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Triple Antithrombotic Therapy in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: A viewpoint

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Abstract

Patients undergoing percutaneous coronary intervention (PCI) are treated with dual antiplatelet therapy to reduce the risk of subsequent myocardial infarction and stent thrombosis. Approximately 5-10% of patients undergoing PCI also have atrial fibrillation (AF). Patients with AF have an additional requirement for anticoagulation, as dual antiplatelet therapy alone is insufficient to adequately reduce the risk of stroke in patients with AF. However, it is now well-established that combining anticoagulants with dual antiplatelet therapy also causes a significant increase in the risk of bleeding. Hence, there is great interest in discovering the optimal blend of antiplatelet therapy and oral anticoagulation in this situation, aiming to reduce the risk of stent thrombosis, recurrent MI, and stroke, whilst also minimizing the risk of bleeding. Recent studies have experimented with combining oral anticoagulation with a single antiplatelet agent, rather than combining oral anticoagulation with dual antiplatelet therapy. These studies show that this reduces the risk of bleeding, but are underpowered to determine whether this still provides as much cardiovascular benefit.

This review summarizes the currently available evidence on this topic and highlights the key questions that remain to be answered including ongoing clinical trials in the field.

Introduction

Over the last decade, revascularization by percutaneous coronary intervention (PCI) has become the standard of care for patients with acute coronary syndrome (ACS).[1,2] Dual antiplatelet therapy has a major role in reducing the risk of secondary events in patients with ACS and in the prevention of stent thrombosis for patients undergoing PCI.[3] Approximately 5-10% of patients undergoing PCI also have atrial fibrillation (AF).[4] The vast majority of these patients will have a clear indication for oral anticoagulation to prevent ischemic strokes in addition to their requirement for antiplatelet therapy. In recent years, the number of available antiplatelet agents and anticoagulants has greatly increased (Table 1). This presents many different possible combinations of treatment, each of varying antithrombotic potency. In this review, we summarise the evidence for currently recommended treatment strategies for the management of these complex patients.

Antiplatelet Therapy in Patients with Acute Coronary Syndromes or Undergoing Percutaneous Coronary Intervention

Most ACS are caused by thrombosis within the coronary arteries at high levels of shear stress, which is largely mediated by platelets. Aspirin inhibits an important amplificatory pathway in platelets, mediated by inhibition of cyclooxygenase (COX)-1 and reduced synthesis of thromboxane A_2 (Figure 1), which is well-known to reduce the risk of cardiovascular death in patients with ACS.[5] Platelet $P2Y_{12}$ receptors have a central role in amplifying the response of platelets to a wide range of different agonists (Figure 1).[6] Each generation of platelet $P2Y_{12}$ inhibitor has incrementally reduced the risk of adverse cardiovascular events, particularly stent thrombosis, in patients with ACS. In patients with ACS or undergoing PCI, the addition of clopidogrel to aspirin (dual antiplatelet therapy) reduces the relative risk of major adverse cardiovascular events by approximately 20% compared to aspirin alone.[3] In patients with ACS undergoing PCI, more potent oral $P2Y_{12}$ antagonists, such as prasugrel[7] and ticagrelor,[8] have been shown to further reduce the relative risk of adverse cardiovascular events by approximately 15-20% compared to clopidogrel, but at the expense of an increased bleeding risk (Figure

2). Increased potency of $P2Y_{12}$ inhibitors has led to less of a need for GPIIb/IIIa inhibitors, which further increase the risk of bleeding and are therefore reserved for "bailout" therapy.[7] Guidelines now recommend the use of prasugrel and ticagrelor in preference to clopidogrel in patients with ACS undergoing PCI, due to the cardiovascular benefit of these newer agents.[1,2]

