTRAL ILLUSTRATION **Antithrombotic Strategies in Coronary Artery Disease With or Without Atrial Fibrillation**



Verheugt, F.W.A. et al. J Am Coll Cardiol. 2019;■(■):■-■.

Physicians need to consider whether the patient with coronary artery disease (CAD) has atrial fibrillation (AF) or not, whether the patient with coronary artery disease is stable or is admitted with acute coronary syndrome, or whether an invasive strategy is planned or not. *Clopidogrel in cases of aspirin tolerance. †See text for duration of therapy. ‡In countries where approved. §Indication for aspirin doubtful. ‖Maximum of duration of therapy 12 months. ¶See Table 1 for dosing.

American guidelines (24,25) on the management of ACS. After MI, prolongation of DAPT beyond the guideline-mandated 12 months, when $P2Y_{12}$ blockade traditionally is discontinued, is still a matter of discussion. In comparison with aspirin monotherapy, extended therapy with ticagrelor-based DAPT in the large randomized PEGASUS TIMI-54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) trial reduced the combined rate of MI, stroke, and cardiovascular death at the expense of higher rates of nonfatal bleeding (39). Cardiovascular death or all-cause mortality alone was not significantly reduced, although subgroup analyses suggested possible reduction in CAD-related death in those with the highest risk characteristics, such as diabetes mellitus, peripheral artery disease, or multivessel CAD (40–42). An alternative option to DAPT prolongation is addition of low-dose rivaroxaban on top of aspirin alone, as shown in the COMPASS-CAD study mentioned earlier (32). Rivaroxaban is also associated with excess bleeding, but it reduces all-cause mortality, unlike prolonged ticagrelor in PEGASUS, where excess bleeding was even greater than with rivaroxaban (43). However, head-to-head comparisons between long-term ticagrelor and rivaroxaban are lacking. So, recommendations will follow in future guidelines.

Finally, oral anticoagulant therapy with VKA should be added in case of comorbid venous thromboembolism or when a mechanical heart valve has been inserted. However, one should realize that this will increase the risk of major bleeding.

Thus, for ACS patients managed noninvasively, a minimum of 12 months of DAPT is mandatory, except in patients at an exceptional risk of bleeding (**Central Illustration**).

ANTITHROMBOTIC THERAPY IN STABLE CAD AND AF MANAGED NONINVASIVELY. One of the most complex problems in CAD management is the use of antiplatelet therapy in patients receiving oral anticoagulation for stroke prevention in AF when their CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke of transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, and sex category [female]) score is ≥2. When antiplatelet agents were combined with warfarin, bleeding increased 2-fold in registry studies (44,45). The same was observed in AF patients taking DOACs (46–49). To reduce the risk of this dual pathway therapy, either oral anticoagulation or antiplatelet therapy or both can be modified. Because DOACs have fewer bleeding complications than VKA, DOACs should be preferred when additional platelet therapy is needed. Modification of antiplatelet therapy may include dropping of aspirin (50). This halves the risk of major bleeding without an apparent increase in ischemic events such as death, stroke, MI, or stent thrombosis (51–53), but this was tested only in patients eligible for triple therapy after percutaneous coronary intervention (PCI; see later). To the best of our knowledge no prospective studies of aspirin on top of DOACs have been carried out or are under way in AF patients managed noninvasively. There are observational data from the 4 large studies on DOACs in stroke prevention in AF showing that concomitant antiplatelet therapy increases the risk of bleeding significantly, but it does not seem the affect the advantages in efficacy and bleeding of DOACs negatively when compared with warfarin (46–49).

Nowadays the DOACs are the standard of care for most patients with AF (50). Although not specifically addressed, patients with stable CAD and AF are good candidates for DOACs, because of their efficacy and acceptable bleeding risk as mentioned earlier (46–49). Most physicians treat these patients with antiplatelet agents as well. However, the only good reason for antiplatelet therapy on top of oral anticoagulation in the combination of stable CAD and AF is coronary revascularization, after which antiplatelet therapy should be discontinued after 6 to 12 months in most patients (54–56).

