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Dual Thrombotic Pathway Inhibition for Secondary and Tertiary Prevention in Patients with Cardiovascular Disease

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ABSTRACT

Advances in antiplatelet therapies for patients with cardiovascular disease have improved patients' outcomes over time, but the challenge of balancing ischemic and bleeding risks remains substantial. Because a residual risk of ischemic events exists in patients with cardiovascular disease despite being on antiplatelet therapy, there is a need for novel strategies that prevent clinical events via mechanisms that extend beyond platelet inhibition at an acceptable risk of bleeding. The advent of non-vitamin K antagonist oral anticoagulants, which attenuate fibrin formation by selective inhibition of factor Xa or thrombin, has refueled the interest in dual-pathway inhibition strategies that combine an antiplatelet agent with an anticoagulant. The objective of this review article is to illustrate the emerging pharmacological rationale and clinical development of dual-pathway inhibition for prevention of atherothrombotic events in patients with different manifestations of cardiovascular disease.

KEY POINTS

- Aspirin has been the standard of care in the chronic atherosclerosis setting, where residual risk remains despite the availability of established therapies for limiting atherosclerosis progression and stabilizing existing plaques.
- Secondary and tertiary prevention with antithrombotic strategies that are not restricted to only aspirin is an emerging paradigm.
- The combination of antiplatelet drugs with low-dose rivaroxaban has proved effective in two large-scale randomized trials across the spectrum of atherosclerosis.
- While such strategy may be of clinical benefit in a broad group of individuals with coronary and peripheral artery disease, patient selection should leverage the baseline residual risk of ischemic events against the expected increased risk of bleeding.
- Whether a dual-pathway antithrombotic strategy for chronic atherosclerosis would be also effective by using other direct factor X inhibitors other than rivaroxaban (i.e., apixaban, edoxaban) is unknown.

INTRODUCTION

Although advances in antiplatelet therapies for patients with cardiovascular disease have improved overall patient outcomes, balancing ischemic and bleeding risks remains challenging and substantial possibility of recurrent ischemic events remains after presentation with acute coronary syndromes and interventions.[1–5] In particular, in trials of patients with chronic vascular disease on high rates of contemporary therapies such as statins and angiotensin converting enzyme inhibitors, the risk of major adverse cardiovascular events at 1 year remains about 3%, with event rates even higher in real world contemporary practice.[3–7] (**Figure 1**) Therefore, there is a need for novel strategies that prevent clinical events via mechanisms that extend beyond platelet inhibition. The advent of non-vitamin K antagonist oral anticoagulants (NOACs), which attenuate fibrin formation by selective inhibition of factor Xa or thrombin, has refueled the interest in dual-pathway inhibition (DPI) strategies that combine an antiplatelet agent with an anticoagulant. The objective of this review article is to illustrate the emerging pharmacological rationale and clinical development of DPI for prevention of atherothrombotic events in patients with different manifestations of cardiovascular disease.

VASCULAR BED INVOLVEMENT

Atherosclerosis is a chronic and progressive disease that begins early in life and typically becomes symptomatic in middle age. Typical locations of atherosclerosis include the coronary arteries, the carotid and cerebrovascular arteries, and the aorta and arteries of the lower limbs. In such vascular territories, atherosclerosis is the leading cause of coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral artery disease (PAD), respectively. Inflammatory and immune pathways are increasingly recognized as the link between cardiovascular risk factors (e.g., hypertension, dyslipidemia, diabetes, smoking) and atherosclerosis.[8] Atherosclerotic disease begins with subclinical states where the presence of underlying atherosclerosis may be suspected by the

presence of cardiovascular risk factors or established by means of imaging studies (e.g., Doppler ultrasound, coronary computed tomography, invasive imaging, PET imaging).[9] In later presentations, the presence of CAD, CVD or PAD may be symptomatic but not yet associated with an acute ischemic event (i.e., stable). Such patients may require elective or emergency revascularization, for example following an acute event such as a myocardial infarction (MI), stroke or acute limb ischemia. Because atherosclerosis is a systemic disease, many patients with known atherosclerotic disease in one vascular territory have subclinical or clinical involvement of other vascular beds. For example, in the REACH (Reduction of Atherothrombosis for Continued Health) registry, which included 67,888 patients with or at risk of CAD, CVD or PAD, 15.9% of patients had polyvascular disease.[6] The rate of ischemic events at 1 year increased from 5.3% for patients with risk factors only to 12.6%, 21.1% and 26.3% for patients with symptomatic involvement of 1, 2, and 3 arterial beds, respectively ($P<0.001$ for trend).[7]

Pathogenesis of atherothrombosis

Thrombi are rich in platelets and stabilized by fibrin. Key platelet activation mechanisms are illustrated in **Figure 2**. Platelet adhesion is mediated by the interaction between platelet receptors and ligands exposed on the injured endothelium (e.g., collagen and von Willebrand factor). Platelet activation is promoted by soluble ligands (e.g., adenosine diphosphate, serotonin, thromboxane A_2, and thrombin), which interact with specific platelet membrane receptors (e.g., purinergic, 5-hydroxytryptamine 2A, thromboxane A_2 receptor isoform α, proteinase-activated receptors [PARs] 1 and 4). This process is amplified by the release of high concentrations of platelet agonists including adenosine diphosphate (ADP) stored in dense granules within the platelet which interacts with the platelet membrane P2Y purinoceptor 12 [$P2Y_{12}$]. Platelet aggregation is achieved and further amplified by outside-in signaling predominantly through the interposition of fibrinogen between glycoprotein IIb/IIIa receptors located on the platelet membrane. Several antiplatelet drugs

block the phase of platelet activation by inhibition of thromboxane A_2 production by cyclooxygenase-1 (aspirin), inhibition of the phosphodiesterase 3 (cilostazol), inhibition of the $P2Y_{12}$ receptor (the oral drugs ticlopidine, clopidogrel, prasugrel and ticagrelor, and the intravenous drug cangrelor), inhibition of the PAR-1 receptor (vorapaxar), or inhibition of the 5-hydroxytryptamine 2A receptor (sarpogrelate and naftidofudryl) with different regulatory status and commercial availability across the world. Also, three intravenous drugs (abciximab, tirofiban, eptifibatide) block the final common pathway of platelet aggregation by targeting the glycoprotein IIb/IIIa receptor.

The coagulation cascade follows an extrinsic pathway, initiated by tissue injury, and an intrinsic pathway, characterized by contact activation. Both pathways converge with the activation of factor X, which, in association with factor Va, converts factor II (prothrombin) to factor IIa (thrombin). Thrombin amplifies its own generation through feedback activation of factors V, VIII and XI, activates factor XIII (or fibrin stabilizing factor) and is responsible for the conversion of fibrinogen (factor I) into fibrin (factor Ia), which contributes to clot formation and stabilization as described above. Several drugs are available that inhibit the coagulation cascade at different levels: the oral vitamin K antagonists (VKAs) [e.g., warfarin, phenprocoumon and acenocumarol (preventing the post-translational gamma carboxylation of thrombin, VII, IX, X)], the NOACs (dabigatran - inhibiting thrombin - and rivaroxaban, apixaban, edoxaban, betrixaban – inhibiting factor Xa), and parenteral agents (fondaparinux – inhibiting factor Xa -, unfractionated heparin, low molecular weight heparin and danaparoid – inhibiting thrombin and factor Xa -, bivalirudin and argatroban – inhibiting thrombin).

Goals of antithrombotic therapy and stages of vascular prevention

In patients with CAD, CVD or PAD, acute ischemic events in most cases cause irreversible harm to an organ or vascular territory. The aim of antithrombotic therapy is to prevent the first or recurrent

atherothrombotic episodes, which are generally characterized by rupture of an atherosclerotic plaque with superimposition of a platelet-rich thrombus stabilized by a fibrin mesh.[9] In this context, antithrombotic drugs are given for primary, secondary or tertiary prevention (**Figure 3**). Of note, primary prevention aims to prevent CAD, CVD or PAD manifestations before they occur, secondary prevention strategies target individuals with established CAD, CVD or PAD who have not yet experienced an ischemic event or revascularization, and tertiary prevention aims to reduce the impact and sequelae of CAD, CVD or PAD manifestations that have already occurred. Notably, the difference between secondary and tertiary prevention is frequently overlooked, and patients with both subclinical or clinically apparent atherosclerosis are typically considered candidates to secondary prevention. However, it is different to incidentally discover an atherosclerotic plaque during a noninvasive examination (e.g., carotid ultrasound or coronary computed tomography) or after a clinical consequence (e.g. stroke or MI). Indeed, trials of atherothrombotic strategies often included patients in need of different levels of prevention, which complicates interpretation of their external generalizability. In addition, while many trials conducted in patients with atherosclerosis were performed in patients with clinical manifestations of CAD, CVD or PAD, scarce evidence has been produced for patients where the detection of atherosclerosis is at the subclinical stage. More research is therefore required to better understand how to treat exactly which kind of atherosclerotic manifestation.

