CHAPTER

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Anti-Platelet Therapy

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The pathophysiology of acute myocardial infarction (MI), ischemic stroke, and limb gangrene is centered around arterial thrombosis. Arterial thrombosis is the complex interplay between platelet activation, aggregation and adhesion and the coagulation system with fibrin formation. Due to the central role of platelets in arterial thrombogenesis, the treatment focuses on drugs that block platelet function.

ROLE OF PLATELETS IN HEMOSTASIS

The initial response of the hemostatic system to tissue or endothelial injury is to produce a platelet plug (primary hemostasis). Platelets have multiple surface receptors, which when stimulated, produce a shape change involving the energy-dependent actin-myosin system. Principal among these receptors are the glycoprotein Ib (GpIb) receptor, which binds to von Willebrand factor (vWF) in response to endothelial injury. Additionally, there are receptors for adenosine diphosphate (ADP), thrombin, and thromboxane A2. With the shape change, the surface of the platelet also changes, leading to expression of a second binding site, the glycoprotein IIb/IIIa (GpIIb/IIIa) receptor. GpIIb/IIIa receptors bind fibrinogen to provide bridging between adjacent platelets. The surface of the platelet also expresses binding sites for factor V, an essential cofactor in the generation of thrombin (Figure 1).[1]

ANTIPLATELET AGENTS

Platelets can be activated in a number of ways. The targets and agents in clinical use or development are shown in figure below.

ORAL ANTIPLATELET AGENTS

I. Aspirn: Acetylsalicylic acid (ASA) is a derivative of salicylic acid that works by inhibiting the enzyme prostaglandin H-synthase also known as cyclooxygenase (COX).

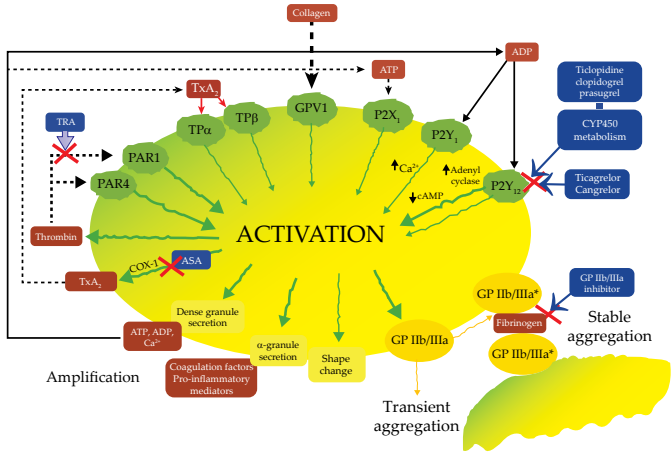

Fig. 1: Platelet Activation Pathways[1]

Mechanism of Action: Prostaglandin H-synthase 1 and 2 (also known as COX 1 and 2) catalyze the conversion of arachidonic acid to prostaglandin H2 (PGH2). Human platelets and vascular endothelial cells convert COX2 primarily to thromboxane A2 (TXA2) and prostaglandin I2 (PGI2).[2] TXA2 induces platelet aggregation and vasoconstriction, whereas PGI2 inhibits platelet aggregation and induces vasodilatation. Platelet TXA2 synthesis is reduced by about 98% following ASA administration.

Clinical Uses: ASA is used in primary as well as secondary prevention of CAD, Ischemic stroke and Peripheral Vascular disease. Also ASA has been studied in a wide range of diseases ranging from preeclampsia, polycythemia vera to bowel cancer, usually at doses of 50 to 100 mg/day. The mechanisms of action for the observed benefits in these conditions remain to be elucidated.

Use of the lowest effective dose (50-100 mg/day for long-term treatment) is currently the most appropriate strategy to maximize efficacy and minimize toxicity.[3]

Side Effects of Aspirin

a. Bleeding: Bleeding is dose-dependent in patients treated for stroke and with acute coronary syndrome.[4] A retrospective subgroup analysis of the relationship between the aspirin dose and risk of major bleeding found that a dose of 100 mg/day to have the lowest rate of major or life-threatening bleeding complications.[(5)] Bleeding risks increased with increasing ASA dose with or without clopidogrel.

b. Hypersenitivity: The mechanism of Aspirin Hypersensitivity is upregulation of the 5-Lipooxygenase pathway leading to increased leukotrienes. The effects include bronchospasm, urticaria, rhinitis, angioedema or anaphylaxis. Aspirin Sensitive Ashtma includes a triad of Bronchial Asthma, Aspirin Sensitivity and Nasal Polyps.

c. Gasterointestinal: Dyspepsia (epigastric distress, heartburn, nausea, ulcers), Gastric mucosal lesions, Peptic ulcers, Hemorrhage and Perforation are some of the gastrointestinal side effects of aspirin.