Thus, in stable CAD patients with AF, oral anticoagulation is necessary when the CHA_2DS_2-VASc score is ≥2. Concomitant antiplatelet therapy is indicated only during 6 to 12 months after coronary revascularization (see later), except in cases of exceptional thrombotic risk such as severe diffuse multivessel CAD, including last-remaining coronary artery or very extensive and complex coronary stenting (**Central Illustration**).

ANTITHROMBOTIC THERAPY IN STABLE CAD MANAGED INVASIVELY. DAPT with aspirin and a $P2Y_{12}$ blocker represents the gold standard of antithrombotic treatment in patients undergoing elective PCI (57,58). The thienopyridine-type $P2Y_{12}$ inhibitor clopidogrel is recommended for elective stenting procedures. DAPT treatment can be initiated with an oral loading dose of aspirin 150 to 300 mg (or 80 to 150 mg intravenously) followed by 75 to 100 mg orally daily plus a clopidogrel loading dose of 600 mg followed by a maintenance dose of 75 mg/day (59). Prasugrel or ticagrelor may be considered only in selected patients for specific high-risk situations of elective stenting (e.g., complex PCI procedures such

as left main coronary artery stenting, chronic total occlusion procedures) or in patients with a history of stent thrombosis during clopidogrel maintenance treatment. Ongoing studies are comparing clopidogrel and ticagrelor in high-risk elective PCI (Assessment of Loading With the P2Y12 Inhibitor Ticagrelor or Clopidogrel to Halt Ischemic Events in Patients Undergoing Elective Coronary Stenting [ALPHEUS]: NCT02617290).

During elective PCI, parallel to antiplatelet treatment, the use of anticoagulant agents is standard of care to inhibit thrombin generation and thrombin activity. Different agents including unfractionated heparin have been tested, and a bolus dose of 70 to 100 IU/kg remains the standard anticoagulant for elective PCI. On the basis of the results of the STEEPLE (Safety and Efficacy of Intravenous Enoxaparin in Elective Percutaneous Coronary Intervention Randomized Evaluation) trial, enoxaparin (0.5 mg intravenous bolus/kg) should be considered as an alternative to the other anticoagulant agents (59). Agents available for intravenous antiplatelet treatment are cangrelor and glycoprotein (GP) IIb/IIIa inhibitors. Cangrelor is a direct reversible, short-acting $P2Y_{12}$ inhibitor, and GP IIb/IIIa inhibitors are potent antiplatelet agents that block the final common pathway of platelet aggregation. These drugs are rarely used in PCI for stable patients and are used only as bail-out strategy to overcome potential complications (e.g., no reflow, thrombotic complications) (59).

For maintenance treatment after elective PCI, aspirin in combination with clopidogrel is the gold standard and administered at a dose of 75 mg/day. Although pharmacodynamic studies showed a more intense inhibition of platelet aggregation with 150 mg versus 75 mg/day, clinical studies failed to show a benefit of a high 150 mg/day maintenance dose. In selected high-risk cases, more potent $P2Y_{12}$ inhibition can be proposed with either prasugrel or ticagrelor for the entire DAPT duration or only the initial phase with higher risk of stent thrombosis. After elective PCI, aspirin will be prescribed lifelong.

DAPT duration after elective PCI has been a matter of great debate for more than a decade, and recent DAPT guidelines have summarized all available evidence on this topic (55). After PCI with new-generation drug-eluting stents, the gold standard in 2018 is still to keep 6 months of DAPT as the rule. However, in patients with higher bleeding risk, DAPT duration can be shortened to 3 months in high-bleeding risk patients (e.g., elderly patients) or even 1 month in very high bleeding risk patients (e.g., patients with oral anticoagulation). This is now being tested in ongoing studies (MAnagement of patients post bioresorbable polymer STEnt implantation with an abbreviated DAPT regimen [MASTER DAPT]: NCT03023020). Conversely, in some specific patients with high ischemic risk (according to clinical and/or procedural characteristics), DAPT can be prolonged beyond 6 months (59). Also, here addition of low-dose rivaroxaban may be useful, as has been tested in the COMPASS-CAD study, where 60% of the patients had a remote PCI (33). However, this has not been part of current guidelines.

