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Dual anticoagulant and antiplatelet therapy for CAD and PAD patients

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Keywords

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Atherosclerosis is an arterial disease that progresses with age and affects many people in the world[1]. In the United States and Western Europe, cardiovascular disease (CVD) caused by atherosclerosis is the leading cause of death. In advanced atherosclerosis, there is narrowing of the arterial lumen to the extent that tissue ischemia can occur when metabolic demands increase (e.g. coronary ischemia with angina). In severe cases, acute rupture or erosion of atherosclerotic plaques lead to the rapid formation of intravascular thrombi, a process referred to atherothrombosis. Clinical manifestations of atherothrombosis occur in the heart (coronary artery disease, CAD, and myocardial infarction, MI), brain (ischemic stroke) and in peripheral arteries (peripheral artery disease, PAD). CAD can be divided into stable disease and unstable disease that includes acute coronary syndrome (ACS) with ST-elevated MI (STEMI) or non ST-elevated MI (NSTEMI).

Arterial thrombi are primarily composed of platelets (so-called “white clots”)[2]. However, cross-linked fibrin strands stabilize the clot. Plaques contain many platelet activators, including collagen (Figure). In addition, plaques contain high levels of tissue factor that activates the coagulation cascade (Figure). Importantly, platelets and the coagulation cascade are activated in parallel and there is crosstalk between the two pathways. For instance, thrombin is a potent activator of human platelets through cleavage of protease-activated receptors (PARs) (PAR1 and PAR4 (reviewed in[3,4]) and fibrinogen is used to bridge activated platelets. Conversely, activated platelets enhance coagulation by providing coagulation factors and by presenting a negatively-charged phospholipid surface that

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facilitates the assembly of cofactor/coagulation protease complexes and thrombin generation.

Platelet inhibitors are the primary therapy used to prevent arterial thrombosis in CVD patients[5,6]. The standard medical treatment for ACS patients and patients receiving percutaneous intervention (PCI) with an intracoronary stent is dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor[5]. Aspirin irreversibly inhibits COX-1 and prevents platelet-dependent thromboxane formation. P2Y12 inhibitors include thienopyridines, such as clopidogrel and prasugrel, and cyclopentyltriazolopyrimidine-type inhibitors, such as ticagrelor[7]. Clopidogrel and prasugrel are prodrugs that require activation by cytochrome P450 enzymes in the liver. Ticagrelor is a direct acting non-competitive inhibitor of P2Y12.

DAPT is recommended for a minimum of 6 months in patients with stable CAD receiving a drug eluting stent and for 12 months in patients with ACS (the majority of whom undergo PCI with stenting)[8]. After this time, therapy can be changed to a single antiplatelet agent depending on the balance between risk of recurrent ischemic event versus risk of bleeding with DAPT. Despite continued antiplatelet therapy, patients remain at risk for recurrent cardiovascular events, particularly in those at highest risk, such as patients with diabetes, PAD and complex CAD. The current recommended treatment for patients with stable CAD is low-dose aspirin or clopidogrel if they do not tolerate aspirin[9]. The recommended treatment for patients with PAD is single antiplatelet therapy[10]. However, despite antiplatelet therapy, ~2-5% of CAD and PAD patients annually have major adverse cardiovascular events (MACE)[11-15].

Clinical trials have compared the efficacy and safety of different antiplatelet agents and combinations of antiplatelet agents in CVD patients, attempting to find more effective and safer strategies to prevent recurrent atherothrombotic events (Table). A recent review discusses these different trials in detail[16]. In this editorial, we selected a few trials to illustrate differences between trials and the relationship between efficacy and safety. Comparison of different trials is difficult because they are performed at different times and include different groups of patients.