Oral Anticoagulation in Atrial Fibrillation

AF is independently associated with an increase in mortality and morbidity and its incidence has steadily increased over the past 20 years.[9] The pathophysiology of stroke in AF is complex and multifactorial, reflecting stasis of blood in the atria, endothelial expression of prothrombotic factors, and a systemic proinflammatory, prothrombic state.[10] Although there is still incomplete understanding of these processes, oral anticoagulation prevents the majority of strokes in patients with AF,[10] while aspirin or the combination of aspirin and clopidogrel do not substantially contribute to stroke prevention in AF patients.[10, 11]

European Society of Cardiology (ESC) guidelines recommend the use of the CHA_2DS_2-VASc score for stratifying stroke risk.[10] Patients with a score of 1 for men, or 2 for women, should be considered for oral anticoagulation, while those with 2 or more stroke risk factors (a score of 3 or more for women), have a clear indication for long-term oral anticoagulation. The complexities of treatment with vitamin K antagonists (VKA), such as warfarin, led to the development of non-vitamin K oral anticoagulants (NOACs). Currently, the direct thrombin inhibitor dabigatran and the Factor Xa inhibitors apixaban, edoxaban, and rivaroxaban are licenced for stroke prevention in AF. NOACs are as effective as warfarin for stroke prevention in AF while reducing stroke, intracranial haemorrhage (ca 50%) and mortality (ca 10%) compared with warfarin in patients with non-valvular AF.[13,14] Notably, the lower risk of bleeding related to the use of NOACs compared to VKAs is also observed in AF patients who are treated with either single or dual antiplatelet therapy.[12]

Evaluation of Triple Therapy in Patients Undergoing Percutaneous Coronary Intervention without Atrial Fibrillation

Unfortunately, antiplatelet therapy does not adequately prevent stroke in patients with AF[11] and anticoagulants do not seem to adequately prevent stent thrombosis in patients undergoing PCI with first generation bare-metal stents (although it is unknown whether this is still the case in the current era of newer, drug-eluting stents with thinner struts).[13] Therefore, when patients with AF undergo PCI, there is a need to combine antiplatelet therapy with oral anticoagulants (triple therapy) to prevent stent thrombosis, recurrent MI and stroke. The efficacy of different combinations of antithrombotic therapy in this situation is a topic for debate with conflicting evidence and a need for more solid evidence from controlled trials.

Recent randomised controlled trials in patients without AF provide insight into the impact of triple therapy on cardiovascular and bleeding endpoints in patients with ACS (Figure 3). In 2013, a meta-analysis evaluated the use of NOACs in addition to dual antiplatelet therapy in patients with ACS on the basis of seven randomised phase 2 and phase 3 trials.[12] This analysis showed that the addition of a NOAC to dual antiplatelet therapy results in only a modest reduction in cardiovascular events compared to placebo (HR 0.87; 95% CI 0.80-0.95) with a substantial increase in bleeding (HR 2.34; 95% CI 2.06 – 2.66). The APPRAISE-2 and ATLAS-2 studies, which compared standard-dose apixaban and very low-dose rivaroxaban respectively to placebo in ACS patients receiving antiplatelet therapy, were the only phase III studies included in the meta-analysis. APPRAISE-2 enrolled 7,392 ACS patients.[14] Most patients were on dual antiplatelet therapy, usually aspirin and clopidogrel. The patients were randomised to apixaban in the dose currently approved for stroke prevention in AF (Table 1) or placebo. The trial was stopped early after recruitment of 7,392 patients because the addition of apixaban to antiplatelet therapy increased TIMI major bleeding compared to placebo with no significant reduction in ischaemic events. Further post-hoc analysis concluded apixaban increased bleeding both in patients treated with single or dual antiplatelet therapy.[15] The ATLAS ACS 2-TIMI-51 study randomised 15,526 ACS patients to twice-daily doses of 2.5 mg rivaroxaban, 5 mg rivaroxaban or placebo in addition to

antiplatelet therapy, mostly consisting of aspirin and clopidogrel. Both rivaroxaban doses were greatly lower than the doses approved for stroke prevention in AF (Table 1).[16] The twice-daily 2.5 mg dose of rivaroxaban significantly reduced the risk of adverse cardiovascular events compared to placebo (8.9% vs. 10.7%; HR 0.84; 95% CI 0.74 – 0.96; P=0.008), but also significantly increased the risk of TIMI major bleeding (2.1% vs. 0.6%; HR 3.96; 95% CI 2.46 – 6.38; P<0.001).