Guideline recommendations for vascular prevention

Table 1 summarizes current European Society of Cardiology and American College of Cardiology/American Heart Association guidelines for use of antiplatelet therapy for primary, secondary and tertiary cardiovascular prevention.[10–17] Guidelines generally recommend against the use of antiplatelet therapy for primary prevention in patients without overt atherosclerotic disease. This recommendation is reinforced by the failure of recent trials to demonstrate sufficiently large

reductions in outcome events with aspirin versus placebo to counterbalance the risk of bleeding in this lower risk population.[18–23] The role of antiplatelet therapy for secondary prevention in patients with established CAD (e.g. incidentally detected at coronary angiography or coronary computed tomography but not necessarily causing ischemia) and with no history of a cardiovascular event is currently unclear but such strategy is prescribed in many patients. According to the 2019 guidelines for chronic coronary syndromes from the European Society of Cardiology, and based on consensus of task force members, aspirin may be considered in patients without a history of MI or revascularization but with definitive evidence of CAD on imaging.[16] In contrast, antiplatelet therapy is an established therapy for tertiary prevention. Thus, patients with acute coronary syndrome (ACS) or those who have undergone percutaneous coronary intervention (PCI) or coronary artery bypass grafting CABG benefit from a period of dual antiplatelet therapy (DAPT) followed by chronic use of single antiplatelet therapy (SAPT). The option of intensified antithrombotic therapy (e.g., DAPT or DPI instead of aspirin for selected patients) has entered the 2019 European guidelines for chronic coronary syndromes with a class IIa of recommendation for patients who are at low risk of bleeding and high ischemic risk (i.e., multivessel disease plus one of the following: diabetes, recurrent MI, PAD or chronic kidney disease) and a class IIb for patients who are at low risk of bleeding and moderate ischemic risk (i.e., multivessel disease, diabetes, recurrent MI, PAD or chronic kidney disease).[16] SAPT is recommended by the European Society of Cardiology for secondary prevention in patients with CVD or PAD, whereas SAPT or DAPT of variable duration is recommended for tertiary prevention. The American College of Cardiology/American Heart Association did not issue specific guidelines for secondary and tertiary prevention of CVD, while they recommend SAPT for secondary prevention in patients with PAD, and DAPT for selected patients after PAD revascularization.

DPI: PHARMACOLOGICAL CONSIDERATIONS

DPI involves simultaneous blockade of two pathways of thrombus formation to gain synergistic benefits.[24] DPI differs from DAPT in that it combines an anticoagulant with a single antiplatelet agent rather than combining two antiplatelet agents. As noted above, thrombin is a key factor for both platelet activation and fibrin formation, as it serves both as a platelet agonist and as a crucial component of the coagulation cascade. In addition, thrombin has been implicated in modulating a number of inflammation pathways, supporting its contributing role towards atherogenesis and its thrombotic complications (**Figure 4**).[25–27] The interplay of thrombin in platelet activation and coagulation is schematized in **Figure 5**. The classic DAPT combination of aspirin and a $P2Y_{12}$ inhibitor targets two pathways of platelet activation, but activation can still occur through thrombin and other receptors. In humans, four PARs (PAR-1, PAR-2, PAR-3 and PAR-4) have been identified on several types of cells.[28] PAR-1 and PAR-4 are expressed on human platelets and are rapidly activated by thrombin (**Figure 6**).[26,27] Thrombin generation is increased in patients with atherosclerotic disease manifestations compared to those without.[29,30] Reducing the concentration of thrombin by use of an anticoagulant has been proposed as a mechanism to inhibit clot formation through both its direct anticoagulant and indirect antiplatelet effects with rivaroxaban being the only agent investigated for this strategy to date (e.g., rivaroxaban at the 2.5 mg bid dose + low dose aspirin and rivaroxaban 5.0 mg bid alone).[24] In combination with aspirin, this effect points towards synergistic benefits in reducing thrombus formation. In a pig model, rivaroxaban reduced the weight of experimentally-induced stent thrombus by 66% versus that in controls, and the effect was dose-dependent, which suggests some degree of thrombin-mediated antithrombotic efficacy.[31] However, adding rivaroxaban to aspirin yielded an 86% reduction in thrombus weight, and rivaroxaban in combination with DAPT suppressed in-stent thrombus formation by 98%.[31] By contrast, the reduction in thrombus formation with DAPT alone was 79%.[31] In vitro investigations have confirmed that rivaroxaban inhibits thrombin generation in a concentration-dependent manner, an effect synergistically enhanced with the addition of ticagrelor or DAPT with ticagrelor and

aspirin.[32] Rivaroxaban alone has shown to increase fibrinolysis on in vitro models, through activation and enhanced secretion of urokinase plasminogen activator from endothelial cells, a mechanism which could help to reduce the thrombi, and also reduced the adhesion of platelets to endothelial cells.[33] In aggregate, these data support that the effects of rivaroxaban are complementary to ADP receptor blockade by means of $P2Y_{12}$ inhibitors and COX-1 inhibition by means of aspirin. Moreover, their synergistic effects support the potential for their combination for clinical use.

LONG-TERM DPI IN PATIENTS WITH CAD

Lessons from studies of VKAs in CAD

The strategy of DPI by combining a VKA with an antiplatelet in patients with CAD and no pre-existing indication to oral anticoagulation (OAC) was never adopted in clinical practice, despite some evidence supporting its efficacy. In a meta-analysis of 14 studies comparing DPI with VKA and aspirin versus aspirin alone, including 25,307 patients who recovered from an ACS, DPI did not affect the risk of major adverse events at a follow-up ranging between 3 months and 5 years (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.90-1.03, P=0.30).[34] However, it did so in patients with a therapeutic international normalized ratio (INR) between 2 and 3 (OR 0.73, 95% CI 0.63-0,84), p<0.0001).[34] Therefore, the strategy of lowering the intensity of anticoagulation therapy by targeting a lower INR to enable a safer combination with antiplatelet agents does not seem to be effective. On the other hand, in patients with a therapeutic INR, the risk of major bleeding was increased by 2.3-fold, but the risk of intracranial bleeding was not increased. No mortality benefit was noted, possibly because the bleeding risk counteracted the observed decrease in MI. Importantly, these data come from studies conducted approximately 15 to 20 years ago, where DAPT was not the control comparison and the doses of aspirin ranged between 75 mg and 325 mg

per day. However, they highlight the benefit of adding an oral anticoagulant on top of aspirin, at the price of increased bleeding.

Lessons from studies of NOACs in atherosclerotic vascular disease

Acute coronary syndromes – NOACs are now considered more than just alternatives to warfarin, because of their favorable safety profile, in particular reduced intracranial hemorrhage, demonstrated in several clinical scenarios, including atrial fibrillation (AF).[35,36] A number of phase 2 placebo-controlled trials have explored the potential of DPI with different NOACs for ACS patients on aspirin and with no baseline indication for OAC. The direct thrombin inhibitor ximelagatran showed promise in ACS patients in the ESTEEM (Efficacy and Safety of Oral Direct Thrombin Inhibitor Ximelagatran in Patients With Recent Myocardial Damage) trial, with no increase in bleeding and a significant reduction in ischaemic events.[37] However, this combination has not been further investigated because the drug was withdrawn from the market (or the applications for marketing approval discontinued in some countries) after reports of hepatotoxicity. DPI with escalating doses of dabigatran (50 mg to 150 mg twice daily), another direct thrombin inhibitor, was investigated in the RE-DEEM (RandomizEd Dabigatran Etexilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel: Multicentre, Prospective, Placebo Controlled, Cohort Dose Escalation Study) trial. When used on top of DAPT in patients with a recent MI, dabigatran produced a dose-dependent increase in bleeding events and a significant reduction in coagulation activity.[38] Because there were no signals of ischemic benefit (although the trial was not powered for efficacy), testing of dabigatran for the ACS indication never progressed to phase 3. Two more phase 2 trials of the factor X inhibitors darexaban and letaxaban showed a dose-dependent increase in bleeding with no apparent ischaemic benefits in the RUBY-1 (Study Evaluating Safety, Tolerability and Efficacy of YM150 in Subjects With Acute Coronary

Syndromes) and AXIOM-ACS (Phase 2 study of TAK-442, an oral factor Xa inhibitor, in patients following acute coronary syndrome) trials. Consequently, further development of these drugs was abandoned.[39,40] The only NOACs with satisfactory results in phase 2 investigations whose clinical development progressed to phase 3 ACS trials are the factor Xa inhibitors apixaban and rivaroxaban.

Escalating doses of apixaban were tested in the APPRAISE-1 (Apixaban for Prevention of Acute Ischemic and Safety Events) trial, where 1,715 patients with recent ACS on aspirin or DAPT were investigated.[41] Randomization to the two higher doses of apixaban (10 mg bid and 20 mg od) was discontinued upon recommendation of the data safety monitoring board due to excess bleeding.[41] The 2.5 mg bid and 10 mg od doses of apixaban resulted in dose-dependent increases in major or clinically-relevant non-major bleeding and numerically lower rates of ischemic events compared with placebo.[41] In the subsequent APPRAISE-2, the 5 mg bid dose and 2.5 mg bid dose for those with estimated creatinine clearance less than 40 ml/min (8.5% of trial) were evaluated.[42] The trial was stopped early after only 7,392 patients were randomized due to an increase in major bleeding with apixaban (hazard ratio [HR] 2.59, 95% CI 1.50-4.46, P=0.001), including intracranial and fatal bleeding, with no apparent reduction in ischemic events at a median follow-up of 241 days (HR 0.95, 95% CI 0.80-1.11, P=0.51). Notably, APPRAISE-2 used a combination of DAPT and the full dose of apixaban as used in trials of atrial fibrillation. This strategy increased the risk of severe bleeding with no added benefit.