The TRITON-TIMI 38 trial enrolled >13000 patients with ACS (either STEMI or NSTEMI) of which 99% underwent PCI. The more potent P2Y12 blocker prasugrel was superior to clopidogrel in reducing the combined endpoint of vascular death, MI or stroke in patients with ACS but there was a higher rate of bleeding with prasugrel (Table)[17,18]. In contrast, prasugrel was not superior to clopidgrel in reducing cardiovascular (CV) death in patients with NSTEMI ACS who did not undergo revascularization in the TRILOGY ACS trial (Table)[19]. In the PLATO trial, the direct acting P2Y12 blocker ticagrelor was superior to clopidogrel in >18000 patients with ACS (either STEMI or NSTEMI) undergoing PCI who were treated with aspirin, but not in the EUCLID trial in which patients with symptomatic PAD were treated with P2Y12 inhibitor monotherapy (Table)[13,17]. However, the beneficial effect of ticagrelor in PLATO was driven by a reduction in MI and vascular death whereas there was no difference in stroke[17]. In addition to differences in receptor binding kinetics, part of the difference in efficacy between clopidogrel and prasugrel/ticagrelor in ACS

patients treated with PCI may be due to a lack of response to clopidogrel. Clopidogrel must be metabolized to an active form via a pathway that involves the CYP2C19 pathway, resulting in a broad variation in concentrations of the active metabolite. Recently, the IGNITE study showed a higher risk for MACE in patients with a *CYP2C19* loss-of-function allele if clopidogrel versus alternative therapy was prescribed[20].

Because of the lack of optimal protection of single antiplatelet therapy in patients with stable CAD and/or risk factors, the use of DAPT was studied in the CHARISMA trial. This study of >15000 patients showed that adding clopidogrel to aspirin did not reduce the risk of cardiovascular death, MI or stroke compared to aspirin alone[21]. While there was no benefit in patients with CAD risk factors, a subgroup analysis of patients with prior MI, stroke or PAD (9,478 patients) found a significant reduction in death without an increase in major bleeding in the patients treated with DAPT compared with aspirin alone[22]. The PEGASUS-TIMI 54 trial investigated the effect of DAPT beyond 1 year in patients with a prior MI and found that addition of ticagrelor to aspirin reduced CV death in patients but significantly increased major bleeding[23].

Vorapaxar is a PAR1 inhibitor that represents a new class of antiplatelet therapy[24]. Two studies determined the effect of triple antiplatelet therapy on CVD patients by adding Vorapaxar on top of standard antiplatelet therapy. The TRACER trial found that vorapaxar did not reduce CV death in ACS patients but increased intracranial hemorrhage[25]. The TRA 2P-TIMI 50 observed a reduced risk of cardiovascular death in patients with stable atherosclerosis but was stopped due to the risk of intracranial bleeding (Table)[25,26]. Interestingly, in the TRA 2P-TIMI 50 trial 14% of the patients had PAD and while vorapaxar had no effect on the composite endpoint of CV death, MI or stroke, vorapaxar significantly reduced acute limb ischemic (ALI) events and peripheral revascularization in PAD patients compared to placebo[15,26]. These studies indicate that, in general, an intensification of antiplatelet therapy is associated with increased efficacy but often with increased bleeding.

An alternative strategy to prevent thromboembolic events in CVD patients is to add an anticoagulant agent to standard antiplatelet therapy. Early studies evaluated warfarin in ACS patients. Warfarin is a vitamin K antagonist that reduces blood coagulation by inhibiting the formation of gamma-carboxyglutamic domains on the coagulation factors prothrombin, factor VII, factor IX and factor X. A meta-analysis of 10 trials found that ACS patients receiving aspirin and warfarin had a decrease in MI and ischemic stroke but at the cost of an increase in major bleeding compared with patients receiving aspirin alone[27]. These studies were performed prior to the widespread usage of PCI and DAPT in patients with ACS and thus do not reflect current practice.

Recently, a new family of anticoagulants has been developed that are called direct oral anticoagulants (DOACs) because they directly bind and inhibit either thrombin or factor[28]. DOACs consist of the thrombin inhibitor dabigatran etexilate and the factor Xa inhibitors apixaban, rivaroxaban, edoxaban and betrixaban[28]. Importantly, DOACs have lower rates of intracerebral bleeding compared to vitamin K antagonists[29]. However, the major side-effect of all antithrombotic agents is bleeding because both platelets and the coagulation cascade are required for hemostasis.