Finally, oral anticoagulant therapy with VKA should be added in case of comorbid venous thromboembolism or when a mechanical heart valve has been inserted. However, one should realize that this will increase the risk of major bleeding.

Thus, for invasive management of stable CAD, aspirin and clopidogrel for a maximum of 6 months are still the standard of care in most patients.

ANTITHROMBOTIC THERAPY IN ACS MANAGED INVASIVELY. As a consequence of plaque rupture and/or erosion, activated platelets (both the $P2Y_{12}$ and the GP IIb/IIIa receptors), platelet-released thromboxane A_2, and generated factor Xa and thrombin have been shown to be targets in the antithrombotic treatment of ACS. From the beginning, the combination of aspirin and unfractionated heparin during hospitalization has been effective and therefore standard of care in the treatment of ACS (23,24,37,38). Game-changing trials both in ACS patients treated mostly conservatively (32) and in patients undergoing PCI have demonstrated that adding a thienopyridine (irreversibly inhibiting the $P2Y_{12}$ receptor; clopidogrel and ticlopidine, respectively) to aspirin is more effective than aspirin alone (57,58). In particular, the devastating complication of stent thrombosis was reduced by treating all ACS patients undergoing stenting with DAPT (aspirin and clopidogrel). The concept of DAPT was not challenged by 2 large-outcome randomized controlled trials in patients presenting with ACS, but these trials have demonstrated the superiority of the irreversible $P2Y_{12}$ inhibitor prasugrel and the reversible inhibitor ticagrelor over clopidogrel (34,35). Both these agents act more rapidly and are stronger platelet aggregation inhibitors than clopidogrel, and they have a more predictable response. In the PLATO (Platelet Inhibition and Patient Outcomes) trial, an "all comers" ACS study group (both non–ST-segment elevation myocardial infarction [non-STEMI] and STEMI) was included, and patients were randomized at hospital admission (before undergoing coronary angiography). Thus, ticagrelor can be used in a broad range of ACS patients treated conservatively as well as those

undergoing PCI or coronary artery bypass surgery (34). Moreover, in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction-38) study, both non-STEMI and STEMI patients were included, but in contrast to PLATO, in TRITON patients were randomized after undergoing PCI (35). Therefore, prasugrel can be used in ACS patients only after coronary angiography and PCI with stenting. In STEMI patients, both ticagrelor and prasugrel can be used and are preferred over clopidogrel. Stronger platelet inhibition always comes with more bleeding complications, as was also shown in both the TRITON and PLATO trials. Furthermore, a post hoc analysis of TRITON demonstrated that bleeding was most frequent in patients with a previous history of stroke or transient ischemic attack, in patients more than of 75 years of age, and in patients with low body weight (less than 60 kg) (35). So, in general, there always has to be an individual judgment of the patient's expected reduction of recurrent ischemic events but also of the induced higher bleeding risk when installing one of the stronger $P2Y_{12}$ inhibitors. For patients with a previous history of stroke or transient ischemic attack, prasugrel is contraindicated. In patients older than 75 years of age and in patients who weigh less than 60 kg, the dose has to be reduced (5 mg once daily instead of a 10-mg maintenance dose).

The timing of the administration of these $P2Y_{12}$ inhibitors is still an issue of debate. In patients presenting with STEMI there is a slight preference to start 1 of the stronger $P2Y_{12}$ inhibitors as early as possible (e.g., in the ambulance or emergency department) to obtain adequate platelet inhibition at the time of the PCI, even though the ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) study did not establish an advantage of pre-treatment with ticagrelor on surrogate ischemic endpoints and the composite of early thrombotic events (60). For non-STEMI patients, pre-treatment with prasugrel should not be done, because the ACCOAST (Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention [PCI] or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction) trial demonstrated no reduction of ischemic events, whereas bleeding was increased with this policy (61). For the use of ticagrelor and clopidogrel, the strategy of pre-treatment has not been prospectively studied versus no pre-treatment, but given that many non-STEMI patients in both the CURE and PLATO trials were pre-treated, this policy seems to be an option.