Rivaroxaban is so far the only NOAC with successful testing of a DPI strategy in a phase 3 trial of ACS. In ATLAS ACS-TIMI 46 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 46), an earlier phase 2 investigation of 3,491 patients with stabilized ACS mostly on DAPT, the risk of clinically significant bleeding with rivaroxaban (at doses 5-20 mg given once daily or the same total daily dose given twice daily) versus placebo was increased in a

dose-dependent manner (HR 2.21, 95% CI 1.25-3.91 for 5 mg, HR 3.35, 95% CI 2.31-4.87 for 10 mg, HR 3.60, 95% CI 2.32-5.58 for 15 mg, and HR 5.06, 95% CI 3.45-7.42 for 20 mg doses; P<0.0001).[43] In addition, the drug numerically reduced the main secondary efficacy endpoint of death, MI, or stroke (5.6% vs. 7.0%, P=0.10).[43] The 2.5 mg and 5.0 mg bid doses showed the most favorable safety-efficacy profile and were accordingly selected for further testing in the phase 3 ATLAS ACS 2-TIMI 51, a double-blind, placebo-controlled trial of 15,526 patients with a recent ACS followed for a mean of 13 months and up to 31 months.[44] The primary efficacy end point, a composite of death from cardiovascular causes, MI or stroke, was reduced with rivaroxaban compared with placebo (8.9% vs. 10.7%, HR 0.84, 95% CI 0.74-0.96, P=0.008), with improvement shown with both doses of rivaroxaban.[44] At variance with the higher dose, however, the lower dose of rivaroxaban reduced the rates of cardiovascular death and all-cause death.[44] The incidence of major bleeding (2.1% vs. 0.6%, P<0.001) and intracranial hemorrhage (0.6% vs. 0.2%, P=0.009) was increased with the two doses of rivaroxaban combined, while the incidence of fatal bleeding was not increased.[44] The 2.5 mg bid dose resulted in a lower incidence of fatal bleeding events than the 5 mg bid dose (0.1% vs. 0.4%, P=0.04).[44] In a pooled analysis of 1,477 patients from the ATLAS ACS-TIMI 46 and ATLAS ACS 2-TIMI 51 trials, including post-ACS patients receiving aspirin monotherapy and randomized to either rivaroxaban 2.5 mg twice daily or rivaroxaban 5 mg twice daily or placebo, the composite of cardiovascular death, MI or stroke was reduced by the combined rivaroxaban group (2.5 or 5 mg BID) compared with placebo (HR 0.65, 95% CI=0.45–0.92, P=0.016).[45] Although the combined rivaroxaban dose groups were associated with higher rates of major bleeding, the 2.5 mg dose group was not.[45] The safety of 2.5 mg bid rivaroxaban plus a $P2Y_{12}$ inhibitor (e.g., clopidogrel or ticagrelor) versus standard DAPT was tested in 3,037 patients with recent ACS in the GEMINI-ACS 1 (A Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Participants With Acute Coronary Syndrome) trial.[46] Because all patients received a $P2Y_{12}$ inhibitor, this was essentially a comparison of the low dose of rivaroxaban with aspirin. Rates of major bleeding at 12

months were similar in the two groups (5% vs. 5%, P=0.58).[46] Establishing the efficacy of DPI for ACS using the GEMINI-ACS 1 regimen, however, would require a larger trial powered for clinical endpoints.

Percutaneous coronary intervention – Strategies of DPI have been the objective of several investigations in PCI patients with an indication for OAC, mostly due to AF.[47] In these trials, DPI was the consequence of combining antiplatelet therapy with pre-existing OAC rather than a strategy where an anticoagulant was added on top of background antiplatelet therapy. However, meaningful lessons on the safety of various regimens of DPI for PCI patients can be drawn from these studies. Of note, before contemporary trials of NOACs, a trial of VKA was performed. In the WOEST (What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing) trial, DPI with warfarin and clopidogrel led to a 64% relative decrease in bleeding episodes at 12 months compared with triple therapy with warfarin and DAPT, driven by a reduced rate of minor bleeding episodes.[48] In essence, the WOEST trial was a pivotal investigation in that it investigated the simplification of the reference "triple therapy" strategy by means of aspirin withdrawal. The pivotal findings from the WOEST trial set the foundations for trials of aspirin-free strategies using a NOAC (rivaroxaban, dabigatran, apixaban, end edoxoban) in patients with AF undergoing PCI.[49]

Trials of NOACs for PCI in patients with AF have been completed with rivaroxaban, dabigatran, apixaban and edoxaban. In the PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) trial, two rivaroxaban-based DPI regimens (e.g., a WOEST-like strategy of 15 mg od rivaroxaban plus a single $P2Y_{12}$ inhibitor, and an ATLAS ACS 2-TIMI 51-like regimen of 2.5 mg bid rivaroxaban [2.5 mg bid] plus DAPT) resulted in 41% and 37% reduced risks of total bleeding events compared with triple-therapy DPI using warfarin and

DAPT.[50] Both rivaroxaban-based DPI regimens were also associated with a reduced risk of all-cause mortality or recurrent hospitalization for adverse events.[51] It is important to note that the dosing regimens of rivaroxaban tested in this trial are not approved for stroke prevention in AF.

In the RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial, compared with patients on triple-therapy with warfarin and DAPT, the risk of major or clinically relevant non-major bleeding at a mean of 14 months was reduced by 48% in the arm of patients on DPI with dabigatran 110 mg bid and clopidogrel and by 28% in the arm of patients on DPI with dabigatran 150 mg bid and clopidogrel.[52] Both PIONEER-AF PCI and RE-DUAL PCI were small and underpowered for ischemic endpoints, although in RE-DUAL PCI the risk of thromboembolic events was noninferior in the two dabigatran groups combined as compared with the reference group.[52]

In the AUGUSTUS (An open-Label, 2 × 2 factorial, randomized controlled trial to evaluate the safety of apixaban vs. vitamin K antagonist and aspirin vs. placebo) trial, 4,614 patients with AF who had an ACS or had undergone PCI on average one week before were randomized two-by-two to apixaban or a VKA and to aspirin or placebo.[53] The primary outcome, a composite of major or clinically-relevant non-major bleeding at 6 months, was reduced by 31% with apixaban compared with VKA and increased by 89% with aspirin compared with placebo.[53] Patients in the apixaban arm had a lower incidence of death or hospitalization than those on VKA, and a similar incidence of ischemic events, while patients in the aspirin group had a similar incidence of death or hospitalization and of ischemic events compared with placebo.[53] Thanks to its multifactorial design, AUGUSTUS clarifies that dropping aspirin reduces the risk of bleeding on top of the bleeding risk reduction already achieved by the use of NOACs (apixaban) versus VKA.

Finally, in the ENTRUST-AF PCI (Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation),

compared with patients on triple-therapy with VKA and DAPT, DPI with edoxaban 60 mg od and a $P2Y_{12}$ inhibitor was noninferior (but not superior) with respect to the risk of major or clinically relevant non-major bleeding at 12 months.[54] Again, there were no differences in ischemic events, but the trial size was small.

In aggregate, PIONEER-AF PCI, RE-DUAL PCI, AUGUSTUS and ENTRUST-AF PCI highlight that DPI with a NOAC and a single antiplatelet agent (i.e., a $P2Y_{12}$ inhibitor, mostly clopidogrel) is a safer regimen than triple therapy, particularly when a VKA is used.[55] Moreover, in this context of AF patients undergoing PCI treated with a single antiplatelet agent, a NOAC should be used at the dosing regimen recommended for stroke prevention in order to allow adequate antithrombotic protection.[56] A meta-analysis of WOEST, ISAR TRIPLE, PIONEER-AF PCI, RE-DUAL PCI, encompassing 5,317 patients, showed a reduction in major or minor bleeding with dual-therapy DPI as compared with triple-therapy DPI, with comparable ischemic outcomes.[57] A subsequent meta-analysis including AUGUSTUS showed that dual-therapy DPI with NOACs reduces major bleeding and intracranial hemorrhage compared with triple-therapy DPI with VKAs.[58] A further updated meta-analysis of the four trials of NOACs in AF-PCI, including ENTRUST-AF PCI, highlighted a numerical trend towards an increased risk of stent thrombosis with dual-therapy DPI, which calls for careful weighing of thrombotic and bleeding risk at the time of establishing the optimal length of aspirin therapy in PCI patients on a NOAC and a $P2Y_{12}$ inhibitor.[54,55]

Stable atherosclerotic vascular disease – In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, two strategies using rivaroxaban (with and without aspirin) were compared with chronic aspirin use for secondary prevention in patients with a history of stable atherosclerotic vascular disease (e.g., CAD or PAD).[59] A total of 27,395 patients (90.6% with CAD, 27.3% with PAD) were randomized to rivaroxaban 2.5 bid plus aspirin, rivaroxaban 5 mg bid alone, or aspirin 100 mg alone. The prevalence of state-of-the-art medications for patients with stable atherosclerosis, such as lipid-lowering agents and angiotensin-converting–enzyme

inhibitors or angiotensin-receptor blockers was high. The trial was event-driven and anticipated to continue until 2,200 primary endpoint events occurred. However, the data safety monitoring board recommended stopping it earlier due to overwhelming proof of efficacy in the DPI arm (rivaroxaban plus aspirin). At a mean follow-up of 23 months, the primary efficacy outcome, a composite of cardiovascular death, stroke or MI occurred in 4.1% of patients in the DPI arm, in 4.9% of patients in the rivaroxaban-only arm, and in 5.4% of patients in the aspirin-alone arm (HR for DPI vs. aspirin 0.76, 95% CI 0.66-0.86, P<0.001; HR for rivaroxaban vs. aspirin 0.90, 95% CI 0.79-1.03, P=0.12). The benefit with DPI was driven by reductions in cardiovascular death and stroke, with no reduction in MI although it was numerically reduced.[59] Further scrutiny of stroke outcomes revealed that, compared with aspirin alone, DPI reduced ischemic/uncertain strokes by 49% and fatal/disabling stroke by 42%, while prior stroke represented the strongest predictor of incident stroke.[60] Overall, outcomes were consistent across pre-specified subgroups.