Evaluation of Triple Therapy in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

The WOEST study randomised 573 patients undergoing PCI with an indication for oral anticoagulation (approximately two thirds had AF) to anticoagulation plus clopidogrel (dual therapy) or to anticoagulation plus clopidogrel plus aspirin (triple therapy) for 1 year.[17] Patients on clopidogrel plus anticoagulation had significantly fewer bleeding episodes (19.4% vs. 44.4%; HR 0.36; 95% CI 0.26 – 0.50; P < 0.001) with no significant difference in the incidence of MI or stent thrombosis compared to patients on triple therapy. A meta-analysis of smaller, randomised studies prior to the WOEST study also showed that triple therapy was associated with an approximately 2-fold increase risk of bleeding compared to anticoagulation combined with a single antiplatelet in patients with AF undergoing PCI.[18] However this meta-analysis also suggested that the risk of major adverse cardiovascular events may be approximately 40% higher in patients treated with dual therapy compared to triple therapy.[18] In contrast, a large Danish registry of over 12,000 patients showed that dual therapy with clopidogrel and an oral anticoagulant was associated with a non-significant reduction in both bleeding and adverse cardiovascular events compared to triple therapy (aspirin, clopidogrel and oral anticoagulant), although these results must be interpreted with caution due to the inherent selection bias of observational studies.[19] Based on this data, the ESC currently recommends to consider the early omission of aspirin as soon as one month after the acute event in ACS patients with AF at high risk of bleeding and low risk of recurrent thrombotic events.[10] Conversely, some patients may require prolonged triple therapy of 12 months or longer if the risk of stent thrombosis is very high. In addition to clinical risk factors (Figure 2), the use of longer stents with smaller diameters, bioabsorbable stents, or complex PCI may indicate a need for

prolonged triple therapy (Figure 2).

The recent PIONEER AF-PCI study compared the effect of 3 different antithrombotic regimens on bleeding in 2,124 patients with AF undergoing PCI.[20] The primary outcome of the trial was bleeding, while the study was not powered to detect differences in ischaemic (stroke) events. Dual therapy with low-dose rivaroxaban (15 mg once daily, which is lower than the 20mg dose approved for stroke prevention in AF patients with normal renal function) and a single $P2Y_{12}$ inhibitor (for 1 year) significantly reduced the incidence of bleeding compared to standard triple therapy, consisting of aspirin (for 12 months), a $P2Y_{12}$ inhibitor (for 1, 6 or 12 months) and warfarin indefinitely at an international normalised ratio (INR) of 2-3 (16.8% vs. 26.7%; HR 0.59; 95% CI 0.47 – 0.76; P < 0.001). There was no significant difference in major adverse cardiovascular events between these 2 groups (41 [6.5%] vs. 36 [6.0%]; HR 1.08; 95% CI 0.69 – 1.68; P = 0.75). Clopidogrel was the the most commonly used $P2Y_{12}$ inhibitor (used in > 90% of patients, with slightly greater usage in the triple therapy group). As only a small number of patients received the more potent $P2Y_{12}$ inhibitors, prasugrel or ticagrelor, it was not possible to determine whether the choice of $P2Y_{12}$ inhibitor influenced the main efficacy results of the study.