The duration of DAPT is another issue of debate. On the basis of the duration of DAPT used in the CURE, TRITON, and PLATO trials, it is advocated to continue DAPT for 1 year after ACS. This advice is irrespective of whether the patient underwent PCI or was treated conservatively for ACS. Recently, the duration of 1 year of DAPT was challenged by the randomized DAPT (Dual Antiplatelet Trial) (62) and PEGASUS TIMI-54 (39) trials, suggesting a longer DAPT duration in patients with a high ischemic risk but also a shorter duration of DAPT in patients with a high bleeding risk. Although a personalized duration of DAPT that is based on risk scores seems to be promising, further evidence for this policy has to come before making it the routine (63-65).

For intravenous platelet inhibition, there are 2 agents available. The very effective rapidly acting irreversible GP IIb/IIIa inhibitors are currently used only during PCI in bail-out and other thrombotic situations (slow flow, distal embolization, stent thrombosis) even though some evidence suggests a benefit in STEMI patients when the drug can be started early after symptom onset (66). Cangrelor also has a rapid onset but has the advantage of being a reversible inhibitor with a short half-life that can therefore be switched off after PCI (67). The CHAMPION (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trials suggest that this agent has no indication for routine use in ACS patients undergoing PCI, but it can be used in patients who cannot be treated with oral strong $P2Y_{12}$ inhibition (e.g., resuscitated ACS patients) or whose risk of bleeding is high (e.g., ACS patient going for immediate coronary artery bypass grafting) (67).

Also, here addition of low-dose rivaroxaban may be useful, as has been tested in the COMPASS-CAD study, where 69% of the patients had a prior MI and 60% a remote PCI (33). However, this has not been part of current guidelines. Finally, oral anticoagulant therapy with VKA should be added in case of comorbid venous thromboembolism or when a mechanical heart valve has been inserted. However, one should realize that this will increase the risk of major bleeding.

Thus, for ACS managed invasively, aspirin and ticagrelor or prasugrel are standard of care. The duration of DAPT is 12 months, but in patients with a high bleeding risk it may be only 6 months. Prolongation of DAPT beyond 1 year after intervened ACS is suitable in patients with prior MI or other risk factors for recurrent ischemic events. Clearly, DAPT duration after ACS is a matter of personalized medicine.

TABLE 1 Major Bleeding, Ischemic Events, and Stent Thrombosis in the 3 Trials on PCI in AF

	WOEST (51)		PIONEER AF-PCI (52)			RE-DUAL PCI (53)		
	Experimental	Control	Experimental		Control	Experimental		Control
Anticoagulant agent	VKA	VKA	Rivaroxaban 15 mg qd	Rivaroxaban 2.5 mg bid	VKA	Dabigatran 110 mg bid	Dabigatran 150 mg bid	VKA
$P2Y_{12}$ blocker	Clopidogrel	Clopidogrel	Clopidogrel*	Clopidogrel*	Clopidogrel*	Clopidogrel†	Clopidogrel†	Clopidogrel†
Aspirin	No	Yes	No	Yes	Yes	No	No	Yes
Major bleeding	3.2	5.6	2.1	1.9	3.3	5.0	5.6	8.8
Ischemic events‡	11.1	17.6	6.5	5.5	6.0	11.0	7.9	8.3
Stent thrombosis§	1.4	3.2	0.8	0.9	0.7	1.1	0.9	0.9

Values are %. *Approximately 1% prasugrel and 4% ticagrelor instead of clopidogrel. †Approximately 12% ticagrelor instead of clopidogrel, prasugrel excluded. ‡WOEST: death, MI, stroke, target vessel revascularization, or stent thrombosis; PIONEER AF-PCI: CV death, MI, or stroke; RE-DUAL: death, MI, stroke, systemic embolism, or unplanned revascularization. §Definite stent thrombosis.

AF = atrial fibrillation; bid = twice daily; CV = cardiovascular; MI = myocardial infarction; PCI = percutaneous coronary intervention; PIONEER AF-PCI = Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; qd = once daily; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; VKA = vitamin K antagonist; WOEST = What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting.