The safety outcome was major bleeding according to a modification of the International Society on Thrombosis and Haemostasis (ISTH) classification, which considered all bleeding that led to presentation to an acute care facility or hospitalization as major. Using this definition, major bleeding occurred more frequently in patients in the DPI arm than in those on aspirin alone (3.1% vs. 1.9%, HR 1.70, 95% CI 1.40-2.05, p<0.001), driven by bleeding (mostly gastrointestinal) that led to presentation to an acute care facility or hospitalization, with no differences in fatal bleeding or intracranial bleeding. The rate of major bleeding was higher with rivaroxaban alone than with aspirin. Overall, a net clinical benefit endpoint incorporating cardiovascular death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ was 20% lower with rivaroxaban plus aspirin than with aspirin, and not different between rivaroxaban alone and aspirin.[59]

In the COMPASS trial, 17,598 participants were further randomized to pantoprazole (40 mg daily, n = 8791) or placebo (n = 8807). At a median of 3 years, there was no statistically significant difference between the pantoprazole and placebo groups in safety events except for increased

enteric infections with pantoprazole.[61] Also, there was no significant difference in upper gastrointestinal events between groups (hazard ratio, 0.88; 95% confidence interval [CI], 0.67-1.15)., but pantoprazole significantly reduced bleeding of gastroduodenal lesions (hazard ratio, 0.52; 95% confidence interval, 0.28-0.94; P = 0.03).[62]

In a post-hoc analysis of COMPASS, subsets of patients at higher risk of recurrent vascular events and best candidates to the DPI regimen were identified, including those with ≥2 vascular beds affected, heart failure, renal insufficiency, or diabetes.[63] Among patients with ≥1 high-risk feature identified from two different methodologies, DPI prevented 33 to 36 serious vascular events, whereas in lower-risk patients, DPI led to the avoidance of 10 to 11 events per 1,000 patients treated for 30 months. A further sub-analysis looked more specifically at patients with mild or moderate heart failure, where DPI produced similar relative but larger absolute benefits compared with patients without heart failure.[64] Another substudy of the overall COMPASS population showed that the benefits of DPI were preserved in patients with moderate renal dysfunction without evidence of an excess hazard of bleeding.[65]

In the COMPASS subgroup of patients with CAD (N=24,824), eligible patients had to have had a prior MI, multivessel CAD, history of stable or unstable angina, prior PCI or prior coronary artery bypass grafting (CABG).[66] DPI with rivaroxaban plus aspirin reduced the primary efficacy outcome by 26% (4% vs. 6%, p<0.0001) and all-cause mortality by 23% (3% vs. 4%, p<0.0012), but increased major bleeding by 66% compared with aspirin (3% vs. 2%, p<0.0001). Conversely, rivaroxaban alone was not associated with a significant benefit and increased bleeding by 51%.[66] In patients with a recent CABG (N=1,448), graft failure diagnosed by computed tomography at 1 year after surgery was not reduced with DPI.[67] In the COMPASS subgroup of patients with PAD (N=7,740), eligible patients had a history of PAD of the lower extremities (e.g., previous peripheral bypass surgery or angioplasty, limb or foot amputation, intermittent claudication with objective evidence of PAD), of the carotid (e.g., previous carotid artery revascularization or asymptomatic

carotid artery stenosis of at least 50%), or CAD with an ankle-brachial index less than 0.90.[68] DPI with rivaroxaban plus aspirin reduced the primary efficacy outcome by 28% (5% vs. 8%, p=0.0047) and major adverse limb events including amputation by 46% (1% vs. 2%, p=0.0037), at the price of a 61% increase in major bleeding (3% vs. 2%, p=0.0089). Conversely, rivaroxaban alone did not reduce the primary efficacy endpoint, but reduced major adverse limb events including amputation by 33% and increased major bleeding by 140%. All-cause death did not change with both rivaroxaban strategies.[68] In the more restricted subgroup of 6,391 patients with lower extremity PAD (N=6,391), after a major limb event, the one year cumulative risks of a subsequent hospitalization, vascular amputation or death were 95.4%, 22.9%, and 8.7%, respectively.[69] DPI lowered the incidence of major limb events by 43% (1.5% vs. 2.6%, p=0.01), total amputations by 58% (1.2% vs. 0.5%, p=0.01) and peripheral vascular interventions by 24% (5.5% vs. 7.1%, p=0.03) compared with aspirin alone.[69] In light of the observations from the COMPASS trial, the 2.5 mg bid dose of rivaroxaban has been labeled as the 'vascular protection' dose in order to differentiate it from dosing regimens used for other indications.

Other clinical scenarios - In patients with CAD and chronic heart failure, thrombin generation may contribute to disease progression by inducing inflammation, endothelial dysfunction, and arterial and venous thrombosis.[70] On this background, evaluation of DPI with rivaroxaban 2.5 mg bid was the objective of the placebo-controlled COMMANDER HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) trial. The study enrolled 5,022 patients with chronic heart failure, a left ventricular ejection fraction of 40% or less, CAD, and elevated plasma concentrations of natriuretic peptides (e.g., decompensated heart failure) who had recently been treated in hospital with an episode of worsening heart failure (within 21 days). The primary efficacy outcome - a composite of death from any cause, MI, or stroke - was not reduced with the DPI strategy, and safety outcomes were similar to placebo.[71] Indeed, rivaroxaban reduced the risk of thromboembolic

events, but these events were not the major cause of morbidity and mortality.[72] The difference between the results of COMMANDER-HF and the heart failure subgroup of COMPASS are therefore mostly explained from the different level of acute decompensation in the study populations. In fact, patients in COMPASS had mild or moderate heart failure, while those in COMMANDER-HF presented with more advanced pump failure.

The risk of ischemic events after transcatheter aortic valve replacement (TAVR) may depend on procedure- (e.g., device manipulation in the aorta), patient- (e.g. concurrent AF and/or CAD), and prostheses-related aspects (e.g., leaflet thrombosis). The choice of antithrombotic therapy after TAVR is evolving.[73] The GALILEO (Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter AortIc Valve Replacement to Optimize Clinical Outcomes) trial tested a strategy of DPI with rivaroxaban 10 mg od and aspirin versus DAPT for 3 months in patients without a clinical indication for OAC, followed by drop of aspirin and clopidogrel in the two arms, respectively. Top line results of the trial have been reported, announcing early halting of the study due to increased mortality in the rivaroxaban arm.[74] Other trials are ongoing with apixaban in TAVR patients with and without baseline indication to OAC, and edoxaban in patients with baseline indication to OAC.[75,76]

DPI: STATUS AND CONSIDERATIONS

Acute coronary syndromes – The current standard of care for patients with ACS is DAPT for 12 months.[77] In 2012, the U.S. Food and Drug Administration's (FDA) Cardiovascular and Renal Drugs Advisory Committee voted against the approval of rivaroxaban for this indication, due to concerns surrounding safety as well as missing data on subjects who were lost to follow-up from the ATLAS ACS 2 trial, at variance with the European Medical Agency (EMA) that approved rivaroxaban one year later. Based on guidelines from the European Society of Cardiology, rivaroxaban 2.5 mg bid may be considered (class IIb, level of evidence B) after discontinuation of

parenteral anticoagulation in both patients with ST-segment elevation and non-ST-segment elevation MI patients with no prior stroke or transient ischemic attack and at high ischaemic risk as well as low bleeding risk receiving aspirin and clopidogrel.[10,11] Such a strategy has not found its way into routine clinical practice due to the higher perceived risk of bleeding in rivaroxaban-treated subjects who are already on DAPT and the availability of potent DAPT combinations with prasugrel or ticagrelor.[78]

Percutaneous coronary intervention – Patients undergoing elective PCI are recommended 6 months of DAPT, with options for prolonging or shortening DAPT based on the balance between the risks of thrombotic and bleeding complications.[77] There is currently no indication for DPI for patients with chronic CAD who receive a stent during the DAPT period and have no pre-existing indication for OAC, since these patients were excluded from the COMPASS trial although they were enrolled once DAPT was discontinued.[59] Conversely, DPI using antiplatelet agents and full-dose OAC is a standard therapy in PCI patients who need oral anticoagulation for concurrent reasons, including AF. Current recommendations from the United States for AF patients undergoing PCI are dated before the publication of the AUGUSTUS trial.[79,80] Conversely, current recommendations from Europe are dated after the publication of the AUGUSTUS trial but before the publication of ENTRUST-AF PCI.[16] The default approach recommended in the most recent North American consensus document is DPI with full dose NOAC and SAPT (e.g., clopidogrel).[16,79–81] The European guidelines assign the same class of recommendation (class IIa) for dual-therapy (with aspirin used in the periprocedural period and ≤1 week) and triple-therapy (e.g., using NOAC and DAPT for at least one month and up to 6 months depending on the thrombotic risk)[16] Dual-therapy is usually maintained up to 12 months, but shorter durations can be envisaged depending on the risk of bleeding. After 12 months from PCI or in patients with chronic CAD, the general recommendation is to maintain oral anticoagulation only and avoid DPI, which is currently corroborated by the results of two randomized trials (one stopped for low recruitment and the other due to increased mortality in the DPI arm) and one large-scale registry.[82–84]

Stable atherosclerotic vascular disease – SAPT with Flow-dose aspirin is the cornerstone for secondary and/or tertiary prevention in patients with chronic atherosclerotic vascular disease.[77] In 2018, rivaroxaban (2.5 mg bid) was approved by both the FDA and the EMA for patients with chronic CAD or PAD, and updated clinical guidelines with new recommendations for DPI in this context are anticipated. Whether a dual-pathway antithrombotic strategy for chronic atherosclerosis would be also effective by using other direct factor X inhibitors other than rivaroxaban (i.e., apixaban, edoxaban) is unknown. Likewise, it is uncertain whether the DPI strategy can be similarly effective when using a combination of rivaroxaban with clopidogrel rather than aspirin. One argument that can be reasonably raised in favour of aspirin for the DPI combination is that clopidogrel, the most commonly used $P2Y_{12}$ inhibitor, is not immune from a certain degree of interindividual variability in antiplatelet drug response with a considerable number of patients showing inadequate platelet inhibition hence at risk for thrombotic complications.[85] Therefore, keeping a patient on chronic clopidogrel-only could expose patients who are clopidogrel-resistant to the risk of being not protected at all. However, the CAPRIE trial suggests that the larger proportions of high on-treatment platelet resistance noted in pharmacodynamic studies of clopidogrel did not translate into significantly incremental risk on the ground of a large-scale clinical evaluation.[2]