The PIONEER AF-PCI study also investigated whether a triple therapy strategy that includes a very low-dose of rivaroxaban (2.5 mg twice-daily – similar to the very low dose regimen in ATLAS-2) in combination with aspirin plus a $P2Y_{12}$ inhibitor causes less bleeding than a standard triple therapy strategy including warfarin plus aspirin plus a $P2Y_{12}$ inhibitor. Very low-dose rivaroxaban triple therapy significantly reduced the incidence of the composite bleeding endpoint compared to the standard triple therapy strategy (18.0% vs 26.7%; HR 0.63; 95% CI 0.5 – 0.8; P < 0.001) with no significant difference in major adverse cardiovascular events (5.6% vs. 6.0%; HR 0.93 [95% CI 0.59 – 1.43]; P = 0.76).

The PIONEER AF-PCI study was too small to evaluate whether such a combination therapy would provide sufficient stroke prevention for AF patients undergoing PCI. Hence, there was no significant difference in the incidence of stroke between the groups (10 vs. 7; 1.5% vs. 1.2%; HR 1.36; 95% CI 0.52-3.58; P=0.53). Of note, a limitation of this study is that none of the treatment arms included a dosing regimen of rivaroxban that has been approved for stroke prophylaxis in patients with AF.

Although there were no significant differences in the incidence of MI or stent thrombosis in the triple therapy and non-triple therapy groups in PIONEERS and WOEST, these studies were not powered to investigate cardiovascular endpoints. The confidence intervals do not rule out a possible increase in risk of myocardial infarction and stent thrombosis of up to approximately 40-70% with even greater uncertainty regarding the risk of stroke. It is therefore not possible to determine whether or not these treatment strategies are non-inferior to triple therapy for the prevention of stroke, myocardial infarction or stent thrombosis (Figure 3).

More Potent $P2Y_{12}$ Inhibitors in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

Antiplatelet therapy in the aforementioned studies mainly consisted of aspirin and clopidogrel in combination with VKAs. The evidence for the use of more potent $P2Y_{12}$ inhibitors in triple therapy or as a single antiplatelet agent in combination with an OAC derives almost entirely from observational studies. Of note these mainly reviewed VKAs at an INR of 2-3 with little evidence on combining the NOACs as dual therapy with the more potent $P2Y_{12}$ inhibitors. An evaluation of bleeding in 11,756 patients after PCI showed that triple therapy with prasugrel, aspirin, and warfarin (91 patients) versus clopidogrel, aspirin, and warfarin (526 patients) was associated with a higher number of patient-reported bleeding events but not an increase in bleeding requiring hospitalisation.[21] Similar findings of increased bleeding with triple therapy including prasugrel, compared to triple therapy including clopidogrel were also demonstrated in a small observational study that included 21 patients receiving prasugrel and VKAs.[22] Another recent study investigated cardiovascular and bleeding outcomes in patients treated with triple therapy regimens (approximately 50% receiving VKAs and 50% NOACs) that included either clopidogrel (n = 205) or one of the more potent $P2Y_{12}$ antagonists; prasugrel or ticagrelor (n = 72).[23] In this study, the incidence of adverse cardiovascular events and bleeding was not significantly different in patients treated with triple therapy including clopidogrel vs. triple therapy including a more potent $P2Y_{12}$ antagonist. Braun et al. studied 109 patients treated with dual therapy with warfarin and ticagrelor, compared to 159 historical controls receiving aspirin, clopidogrel and warfarin (triple

therapy).[24] The incidence of major bleeding and a composite of all thrombotic events were similar between the groups. In alignment with this finding, in 2 recent large randomised controlled trials, ticagrelor does not appear to cause significantly more bleeding than either aspirin or clopidogrel in the context of its use as a single antiplatelet agent.[25,26]

Alleviating Bleeding Risk and Future Studies

Bleeding risk is predominantly determined by clinical risk factors (Figure 2), but it has also been shown that certain genetic polymorphisms increase the risk of bleeding, mostly by influencing the metabolism of clopidogrel[27] and warfarin [28]. Proton pump inhibitors (PPIs) are effective at reducing the risk of gastrointestinal bleeding in patients treated with antithrombotic therapy[29], but they also increase the risk of other serious medical conditions such as pneumonia. PPI may be useful in patients at risk of gastric ulcers receiving triple therapy. As there is some evidence to suggest that omeprazole may interfere with the metabolism of clopidogrel, treatment with lansoprazole or pantoprazole is preferable in clopidogrel-treated patients.[1,29]