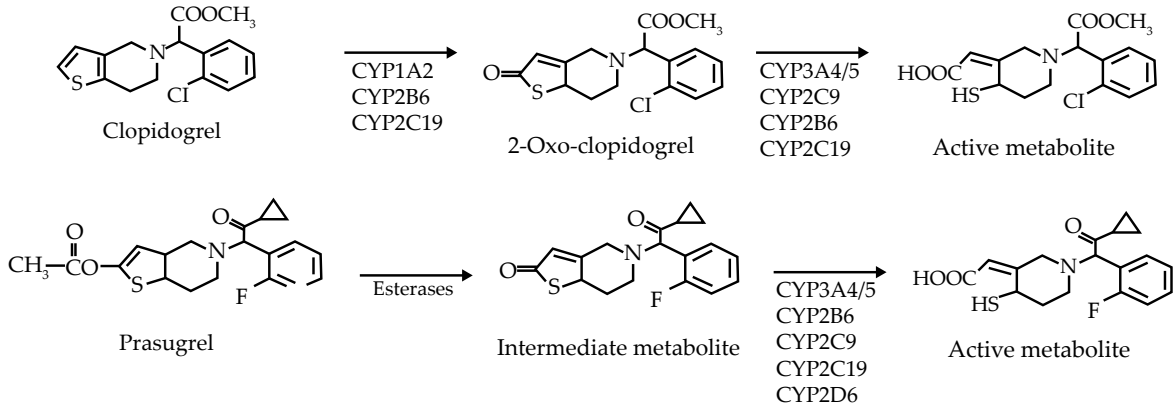

Fig. 2: Major pathways leading to activation of Thienopyridines. Clopidogrel requires two CYP-Dependanct steps to get converted to its active metabolite. Prasugrel requires one CYP–Dependant step for conversion to its active metabolite.[1]

II. Dipyridamole: Mechanism of Action: Dipyridamole is a pyrimidopyrimidine derivative with vasodilator and antiplatelet properties. The mechanism of action of dipyridamole as an antiplatelet agent involves increased intracellular cyclic adenosine monophosphate (cAMP), which inhibits the platelet shape change. Increased cAMP concentration is due to two mechanisms: (1) inhibition of phosphodiesterase and (2) blockade of uptake of adenosine (which acts at adenosine A2 receptors to stimulate platelet adenylyl cyclase and thus increase cAMP).

Clinical Uses: Though early clinical trials questioned the efficacy of dipyridamole, recent studies have suggested significant benefit with new formulation. In a study addition of modified-release dipyridamole 200 mg twice daily to ASA 25 mg twice daily was associated with a 22% relative risk reduction of major vascular events compared with ASA alone.[6] In another study of ASA (30-325 mg/day) with or without dipyridamole (200 mg twice daily) in patients within 6 months of a transient ischemic attack (TIA) or minor stroke showed 20% reduction of a composite of major vascular events by the combined treatment.[7]

III. Platelet Receptor Inhibitors: Purigenic Receptors: There are three known subtypes of ADP receptors on platelets: $P2X_1$, $P2Y_1$, and $P2Y_{12}$.

Sustained ADP-induced platelet aggregation requires coactivation of $P2Y_1$ and $P2Y_{12}$ receptors. The $P2Y_{12}$ receptor acts by inhibiting adenylyl cyclase via a Gi protein and potentiates dense granule secretion, procoagulant activity, and platelet aggregation. Without continued $P2Y_{12}$ activation, aggregated platelets disaggregate. Inhibition of the $P2Y_{12}$ receptor is a major target for anti-platelet drug development.