The concept of combined antiplatelet and anticoagulant agents for the secondary prevention of atherothrombotic events has been revisited since the approval of DOACs because they have a lower risk of intracerebral bleeding compared with vitamin K antagonists[28]. Two trials have analyzed the effect of adding two different factor Xa (FXa) inhibitors to standard antiplatelet therapy in ACS patients (Table). In APPRAISE-2, the addition of apixaban to DAPT did not significantly affect the primary outcome of cardiovascular death (7.5% versus 7.9%) but significantly increased major bleeding which led to the termination of the study[30]. The dose of apixaban used in this trial was 5 mg bid, which is the same dose used to treat patients with venous thromboembolism or atrial fibrillation. In ATLAS ACS 2-TIMI 51, ACS patients received low doses of rivaroxaban (2.5 or 5 mg bid)[31] which are lower than the therapeutic doses used to treat patients with venous thromboembolism or prevent thromboembolic stroke in atrial fibrillation (20 mg qd). Both low doses of rivaroxaban reduced the primary endpoint of cardiovascular death, MI or stroke when compared to placebo. Importantly, the 2.5 mg bid dose of rivaroxaban significantly reduced cardiovascular death (2.7% versus 4.1%) compared with standard antiplatelet therapy alone, whereas no survival benefit was observed with the 5 mg bid dose. Compared to placebo, rivaroxaban was associated with increased rates of major bleeding and intracranial hemorrhage but not fatal bleeding. This study indicates that addition of rivaroxaban at a dose of 2.5 mg bid to standard antiplatelet therapy reduced death in ACS patients but at the cost of increased bleeding. Rivaroxaban is approved together with antiplatelet therapy for ACS in Europe but not the US.

It is intriguing that the lower dose of rivaroxaban improved survival whereas the higher dose did not have this effect. This result has to be interpreted very cautiously as the study was not designed nor powered to look at differences in death between the two doses. It is interesting however to speculate on possible etiologies. One potential explanation is that this effect is because of the higher rates of bleeding with rivaroxaban 5 mg bid compared with 2.5 mg bid. Another explanation is that thrombin can act as both a procoagulant and an anticoagulant. When thrombin binds its receptor thrombomodulin on endothelial cells it changes its substrate specificity and is able to activate the anticoagulant protein C. Indeed, infusion of a low dose of thrombin into baboons increases levels of activated protein C (APC)[32]. In addition to its anticoagulant activity, APC has anti-inflammatory and cytoprotective activities[33,34]. Therefore, it is possible that thrombin-dependent generation of the APC and its vascular protective functions is preserved with a low dose of rivaroxaban. It would be interesting to test this hypothesis by measuring levels of plasma APC in patients treated with 2.5 mg bid and 5 mg bid doses of rivaroxaban.

The standard therapy for patients with stable CAD and/or PAD is treatment with a single antiplatelet agent, such as aspirin or clopidogrel. To determine if outcomes would be improved by adding an anticoagulant, the recent COMPASS trial compared the effect of aspirin alone (100 mg qd), rivaroxaban alone (5 mg bid) or aspirin (100 mg qd) plus rivaroxaban (2.5 mg bid) in stable CAD and PAD patients[35]. Importantly, the composite of CV death, stroke, or MI was significantly decreased in the rivaroxaban-plus-aspirin group compared to the aspirin group (4.1% versus 5.4%). However, there was a significant increase in major bleeding (3.1% versus 1.9%)[35]. Interestingly, rivaroxaban alone also reduced the primary outcome of CV death, MI or stroke compared with aspirin but this reduction was

not statistically significant (p = 0.12). Similar results were observed when the stable CAD patients (24,824 patients) and the PAD patients (7470 patients) were analyzed separately, although the net clinical benefit was stronger in PAD compared to CAD patients[36,37].