The ISAR-TRIPLE randomised 614 AF patients with ACS to receive either 6 weeks or 6 months of clopidogrel with concomitant aspirin and OAC.[30] They found no statistical difference between the groups (p=0.63) of a composite end point of death, MI, stent thrombosis, stroke and TIMI major bleeding. The authors concluded that a shorter duration of clopidogrel in triple therapy was not superior in regards to clinical outcomes and the optimal duration of triple therapy is therefore still not known.

Further studies, including REDUAL-PCI (clinicaltrials.gov NCT02164864), AUGUSTUS (clinicaltrials.gov NCT02415400) and ENTRUST AF-PCI (clinicaltrials.gov NCT02866175) are comparing dual therapy with a NOAC and $P2Y_{12}$ inhibitor compared to triple therapy with aspirin, a $P2Y_{12}$ inhibitor and warfarin in patients with AF undergoing PCI. These studies will help to answer many unanswered questions in this group of patients. The REDUAL-PCI and AUGUSTUS studies will provide evidence as to whether or not dual therapy with dabigatran and apixaban respectively, at their normal stroke prophylaxis doses, offer benefit compared to triple therapy that includes a VKA. Furthermore, AUGUSTUS will provide insight into whether dual therapy that includes apixaban is

preferable to dual therapy that includes a VKA. In addition, the factorial design of AUGUSTUS will simultaneously help to determine whether it is of benefit to withhold aspirin in patients that are treated with a $P2Y_{12}$ inhibitor and apixaban.

The results of these studies, in combination with WOEST and PIONEER-AF-PCI, and eventually meta-analyses using individual patient data sets from further studies, will help to establish whether dual therapy strategies are non-inferior for preventing stent thrombosis and recurrent MI compared to triple therapy strategies. Many, but not all, of the pathways inhibited by aspirin are also inhibited by potent $P2Y_{12}$ inhibitors.[31] It still remains to be determined whether aspirin is needed to prevent adverse cardiovascular events in patients with ACS if they are also treated with a $P2Y_{12}$ inhibitor and anticoagulant. We will have to indirectly deduce what the effects of dual therapy with a potent $P2Y_{12}$ inhibitor and VKAs are. The GLOBAL LEADERS study (clinicaltrials.gov NCT01813435), COMPASS study (clinicaltrials.gov NCT01813435), TWILIGHT study (NCT02270242) and GEMINI study (clinicaltrials.gov NCT02293395) will help to clarify whether aspirin is still necessary in patients with ACS or undergoing PCI who are treated with potent $P2Y_{12}$ inhibitors.

Recommendations

Management of antithrombotic therapy for patients with AF undergoing PCI is discussed in detail in the most recent 2016 ESC AF guidelines,[10] as well as the 2015 non-ST-elevation ACS guidelines[1] and ST-elevation myocardial infarction guidelines.[2] These guidelines recommend initial triple therapy consisting of an anticoagulant, aspirin, and clopidogrel for a relatively short duration. Although there is very little randomized evidence to guide the decision, the duration of triple therapy (between 1 and 6 months, and in some patients, up to 12 months) should be chosen by balancing the risk of bleeding and recurrent ACS (Figure 2). Following this initial period of triple therapy, dual therapy with an oral anticoagulant and either aspirin or clopidogrel should be continued for the remainder of the 12-month period. After this, the patient should be switched to oral anticoagulant monotherapy. If the patient has non-valvular AF then the anticoagulant can be either a VKA or a NOAC. As the PIONEER AF-PCI study was not powered to investigate efficacy endpoints, further randomized studies and meta-analyses

will be required before these recommendations can be modified.