On this background, the practical question is who are the ideal candidates for DPI therapy with aspirin and rivaroxaban? To address that question, it is useful to consider the inclusion and exclusion criteria for the COMPASS trial.[86] A study applying these criteria to 31,873 patients with CAD or PAD in the REACH registry found that 29.9% patients had exclusion criteria and an additional 17.2% did not fulfil the inclusion criteria and thus would not have been eligible for COMPASS.[87] The main reasons for exclusion were high-bleeding risk (51.8%), use of oral anticoagulation therapy (44.8%), requirement for DAPT within 1 year, ischemic stroke <1 year (12.4%), and severe renal failure (2.2%). As such, a substantial proportion of patients in the REACH registry (52.9%), which reflects a real-world cohort of candidates for secondary and tertiary prevention, would be theoretically eligible for the DPI regimen. Notably, these patients

experienced higher annualized primary outcome event rates than patients enrolled in the reference aspirin arm of COMPASS (4.2% vs. 2.9% per year, P<0.001), implying they would have likely also had greater benefit.[87] Another practical consideration is how DPI compares with other antithrombotic strategies in the CAD and PAD setting.[86] In patients with prior MI, ticagrelor 60 mg bid is approved for long-term DAPT, based on the results of the PEGASUS (Prevention with Ticagrelor of Secondary Thrombotic Events in High-Risk Patients with Prior Acute Coronary Syndrome) trial.[4] Because prior MI represented an inclusion criterion for COMPASS, a proportion of MI patients at low bleeding risk would be theoretically eligible for either DAPT or DPI (or SAPT as an alternative). In comparing the PEGASUS and COMPASS cohorts to reflect on the external generalizability of the trial results (**Table 2**), one should consider that, in PEGASUS, patients were included if they had a MI 1 to 3 years earlier (median 1.7 years), while in COMPASS patients were included up to 20 years from the MI (median 7 years). Also, prior stroke was an exclusion criterion in PEGASUS but not in COMPASS. Interestingly, the benefit of ticagrelor vs. placebo in PEGASUS was mostly confined to patients who were within 30 days of stopping the $P2Y_{12}$ inhibitor, while in both PEGASUS and COMPASS there was no interaction between the treatment effect of the investigational drug and the proximity of the MI. In aggregate, the two cohorts represent patients at different stages from the index event.[86] Candidates for the PEGASUS strategy may mostly benefit from uninterrupted DAPT after the recommended 12 month course of DAPT following the MI, and extending long-term as per the drug instructions for use, while candidates for the COMPASS strategy may be considered at any time after an MI. Importantly, PEGASUS excluded patients with any prior stroke, while in COMPASS only patients with a recent (<1 month) stroke or previous hemorrhagic or lacunar stroke were excluded. It should also be noted that the COMPASS trial results were driven by a reduction in cardiovascular death and stroke, while in PEGASUS the benefit was driven by a reduction in MI. These findings may suggest the differential role of DAPT compared with DPI on ischemic recurrences, with the former likely more effective on arterial thrombotic complications and the latter in cardioembolic events.[86,88,89] The differential

impact of these strategies on vascular inflammation and atherothrombotic complications cannot be excluded and warrants further investigation. A practical algorithm for the choice of antithrombotic treatment in patients with CAD, particularly after an MI, is provided in **Figure 7**.[90] Indeed, areas of needed investigation include understanding modalities and timing of switching from DAPT to DPI.

With respect to PAD, the COMPASS strategy enters an area where few antithrombotic options exist. In fact, the only evidence of a strategy superior to aspirin in PAD patients was that demonstrated in the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial in which clopidogrel monotherapy reduced ischemic events compared with aspirin monotherapy in patients with stable vascular disease, a finding which was driven mostly by the PAD cohort.[2] However, more potent $P2Y_{12}$ inhibition with ticagrelor monotherapy failed to show any benefit over clopidogrel monotherapy.[91] Moreover, the benefit of a DAPT regimen over single antiplatelet treat in PAD patients is unclear and derives from small subgroup analysis.[92,93] Drugs such as cilostazol and naftidrofuryl are used to alleviate symptoms of limb ischemia. Ultimately, although adjunctive treatment with vorapaxar showed a reduction in hospitalization for acute limb ischemia and peripheral revascularization compared to standard of care therapy (aspirin and/or clopidogrel), this strategy did not reduce the primary composite ischemic endpoint and increased major bleeding, including intracranial hemorrhage, which contributes to explain its infrequent use in the countries where the drug is available.[94] Due to reduction in cardiovascular mortality, major limb adverse events and amputations, DPI may represent a major advance in the management of PAD.[88]

CONCLUSIONS

Secondary and tertiary prevention with antithrombotic strategies that are not restricted to only aspirin is an emerging paradigm. The combination of antiplatelet drugs with low-dose rivaroxaban has proved effective in two large-scale randomized trials across the spectrum of atherosclerosis

(e.g., CAD and PAD patients from COMPASS and ACS patients from ATLAS-ACS 2). Such DPI strategy has been granted approval from regulatory authorities in both Europe (stable atherosclerosis and ACS) and the United States (stable atherosclerosis only), becoming available for clinical use. Aspirin has been the standard of care in the chronic atherosclerosis setting, where residual risk remains despite the availability of established therapies for limiting atherosclerosis progression and stabilizing existing plaques. The COMPASS trial shows that, on top of control of lipids, blood pressure and renin-angiotensin-aldosterone system blockade, rivaroxaban 2.5 mg bid plus aspirin reduced the composite endpoint of stroke, MI or cardiovascular death by 26% in CAD patients (stroke by 44%, cardiovascular death by 25%) and by 28% in PAD patients (major adverse limb events by 46%, major amputations by 70%). Despite an increase in major bleeding events with rivaroxaban 2.5 mg bid plus aspirin, there was no increase in fatal or critical organ bleeding. While DPI may be of clinical benefit in a broad group of individuals with CAD and PAD, patient selection for the COMPASS strategy should leverage the baseline residual risk of ischemic events against the expected increased risk of bleeding. Areas of uncertainty remain, which are the objective of future investigations. These include ascertaining the comparative efficacy and safety of DPI versus DAPT or even triple therapy in patients at high risk in whom the benefits would outweigh the bleeding risk.

FIGURE LEGENDS

Figure 1 – Residual risk of vascular events in trials of patients with chronic coronary artery disease (CAD) despite currently available medical therapy. Data are shown for landmark studies of antithrombotic therapies for secondary and tertiary prevention with respect to the rates of major adverse cardiac events in the intervention and control groups. A mean residual risk of 3% is shown in most recent randomized trials. Data from references[1–5] Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MACE, major adverse cardiac events; NR, not reported.

Figure 2 - Platelet activation mechanisms. Platelet activation is initiated by soluble agonists, such as thrombin, thromboxane A2 (TXA_2), 5-hydroxytryptamine (5-HT), adenosine diphosphate (ADP), and adenosine triphosphate (ATP), and by adhesive ligands, such as collagen and von Willebrand factor (vWF). Consequently, dense granule secretion of platelet agonists and secretion of TXA_2, as a result of phospholipase A_2 activation, lead to amplification of platelet activation and the associated responses. The P2Y purinoceptor 12 ($P2Y_{12}$) receptor has a major role in the amplification of platelet activation, which is also supported by outside-in signaling via integrin αIIbβ3 (the glycoprotein IIb/IIIa receptor). Combined blockade of $P2Y_{12}$ and integrin αIIbβ3, therefore, has additive effects on platelet activation and the associated platelet responses. 5-HT2A, 5-HT receptor 2A; GPVI, platelet glycoprotein VI; NO, nitric oxide; PAR, proteinase-activated receptor; PGI_2, prostacyclin receptor; TPα, TXA_2 receptor isoform α. Reproduced with permission from [49]

Figure 3 - Stages of cardiovascular prevention. Primary prevention is aimed at preventing coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral artery disease (PAD), secondary prevention targets individuals with established CAD, CVD or PAD who have yet to

experience an ischemic event or undergo revascularization, and tertiary prevention is aimed at reducing the impact and sequelae of CAD, CVD or PAD that have already occurred. Abbreviations: ALI, acute limb ischemia; CV, cardiovascular; MI, myocardial infarction.

Figure 4 - Overview of pathophysiology of atherothrombosis and the role of factor Xa and thrombin. Dysregulation of endothelial cells forms the basis for the initial development of atherosclerosis. Atherosclerotic plaques subsequently develop through a complex inflammatory mediated process. Increased expression of adhesion molecules and release of proinflammatory cytokines by activated endothelial cells promotes recruitment of inflammatory cells. This process coupled with cell proliferation and accumulation of lipid deposits and foam cells favors atherosclerotic plaque growth. The sustained inflammation reduces plaque stability and promotes plaque rupture with thrombotic complications. Both factor Xa and thrombin contribute to the development of atherothrombosis. Abbreviations: F, factor; PAR, proteinase-activated receptor; SMC, smooth muscle cell. Reproduced with permission from [26]

Figure 5 - Synergy of direct factor Xa inhibition and antiplatelet therapy. Direct inhibitors of factor Xa, such as rivaroxaban, and antiplatelet agents, such as acetylsalicylic acid, synergistically target two essential components of atherothrombosis: coagulation and platelet activation. Inhibition of factor Xa modulates thrombin generation; thrombin is the most potent inducer of platelet activation and the prothrombinase complex on the platelet membrane is key generator of thrombin. Combination of rivaroxaban with antiplatelet agents works synergistically to reduce platelet activation, leading to the delayed/reduced formation of coagulation complexes and vice versa, thereby enhancing antithrombotic potency. COX1, cyclooxygenase 1; PAR, protease-activated receptor; $P2Y_{12}$, P2Y purinoceptor 12; TXA_2, thromboxane A_2; TPα, TXA_2 receptor isoform α.