The combination of rivaroxaban-plus-aspirin was associated with fewer CV deaths and death from any cause than aspirin alone. What is the mechanism by which rivaroxaban-plus-aspirin reduced death in stable CAD and PAD patients compared with aspirin alone? The simplest explanation is that the combination of an anticoagulant agent and an antiplatelet agent has superior antithrombotic activity compared to aspirin alone in preventing major thrombotic events. Anticoagulants, such as rivaroxaban, not only reduce fibrin generation but also indirectly inhibit platelet activation by reducing the amount of thrombin (Figure). This hypothesis is supported by the reduction in ischemic endpoints in the COMPASS trial.

Interestingly, the combination of rivaroxaban and aspirin significantly reduced major adverse limb events in the PAD patients compared with aspirin alone[37]. Similarly, PAD patients treated with the PAR1 inhibitor had a significant reduction in ALI events and revascularization compared to placebo[15]. At present, the relative contribution to vascular pathogenesis in PAD patients of thrombotic events and vascular inflammation are not well understood.

It is intriguing to speculate that dual aspirin and rivaroxaban therapy in the COMPASS trial has an effect beyond simply reducing thrombosis. Platelets and activation of PARs by coagulation proteases can enhance inflammation and atherosclerosis. Aspirin has anti-inflammatory activity and blocking FXa would reduce PAR signaling (Figure). In mouse studies, a deficiency of P-selectin, P2Y12 or CalDAG-GEFI, which is required for calcium-dependent platelet activation, is associated with reduced atherosclerosis[38-40] Mouse studies have also shown that thrombin and FXa inhibitors stabilize plaques by reducing plaque inflammation and increasing the fibrous cap[41]. An early study found that the thrombin inhibitor melagatran reduced atherosclerosis in ApoE$^{-/-}$ mice and this was associated with reduced MMP9 expression and an increase in the fibrous cap[42]. Similar results were observed with the thrombin inhibitor dabigatran[43-45]. Importantly, rivaroxaban also reduced atherosclerosis in ApoE$^{-/-}$ mice and this was associated with reduced levels of MMP9 and macrophages[46]. A further study found that rivaroxaban did not affect established lesions in ApoE$^{-/-}$ mice but decreased inflammatory mediators and increased plaque stability[47]. However, thrombin and FXa inhibitors may not be equal since FXa is upstream of thrombin and is a more potent activator of PAR2 than thrombin. For instance, in a mouse model of sickle cell disease we found that rivaroxaban but not dabigatran reduced IL-6 expression[48]. Furthermore, we found that PAR2$^{-/-}$ mice but not PAR1$^{-/-}$ mice have reduced atherosclerosis in Apoe-/- and Ldlr-/- models[49](Owens, Mackman, in revision). Despite these interesting mouse studies, we need clinical data on the plaques themselves and/or levels of circulating biomarkers before we can conclude that the protection by dual aspirin-plus-rivaroxaban therapy observed in COMPASS is due to effects beyond simply antithrombotic activity.

DOACs target coagulation proteins in the common pathway of the coagulation protease cascade. This pathway is essential for hemostasis since in mice deficiencies in either

prothrombin, factor V or factor X leads to fatal bleeding[50-53]. The use of DOACs are associated with an increased the risk of bleeding and this has led to the search for new, safer target for anticoagulant therapy. One such target is factor XI, which is near the top of the intrinsic pathway of the coagulation protease cascade. One recent small phase II proof of concept study found that reducing levels of factor XI using an antisense oligonucleotide led to a reduction in VTE in patients undergoing total knee arthroplasty with less bleeding than patients receiving the low-molecular-weight heparin enoxaparin[54]. This suggests that factor XIa might have a larger therapeutic window (efficacy versus safety) than factor Xa (Weitz J, ATVB in press). However, these studies need to be confirmed in larger studies. An intriguing possibility is that addition of a factor XIa inhibitor to aspirin in patients with CAD or PAD will reduce cardiovascular death without increasing bleeding.