Conclusion

As demonstrated there is a balance to be struck between safety and efficacy when combining antiplatelet drugs with anticoagulants. Although we now have more evidence to guide these decisions, there are still many ongoing questions regarding whether to use dual or triple therapy, which antiplatelet medications and anticoagulants should be used, and how long they should be given for.

Figures

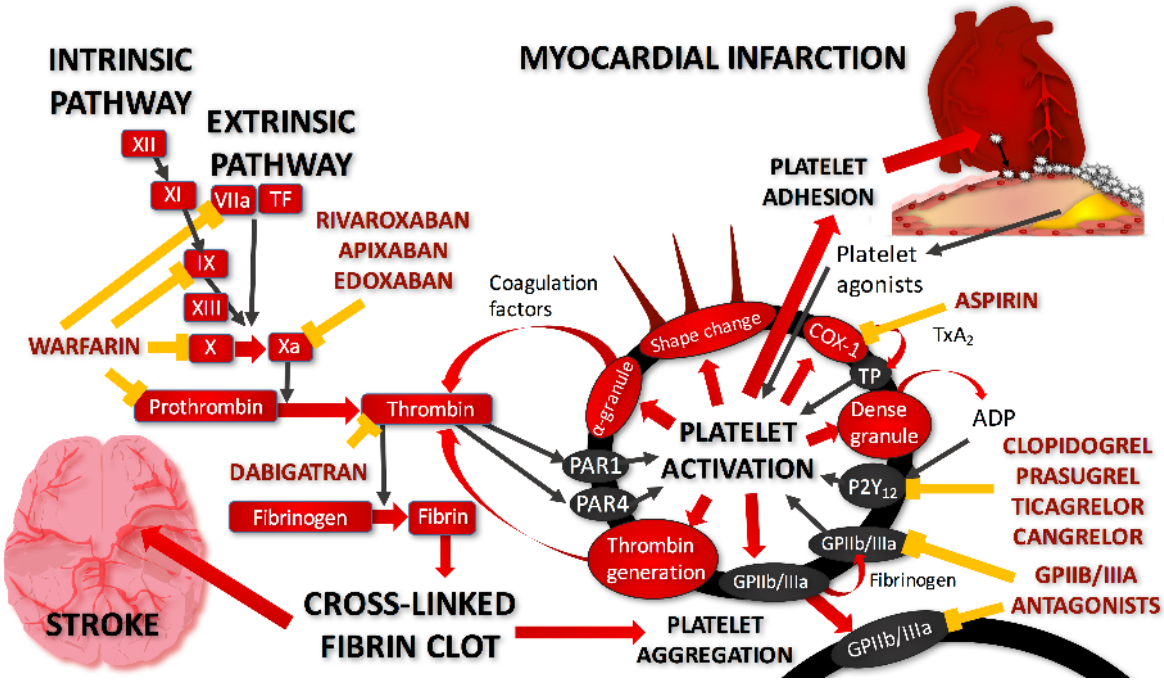

Figure 1. Mechanisms of action of antithrombotic therapy for the prevention of myocardial infarction and stroke.