Figure 6 - Schematic representation of coagulation factor-mediated activation of PARs and cell types in which each PAR is expressed. Four PARs (PAR-1–4) are expressed on the membranes of platelets and other cells. Thrombin (factor IIa) activates PAR-1, -3 and -4 (but not PAR-2). Factor Xa and TF–factor VIIa complex can each activate both PAR-1 and PAR-2. Once activated, factor Xa initiates intracellular signaling in various cell types of the cardiovascular system, preferentially mediated by PAR-2 or, when in ternary complex with tissue factor–FVIIa, through both PAR-1 and PAR-2. PAR-1, PAR-2, or both are present in abundance on endothelial cells, leukocytes, VSMCs, fibroblasts, and dendritic cells. Factor Xa–dependent, PAR-mediated signaling contributes to the production of proinflammatory cytokines (e.g., interleukin-6, interleukin-8, and chemokine ligand 2), and to the expression of cell-adhesion molecules (e.g., E-selectin, intracellular adhesion molecule 1 [ICAM-1], and vascular-cell adhesion molecule 1 [VCAM-1], along with tissue factor up-regulation, VSMC proliferation, and the release of growth factors (e.g., vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor β). All these may contribute to the inflammatory process leading to atherosclerotic plaque progression. F, factor; PAR, proteinase-activated receptor; SMC, smooth muscle cell; TF, tissue factor. Reproduced with permission from[27]

Figure 7. Choice of antithrombotic treatment strategy in patients with coronary artery disease. Decision algorithm for DPI (e.g., aspirin plus rivaroxaban 2.5 mg bid) or prolonged DAPT (e.g., aspirin plus ticagrelor) in patients with stable CAD on aspirin monotherapy or patients with myocardial infarction and treated with DAPT, respectively. CABG, coronary artery bypass surgery; CAD, coronary artery disease; CKD, chronic kidney disease (eGFR < 60 mL/min and not requiring dialysis for prolonged DAPT; eGFR < 60 mL/min and > 15 mL/min for low dose rivaroxaban); DAPT, dual antiplatelet therapy; DM, diabetes mellitus; PAD, peripheral artery disease; MI: myocardial infarction. Reproduced from [90]

Table 1 - Options for cardiovascular prevention with antiplatelet therapy for patients with CAD, CVD and/or PAD

	Guidelines	CAD	CVD	PAD
Primary prevention	ESC	Antiplatelet therapy is generally not recommended		
	ACC/AHA			
Secondary prevention	ESC	SAPT may be considered in selected cases	SAPT with aspirin or clopidogrel	SAPT in symptomatic subjects
	ACC/AHA	Not covered	Not covered	SAPT is generally recommended in both symptomatic and asymptomatic subjects. Role of vorapaxar uncertain
Tertiary prevention	ESC	DAPT followed by SAPT immediately after an ACS, immediately after PCI and in the chronic phase after an MI	SAPT with aspirin or clopidogrel, or combination of aspirin and dipyridamole after a stroke or TIA; DAPT followed by SAPT immediately after CAS; SAPT after carotid surgery	DAPT followed by SAPT immediately after percutaneous revascularization; SAPT after surgical revascularization
	ACC/AHA		Not covered	DAPT reasonable immediately after revascularization.

Abbreviations: ACC, American College of Cardiology; ACS, acute coronary syndromes; AHA, American Heart Association; CAD, coronary artery disease; CAS, carotid artery stenting; CVD, cerebrovascular disease; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology;

MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; TIA, transient ischemic attack.

Table 2. Key difference between patients enrolled in the COMPASS and PEGASUS trials

	COMPASS	PEGASUS
Inclusion criteria	CAD (prior MI <20 years earlier; multivessel CAD; multivessel PCI; CABG 4 to 14 days earlier); PAD (revascularization; amputation; claudication with ABI <0.9 or >50% stenosis; carotid revascularization or carotid stenosis >50%)	Prior MI 1 to 3 years earlier with at least one additional factor
Exclusion criteria	Previous lacunar stroke, previous ICH	Previous stroke, previous ICH, GI bleeding <6 months earlier
Age	68	65
Diabetes mellitus	38	32
Heart failure	21	NA
CrCl <60 ml/min	22%	23%
CAD	91%	100%
Multivessel disease	62%	59%
Previous MI	62% (median 7 yrs)	100% (median 1.7 yrs)
Previous PCI	60%	83%
PAD	27%	5%

Previous stroke	4%	-
Statin use	90%	92%
Beta-blocker use	70%	82%
ACEI/ARB use	71%	80%

Abbreviations: ABI, ankle-brachial index; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CAD, coronary artery disease; CrCl, creatinine clearance; GI, gastro-intestinal; ICH, intracranial hemorrhage; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

FIGURE 1

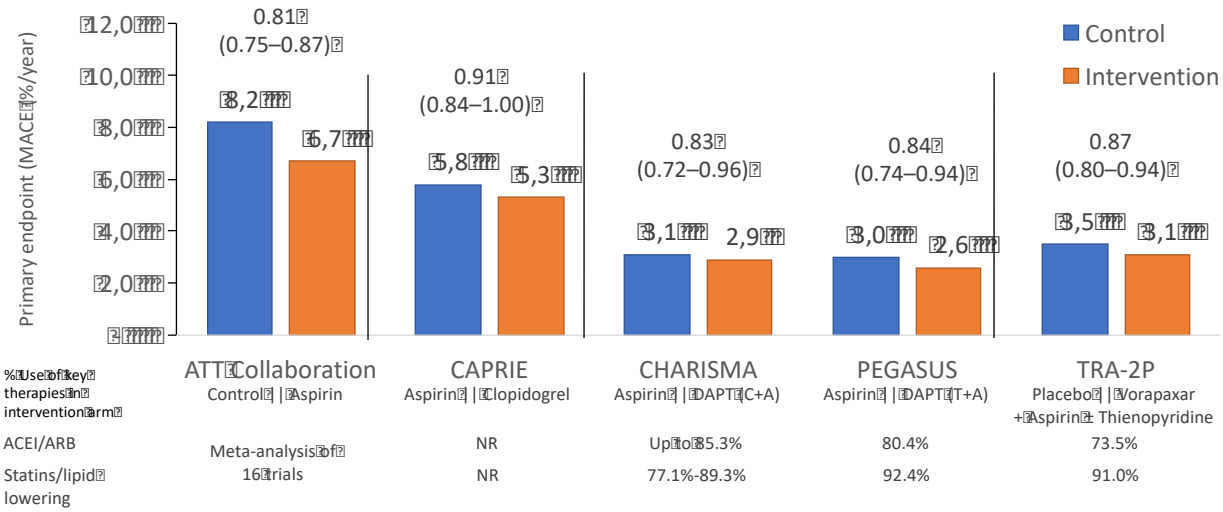

Primary endpoint (MACE) (%/year)
12,0
10,0
8,0
6,0
4,0
2,0
0.81
(0.75–0.87)
8,2
6,7
0.91
(0.84–1.00)
5,8
5,3
0.83
(0.72–0.96)
3,1
2,9
0.84
(0.74–0.94)
3,0
2,6
0.87
(0.80–0.94)
3,5
3,1
Control
Intervention
ATT Collaboration
Control | Aspirin
CAPRIE
Aspirin | Clopidogrel
CHARISMA
Aspirin | DAPT (C+A)
PEGASUS
Aspirin | DAPT (T+A)
TRA-2P
Placebo | Vorapaxar +Aspirin ± Thienopyridine
% Use of key therapies in intervention arm
ACEI/ARB
Meta-analysis of 16 trials
NR
Up to 85.3%
80.4%
73.5%
Statins/lipid lowering
NR
77.1%-89.3%
92.4%
91.0%

FIGURE 2

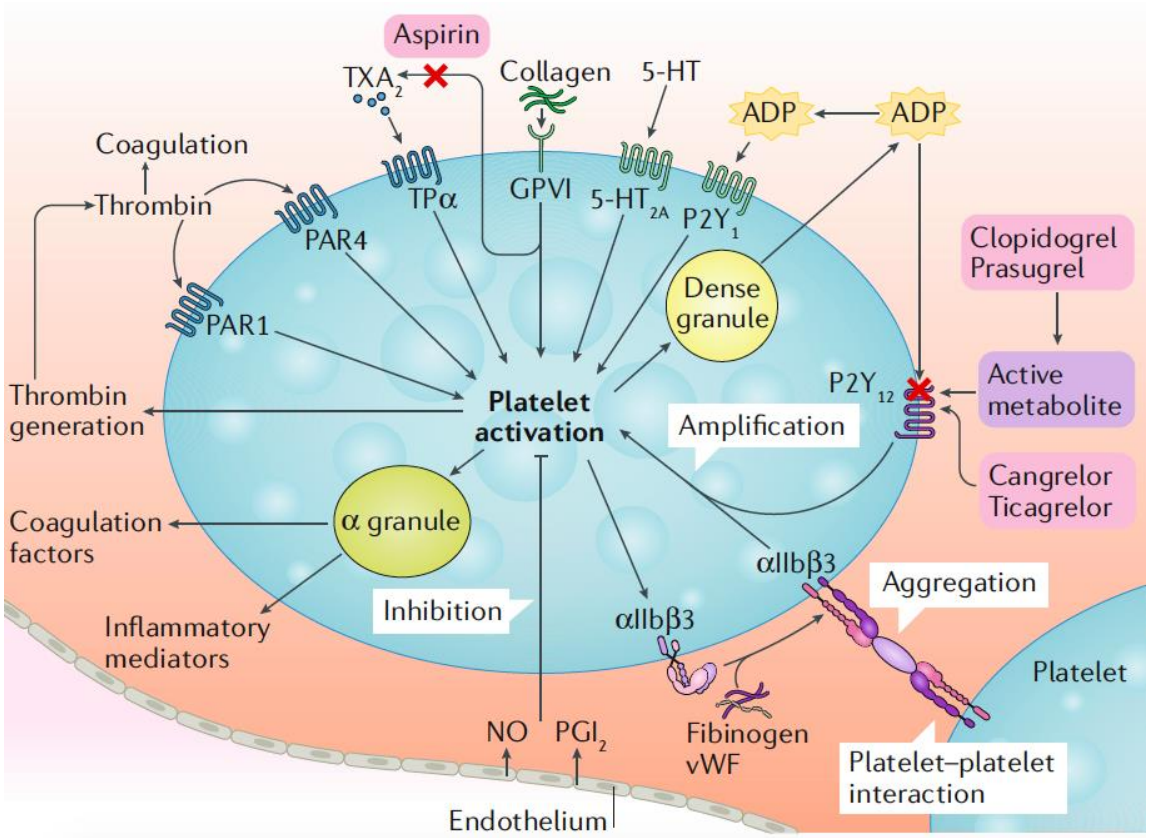

Aspirin
TXA2
Collagen
5-HT
ADP
ADP
Coagulation
Thrombin
TPα
GPVI
5-HT2A
P2Y1
PAR4
Dense granule
Clopidogrel
Prasugrel
PAR1
P2Y12
Active metabolite
Thrombin generation
Platelet activation
Amplification
Cangrelor
Ticagrelor
α granule
Coagulation factors
αIIbβ3
Aggregation
Inhibition
αIIbβ3
Inflammatory mediators
Platelet
NO
PGI2
Fibinogen
vWF
Platelet–platelet interaction
Endothelium