Antiplatelet agents have been the cornerstone of therapy for preventing ischemic events and death in cardiovascular disease patients. Intensification of antiplatelet therapy with more potent antiplatelet agents or combinations of antiplatelet agents reduces thrombotic events and CV death in CVD patients. However, this is often associated with an increase in bleeding, such as seen in studies with triple antiplatelet therapy, because platelets are essential for hemostasis. The ATLAS ACS 2-TMI 51 and COMPASS trials show that addition of low doses of the FXa inhibitor rivaroxaban to antiplatelet agents can have a beneficial effect on ischemic events in CVD patients, although there is an increase in bleeding. Future challenges include 1/finding patients that will benefit most from combined antiplatelet and anticoagulant therapy, 2/what are the optimal doses of each agent, 3/what are the best anticoagulant and antiplatelet drugs, 4/understanding of the mechanisms by which this dual therapy protects CVD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard abbreviation and acronyms

ACS	acute coronary syndrome
APC	activated protein C
APT	antiplatelet therapy
CAD	coronary artery disease
CVD	cardiovascular disease

DAPT	dual antiplatelet therapy
DOAC	direct oral anticoagulant
FXa	factor Xa
MACE	major adverse cardiovascular event
MI	myocardial infarction
NSEMI	non ST-elevated myocardial infarction
PAD	peripheral artery disease
PAR	protease-activated receptor
PCI	percutaneous coronary intervention
STEMI	ST-elevated myocardial infarction

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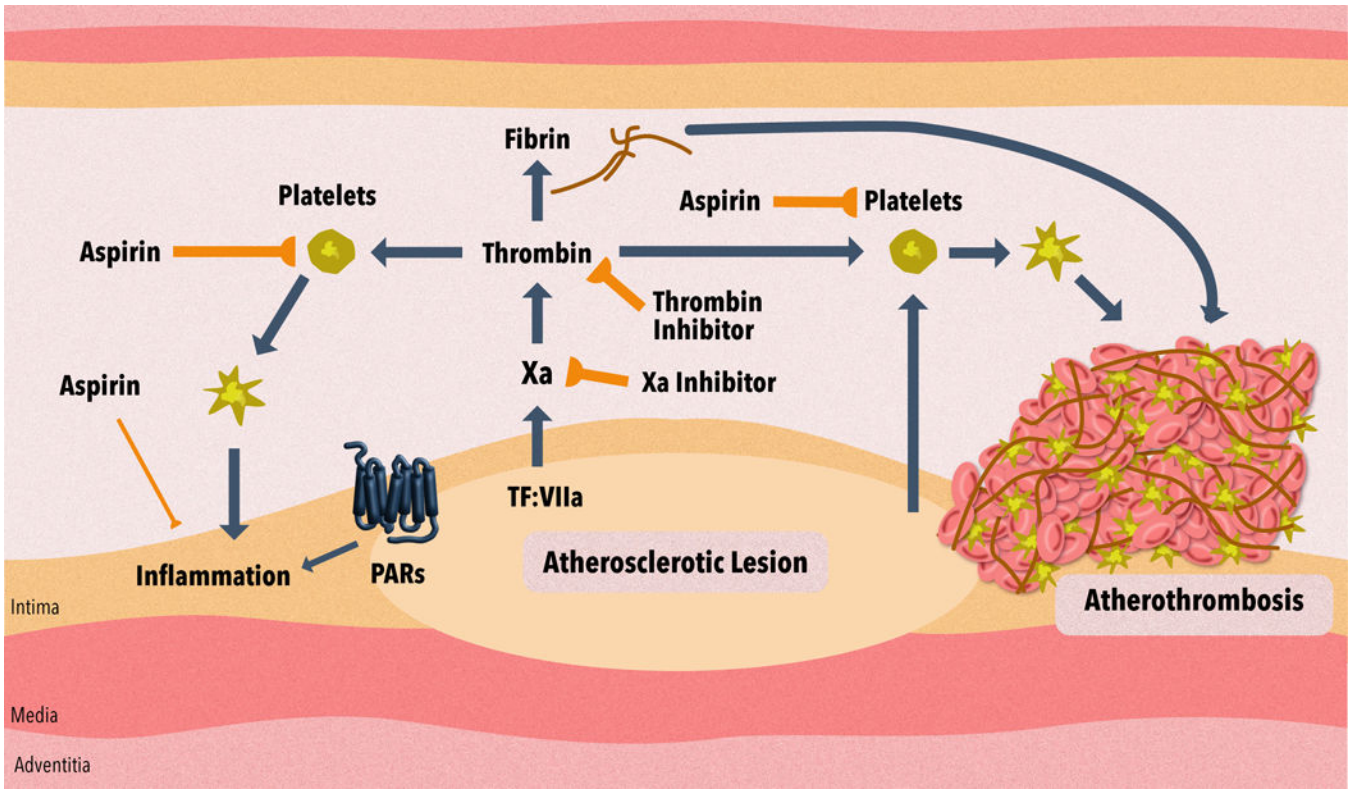