A. Thienopyridines: Thienopyridines which are CLOPIDOGREL and PRASUGREL (Ticlopidine not in use now), selectively inhibit ADP-induced platelet aggregation with no direct effects on arachidonic acid metabolism. The thienopyridines do not act directly, but are administered as prodrugs requiring hepatic transformation. The active metabolites of both clopidogrel and prasugrel couple through a covalent disulfide bond to $P2Y_{12}$ receptors rendering the receptor unresponsive to ADP, and as the bond is covalent it causes irreversible inhibition (Figure 2).

B. Adenosine Diphosphate Analogues

i. Ticagrelor: Ticagrelor is a cyclopentyl-triazolopyrimidines, and is an oral $P2Y_{12}$ receptor antagonist that exerts antiplatelet effects by blocking ADP. Ticagrelor is not a prodrug, and the block is reversible. The parent drug is metabolized, principally by CYP 3A to about 10 metabolites. The major metabolite, AR-C124910XX, formed by O-deethylation, is as active as ticagrelor in inhibiting ADP-induced platelet aggregation.

ii. Cangrelor: Cangrelor is an intravenous $P2Y_{12}$ purinoreceptor antagonist.[17] Cangrelor is not a prodrug and produces concentration-dependent inhibition of thrombin receptor-activating, peptide-induced aggregation in human platelets.

Cangrelor was studied in two large-scale phase 3 studies that were both ended early as it did not show any clinical efficacy needed for regulatory approval

Clinical Use in CAD

Clopidogrel, Prasugrel and Ticagrelor are indicated in patients with acute coronary syndromes, which includes patients with unstable angina or non-ST-elevation myocardial infarction (NSTEMI) and patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed percutaneous coronary intervention (PCI) (Table 1).

Specific Regimens in CAD Patients

A. Antiplatelets in Stable Ischemic Heart Disease: Aspirin at dose of 75 to 162 mg daily, is preferred for secondary prevention in the absence of recent intracoronary stenting.

Clopidogrel may be substituted for aspirin, in patients intolerant or resistant to aspirin.

Table 1: Basic Pharmacology and Safety aspects of $P2Y_{12}$ Receptors Antagonists

	Clopidogrel	Prasugrel	Ticagrelor
Chemical Structure	Thienopyridine	Thienopyridine	Cyclopentyltirazolopyridine
Prodrug	Yes	Yes	No
Administration	Oral	Oral	Oral
Time to peak effect	Dose dependent	2 hr	2 hr
% Platelet Inhibition 2 hrs after loading dose	40-50%	70-90%	80-90%
Half Life	6 hr	8 hr	6-12 hr
Time to recovery of platelet inhibition	4-5 days	2-4 days	2-3 days
Reversible	5 days	7 days	24-48 hr
Indications	ACS and Stable CAD undergoing PCI	ACS undergoing PCI	ACS (full spectrum)
Safety with prior CVA	Yes	No	Yes
Non-CABG bleeding		Increased risk	Increased risk
CABG bleeding		Increased risk	Reduced risk
Side Effects	Bleeding	Bleeding. Caution in 1. Weight <60 kg, 2. Age >75 years, 3. Prior CVA	Bleeding Dyspnoea Sinus pauses

There is no significant benefit in adding clopidogrel to aspirin.

B. Antiplatelets in ACS - NSTEMI: All patients should be given 162 to 325 mg of uncoated aspirin, which should be taken as chewed or crushed, as soon as possible after the diagnosis has been made.

All patients should receive $P2Y_{12}$ receptor inhibitor in addition to aspirin.

For most patients going for an early invasive strategy, ticagrelor 180 mg as loading dose is preferred choice.

For patients in whom there is a concern about a need for urgent coronary artery bypass graft surgery, the $P2Y_{12}$ receptor blocker may be given after diagnostic coronary angiography.

If the $P2Y_{12}$ receptor blocker is given after angiography, ticagrelor (180 mg as loading dose followed by 90mg twice a day as maintainence) or prasugrel (60 mg as loading dose followed by 10 mg once a day as maintainence dose) should be given.

If ischemia guided (conservative) strategy is used, ticagrelor is preferred. Clopidogrel (600mg loading dose followed by 75mg once a day) can also be used.

Aspirin at dose of 75-100 mg should be continued indefinitely for secondary prevention.