FIGURE 3

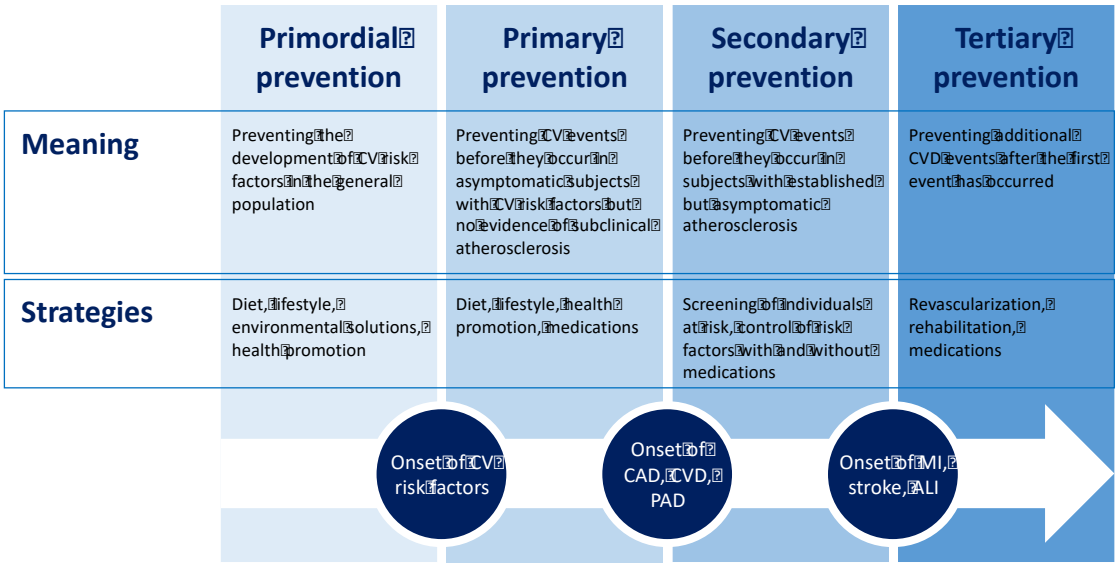

Primordial prevention
Primary prevention
Secondary prevention
Tertiary prevention
Meaning
Preventing the development of CV risk factors in the general population
Preventing CV events before they occur in asymptomatic subjects with CV risk factors but no evidence of subclinical atherosclerosis
Preventing CV events before they occur in subjects with established but asymptomatic atherosclerosis
Preventing additional CVD events after the first event has occurred
Strategies
Diet, lifestyle, environmental solutions, health promotion
Diet, lifestyle, health promotion, medications
Screening of individuals at risk, control of risk factors with and without medications
Revascularization, rehabilitation, medications
Onset of CV risk factors
Onset of CAD, CVD, PAD
Onset of MI, stroke, ALI

FIGURE 4

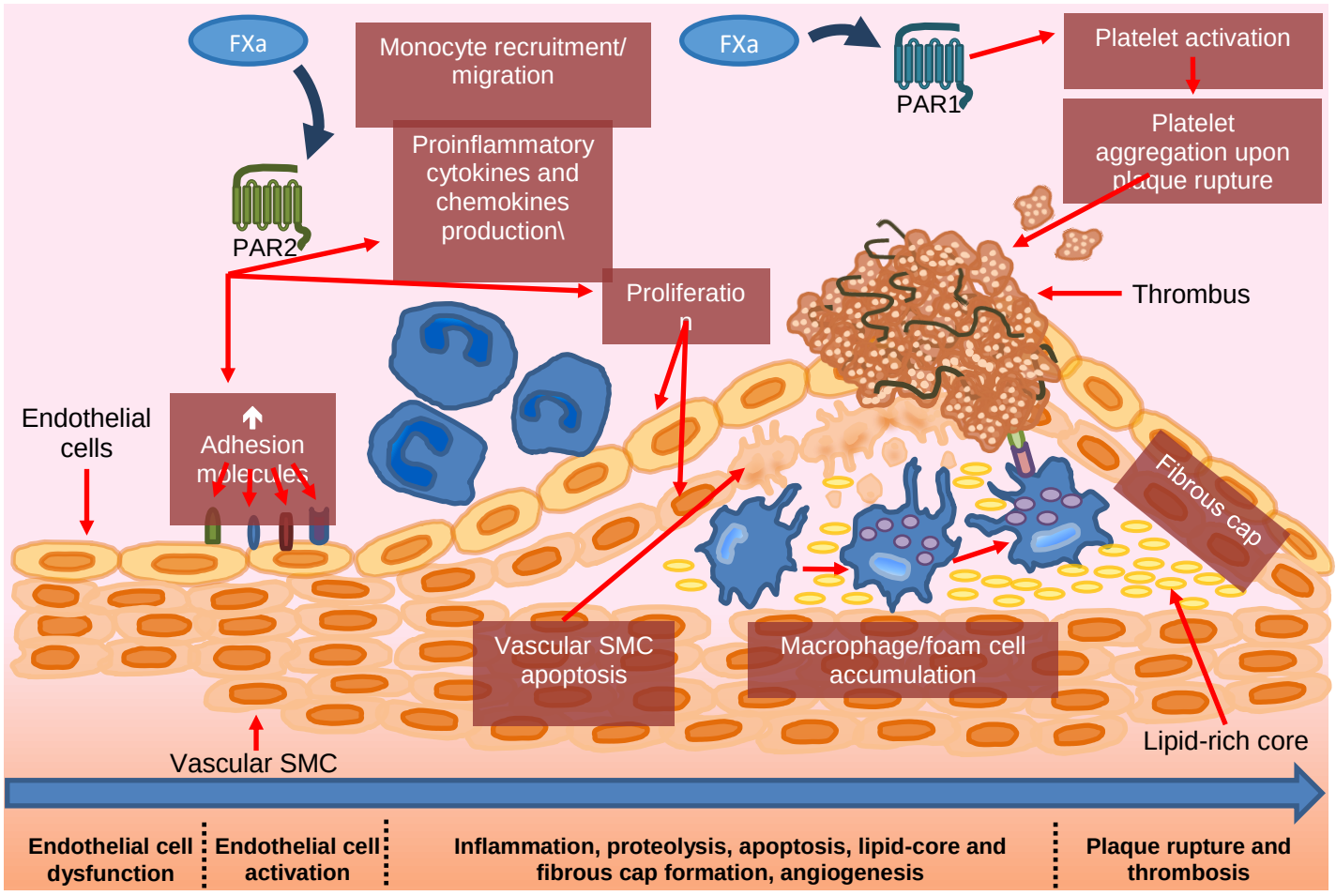

FXa
Monocyte recruitment/ migration
FXa
PAR1
Platelet activation
Platelet aggregation upon plaque rupture
Proinflammatory cytokines and chemokines production\
PAR2
Proliferation
Thrombus
Endothelial cells
Adhesion molecules
Fibrous cap
Vascular SMC apoptosis
Macrophage/foam cell accumulation
Lipid-rich core
Vascular SMC
Endothelial cell dysfunction
Endothelial cell activation
Inflammation, proteolysis, apoptosis, lipid-core and fibrous cap formation, angiogenesis
Plaque rupture and thrombosis

FIGURE 5

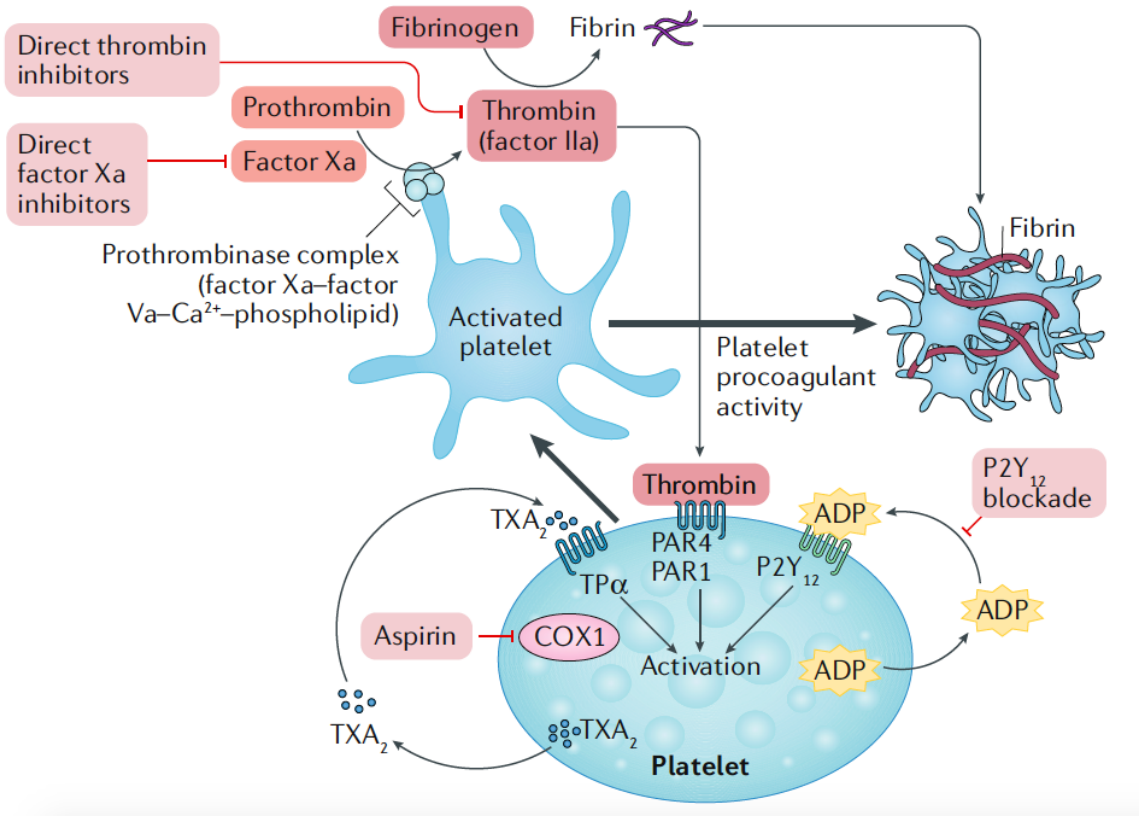

Fibrinogen
Fibrin
Direct thrombin inhibitors
Prothrombin
Thrombin (factor IIa)
Direct factor Xa inhibitors
Factor Xa
Prothrombinase complex (factor Xa–factor Va–Ca2+–phospholipid)
Activated platelet
Fibrin
Platelet procoagulant activity
Thrombin
P2Y12 blockade
TXA2
PAR4
PAR1
TPα
P2Y12
ADP
ADP
ADP
Aspirin
COX1
Activation
TXA2
TXA2
Platelet