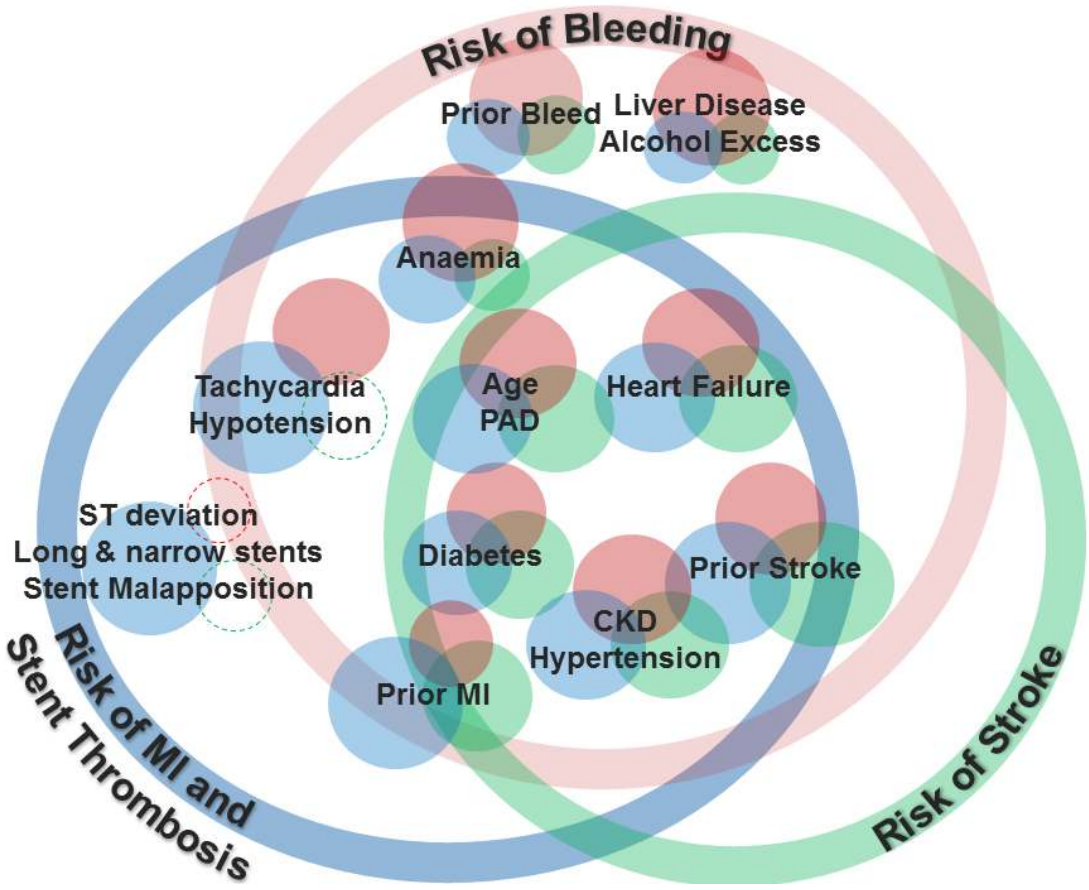

Figure 2. Balancing risk factors for bleeding, stroke, MI and stent thrombosis. The individual circles represent approximate degree of risk for MI and stent thrombosis (blue), stroke (green) and bleeding (red). The circles with dotted lines illustrate factors where it is unknown whether the risk factor is a risk factor for bleeding and/or stroke.