ANTITHROMBOTIC THERAPY IN ACS AND AF MANAGED INVASIVELY. The number of patients with AF who are undergoing PCI is rapidly increasing (68). ACS patients with AF are in the need of oral anticoagulant agents for stroke prevention and of antiplatelet drugs (aspirin plus prasugrel or ticagrelor for ACS) for prevention of stent thrombosis and other ischemic events. The combination of anticoagulant and 2 antiplatelet agents therapy (triple therapy) leads to a large increase of the bleeding risk and bleeding is associated with mortality (44,45,69). Two options to reduce this high bleeding risk are dropping of aspirin and/or the use of DOACs rather than VKA because of their better safety profile (50). There have been 3 trials published studying the concept of dropping aspirin post-PCI and thus treating these patients with double therapy (anticoagulation plus $P2Y_{12}$ inhibition alone). In the small randomized open-label 567-patient WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) trial, VKA plus clopidogrel was tested versus triple therapy (51). Only 25% of patients had ACS. In the much larger PIONEER AF-PCI (Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) 2,124 patients undergoing successful PCI, 52% with ACS, were randomized to a lower-dose rivaroxaban 15 mg plus $P2Y_{12}$ inhibition (mostly clopidogrel), to very low dose rivaroxaban 2.5 mg twice daily, aspirin and $P2Y_{12}$ inhibition, or to triple therapy with warfarin (52). In the even larger RE-DUAL PCI (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting) trial 2,725 patients (51% with ACS) were randomized to dabigatran 110 mg plus $P2Y_{12}$ inhibition (mostly clopidogrel), to dabigatran 150 mg plus $P2Y_{12}$ inhibition, or to triple therapy with warfarin (53). The primary endpoint was major bleeding and differed in the 3 trials, but was significantly reduced in the dual therapy groups (oral anticoagulation plus $P2Y_{12}$ inhibition alone) when compared with triple therapy (**Table 1**). Neither death nor the thromboembolic events MI or stroke were increased by dropping aspirin in any of these studies, acknowledging the fact that none of these trials was powered for this endpoint. In the European Society of Cardiology guidelines on AF triple therapy is still the default strategy (54), but there are now new options as suggested by the recent European Society of Cardiology guideline on DAPT and the American consensus statement: VKA plus clopidogrel, or rivaroxaban 15 mg once daily plus $P2Y_{12}$ inhibition, or dabigatran 150 mg twice daily, or dabigatran 110 mg twice daily plus $P2Y_{12}$ inhibition, especially in the elderly and those patients with a higher bleeding risk (55,56).

Thus, for ACS patients with AF managed invasively, aspirin and clopidogrel in combination with an oral anticoagulant are most often used. Given the results of recent trials, rivaroxaban or dabigatran reduce bleeding when compared with VKA in this setting. Moreover, removing aspirin is associated with a large reduction bleeding whether VKA or a DOAC is used. This so-called dual pathway strategy is especially attractive in patients with a high bleeding risk, whereas triple therapy for 1 month may still be used in patients with a high thrombotic risk. So far, antithrombotic management after ACS in AF is a matter of personalized medicine. New data from currently running studies will elucidate this difficult strategy of these high-risk patients.

CONCLUSIONS AND FUTURE DIRECTIONS

Antiplatelet therapy, either single or dual, is essential in the management of both stable and unstable CAD whether an invasive or conservative approach has been chosen. For most patients with AF, oral anticoagulant therapy is necessary. In that situation DOACs are as effective as VKA and much safer where ICH is concerned.

When AF complicates CAD, or vice versa, a cocktail of antiplatelet and anticoagulant agents is mandatory for prevention of ischemic complication in both conditions. In the current era both effective antiplatelet agents and relatively safe anticoagulant agents are available, but bleeding complications using such a combined treatment are common. Options to reduce bleeding in AF include the use of DOACs rather than VKA, and in case of AF plus PCI the dropping of aspirin, although more data will become available in the near future. So far, antithrombotic management after ACS in AF is a matter of personalized medicine in these high-risk patients.

Remaining questions are the potential benefit of low-dose oral anticoagulation in stable CAD or after cessation of DAPT after PCI, as well the deletion of aspirin after PCI in AF patients. The 2018 American perspective statement and the most recent European guideline do address this issue, but more data will become available when the results of currently running trials in this arena have been published.

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