Figure 1. Role of platelets and the coagulation cascade in atherothrombosis and vascular inflammation

Atherothrombosis involves atherosclerotic plaque rupture or erosion and the formation of an intravascular thrombus. The atherosclerotic plaque contains agents, such as collagen, that activate platelets, and tissue factor (TF) that activates the coagulation cascade. Aspirin reduces the thrombus by inhibiting platelet activation. Anticoagulants reduce the thrombus by inhibiting fibrin generation and also by reducing thrombin activation of platelets. These inhibitors include the thrombin inhibitor dabigatran etexilate and the factor Xa inhibitors rivaroxaban, apixaban, edoxaban or betrixaban. Activated platelets and activation of protease-activated receptors (PARs) by coagulation proteases may also increase inflammation in the vessel wall. Aspirin and anticoagulants may also reduce vascular inflammation and limit the progression of atherosclerosis.

Table

Effect of different single and combined antithrombotic drugs on thrombotic events and bleeding in patients with cardiovascular disease. The table shows a select group of the different clinical trials. Details of each study are provided in the original references.

Abbreviations. ACS: acute coronary syndrome, ASA: aspirin, CAD: coronary arterial disease, CV: cardiovascular, CVD: cardiovascular disease, DAPT: dual antiplatelet therapy, ICH: Intracerebral hemorrhage, MI: myocardial infarction, PAD: peripheral arterial disease.

Name of Trial	Patient Group	# Patients	Therapeutic Strategy	Efficacy	Safety	Ref
CHARISMA	CVD	15,603	ASA vs ASA+Clopidogrel	No effect on CV death	Similar bleeding	22
TRITON-TIMI 38	ACS with PCI	13608	Prasugrel vs Clopidogrel	Decrease in CV death	Increased bleeding	18
PLATO	ACS with or without ST-elevation	18624	Tricagrelor vs Clopidogrel	Decrease in CV death	Similar bleeding	17
TRILOGY ACS	Unstable angina or MI with or without ST-elevation	7243	Prasugrel vs Clopidogrel	No effect on CV death	Similar bleeding	19
PEGASUS-TIMI 54	MI within 3 yrs	21,162	ASA vs ASA+Ticagrelor	Reduced CV death	Increased bleeding	23
EUCLID	Symptomatic PAD	13885	Tricagrelor vs Clopidogrel	No effect on CV death	Similar bleeding	13
TRA 2P-TIMI 50	History of MI, ischemic stroke or PAD	26,449	ASA vs ASA/DAPT+Vorapaxar	Reduced CV death in patients with stable atherosclerosis	Increased bleeding, ICH	26
TRACER	ACS without ST-elevation	12,944	ASA vs ASA/DAPT+Vorapaxar	No effect on CV death	Increased bleeding, ICH	25
APPRAISE-2	Recent ACS and 2 risk factors	7,392	DAPT vs DAPT+Apixaban	No effect on CV death	Increased bleeding	30
ATLAS ACS 2-TIMI 51	ACS	15,526	DAPT vs DAPT+Rivaroxaban	Reduced CV death*	Increased bleeding	32
COMPASS	Stable atherosclerotic disease, CAD and PAD	27,395	ASA vs ASA+Rivaroxaban	Reduced CV death*	Increased bleeding	35

*Reduced the composite end point of death from cardiovascular causes, myocardial infarction, or stroke.