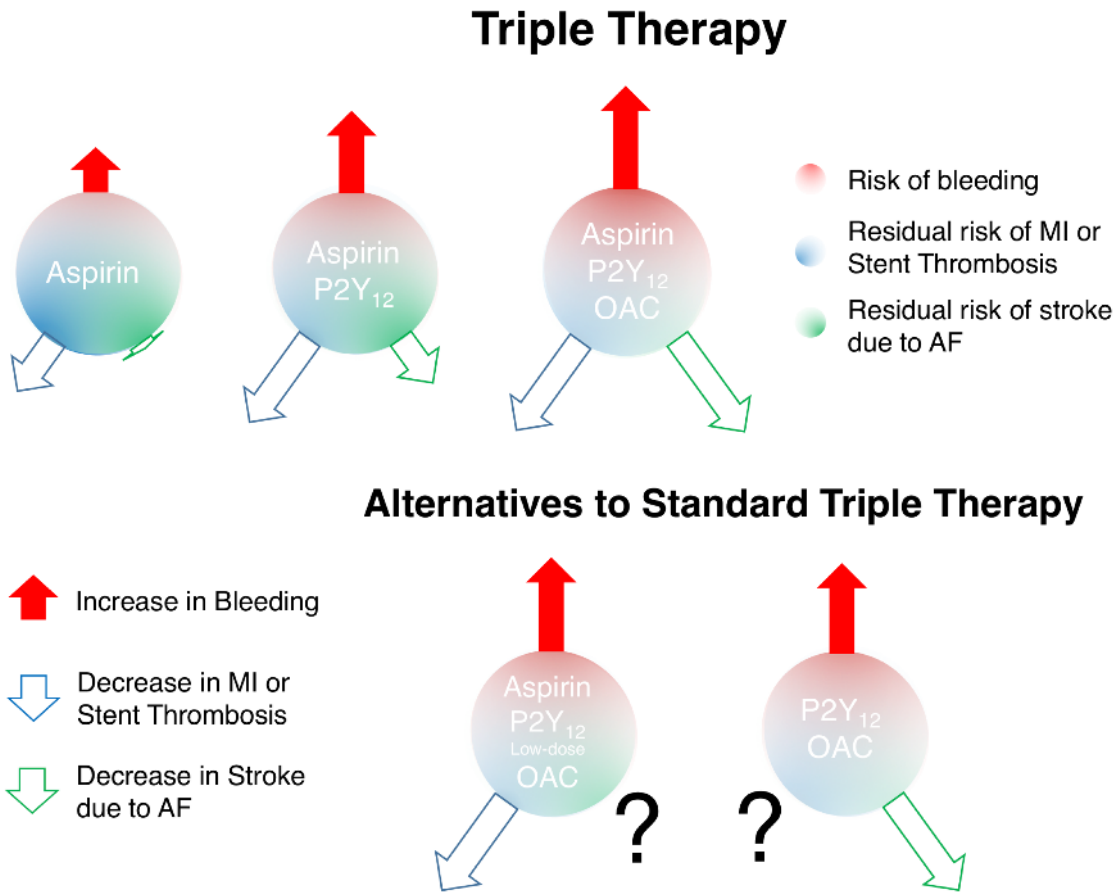

Figure 3. The impact of different antithrombotic strategies on the risk of recurrent MI and stent thrombosis, risk of stroke and risk of bleeding. This figure is intended to be illustrative only and is based on the studies referenced in the text.

Tables

Table 1. Approved doses of antithrombotic therapy

Drug Type	Name	Usual treatment dose
Oral antiplatelet therapy	Clopidogrel	300-600 mg loading dose then 75 mg once daily (od) maintenance dose
	Prasugrel	60 mg loading dose then 10 mg od maintenance dose
	Ticagrelor	180 mg loading dose then 90 mg twice daily (bd) maintenance dose for 1 year after ACS 60 mg bd maintenance dose for the period 1-3 years after ACS
Intravenous antiplatelet therapy	Abciximab	250 mcg/kg over 1 minute then infusion of 250 nanogram/kg/min before PCI and up to 12 hrs afterwards
	Eptifibitide	180 mcg/kg, then 2 mcg/kg/min for up to 96 hours
	Tirofiban	25 mcg/kg over 3 minutes then infusion of 150 nanograms/kg/min for 48hrs maximum
	Cangrelor	30 mcg/kg bolus then infusion of 4 mcg/kg/min before PCI up to 4 hrs afterwards
Vitamin K antagonists	Warfarin ~~Acenocoumarol~~ ~~Phenprocoumon~~ ~~Fluindione~~	Dose adjusted according to INR
Non-Vitamin K Oral Anticoagulants (NOACs) used for non-valvular AF	Apixaban	5 mg bd 2.5 mg bd if > 80 yrs old and <60 kg
	Dabigatran	150 mg bd 110 mg bd may be considered in patients over 80 yrs old, or with moderate renal impairment or at increased risk of bleeding (EMC approved, but not FDA approved)
	Edoxaban	60 mg od or 30 mg od if <60 kg
	Rivaroxaban	20 mg od 15 mg od (if CrCl 15-49) (2.5 mg bd for ACS)

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