FIGURE 6

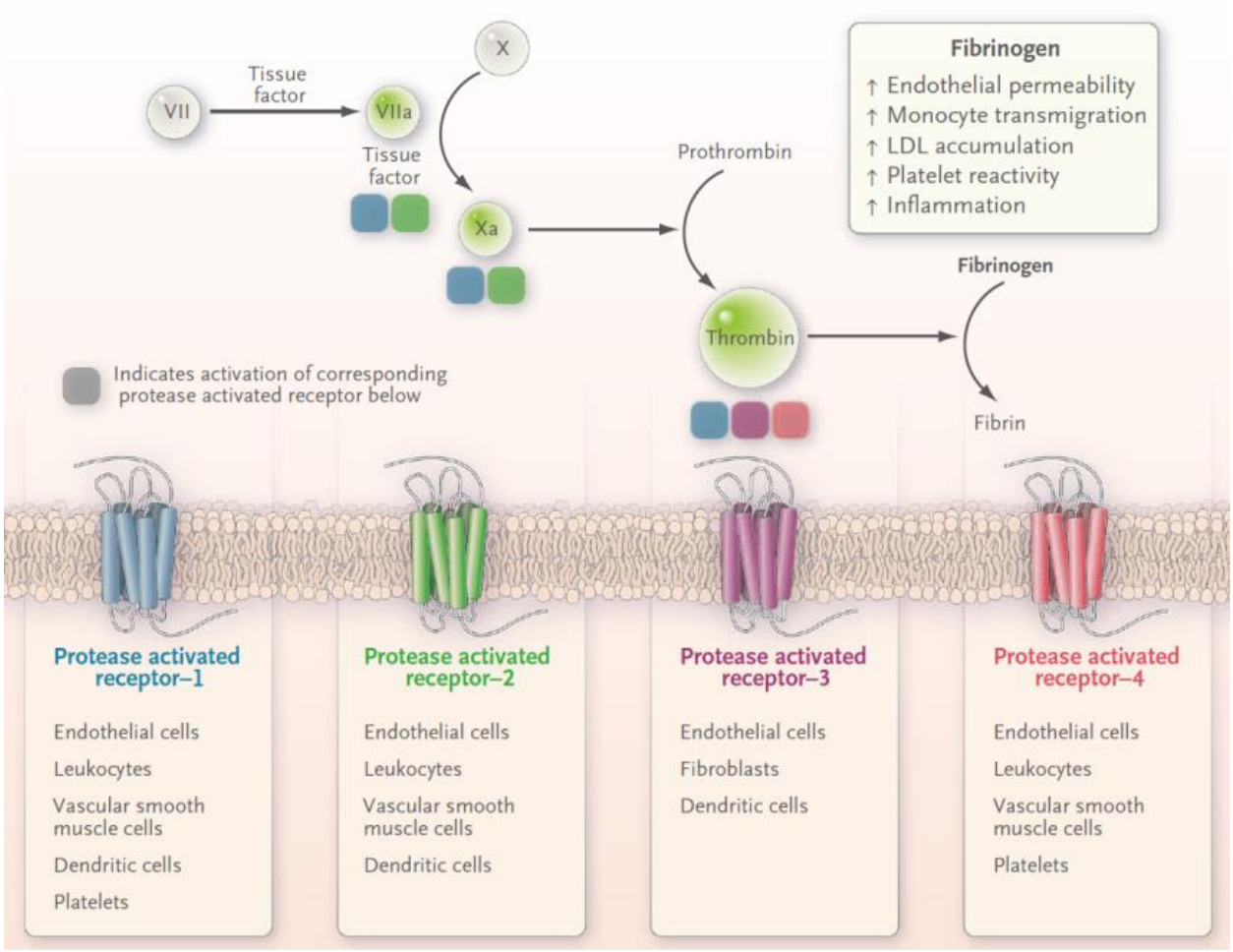
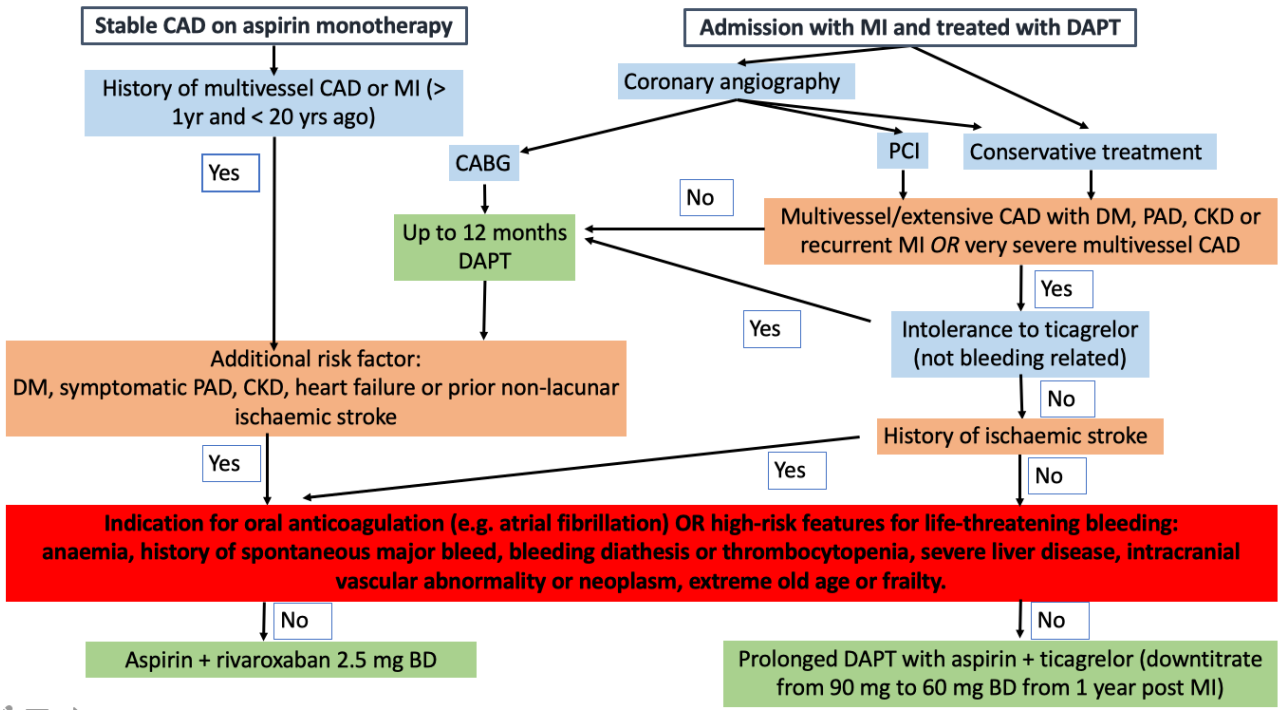

VII
Tissue factor
VIIa
Tissue factor
X
Xa
Prothrombin
Thrombin
Fibrinogen
Fibrin
Fibrinogen
↑ Endothelial permeability
↑ Monocyte transmigration
↑ LDL accumulation
↑ Platelet reactivity
↑ Inflammation
Indicates activation of corresponding protease activated receptor below
Protease activated receptor–1
Endothelial cells
Leukocytes
Vascular smooth muscle cells
Dendritic cells
Platelets
Protease activated receptor–2
Endothelial cells
Leukocytes
Vascular smooth muscle cells
Dendritic cells
Protease activated receptor–3
Endothelial cells
Fibroblasts
Dendritic cells
Protease activated receptor–4
Endothelial cells
Leukocytes
Vascular smooth muscle cells
Platelets

FIGURE 7


Stable CAD on aspirin monotherapy
History of multivessel CAD or MI (> 1yr and < 20 yrs ago)
Yes
Additional risk factor:
DM, symptomatic PAD, CKD, heart failure or prior non-lacunar ischaemic stroke
Yes
Admission with MI and treated with DAPT
Coronary angiography
CABG
PCI
Conservative treatment
No
Up to 12 months DAPT
Multivessel/extensive CAD with DM, PAD, CKD or recurrent MI OR very severe multivessel CAD
Yes
Yes
Intolerance to ticagrelor (not bleeding related)
No
History of ischaemic stroke
Yes
No
Indication for oral anticoagulation (e.g. atrial fibrillation) OR high-risk features for life-threatening bleeding:
anaemia, history of spontaneous major bleed, bleeding diathesis or thrombocytopenia, severe liver disease, intracranial vascular abnormality or neoplasm, extreme old age or frailty.
No
Aspirin + rivaroxaban 2.5 mg BD
No
Prolonged DAPT with aspirin + ticagrelor (downtitrate from 90 mg to 60 mg BD from 1 year post MI)

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