For patients on ticagrelor, aspirin dose should be <100 mg.

C. Anti-Platelet use In STEMI: Aspirin should be given to all patients at a loading dose of 162-325mg in uncoated form and to be chewed or crushed. Aspirin at maintainence dose should be continued thereafter.

P2Y12 receptor blocker should be added but its choice depends on choice of reperfusion strategy.

In patients undergoing fibrinolytic therapy, only clopidogrel is to be used.

In patients undergoing primary PCI, prasugrel or ticagrelor should be used rather than clopidogrel.

In patients undergoing Fibrinolysis - Loading dose of clopidogrel 300mg can be given, followed by 75mg once a day. In patients>75 years of age, 75mg once a day without loading dose can be given.

Duration of Anti-Platelet Therapy in Patients with CAD

The addition of a P2Y12 inhibitor to aspirin and prolongation of DAPT requires an assessment of the risk benefit ratio of ischemic risk versus the bleeding risk.

Clinical Use in TIA or Stroke

1. In TIA or Acute Ischemic Stroke, Aspirin and Clopidogrel are given as 300mg loading dose each (to be given within 24-48 hours, not to be loaded if thrombolysed), followed by 75mg each as once a day for 3 weeks. Aspirin is continued thereafter.
2. Clopidogrel has not been proved to be superior to Aspirin for secondary prevention, no dual antiplatelet therapy.

Table 2: Major Clinical studies on use of P2Y12 Receptor Inihibitors

Trial	Pateints enrolled	Treatment arms	Primary endpoint	Result
Cure	Patients with ACS without STEMI	Aspirin plus Clopidogrel vs Aspirin plus Placebo	CV deaths, nonfatal MI, or Stroke	9.3% vs 11.4%, RR 0.80, p<0.001
Triton-TIMI 38	ACS undergoing PCI	Aspirin plus Prasugrel vs Aspirin plus Clopidogrel	CV death, nonfatal MI, or nonfatal Stroke at 14.5 months	9.9% vs 12.1% HR 0.81, 95% CI 0.73-0.90, P<0.001
Triology – ACS	Medically managed NSTE-ACS	Aspirin plus Prasugrel vs Aspirin plus Clopidogrel	CV death, MI, or Stroke at 17 months in patients age <75 years	13.9% vs 16% HR 0.91. 95% CI 0.79.1.05, p-0.21
ACCOAST	Patients with NSTEMI scheduled for CAG	Pretreatment with Prasugrel 30 mg vs placebo	CV death, MI, Stroke, GP IIb/IIIa inhibitor bailout, or urgent revascularization at 7 days	10% vs 9.8%, HR 1.02, 95% ci 0.84.1.25, p-0.81
Plato	Patients with ACS	Aspirin plus Ticagrelor vs Aspirin plus Clopidogrel	Death from vascular causes, MI, or Stroke at 12 months	9.8% vs 11.7%, HR 0.84, 95% CI 0.77-0.92, p<0.001
Pegasus TIMI 54	Patients with a MI 1-3 years ago	Ticagrelor 90 mg BD plus Aspirin, Ticagrelor 60 mg BD plus Aspirin, Placebo plus Aspirin	Cardiovascular Death, MI or Stroke at 3 years	Ticagrelor 90 mg vs Placebo – HR 0.85, 95% CI 0.75-0.96 (p=0.008); Ticagrelor 60 mg vs Placebo HR 0.84, 95% CI 0.74-0.95 (p=0.004)
Champion-Phoenix	Patients undergoing PCI	Aspirin plus Clopidogrel plus cangrelor vs Aspirin plus Clopidogrel	Death from any cause, MI, Ischemia-driven revascularisation, and Stent thrombosis at 48 hours	4.7% vs 5.9%, OR 0.78, 95% CI 0.66-0.93, p=0.005

3. Aspirin and Dipyridamole combination has been proved to be superior to Aspirin alone in secondary prevention.
4. Other anti-platelets have not been studied in stroke patients.

Side Effects of $P2Y_{12}$ Receptor Blockers

a. Bleeding: The principal adverse outcome related to the use of thienopyridines is bleeding.[9] The CURE study showed similar rates for nonfatal and major hemorrhage but highlighted dose-dependent effects of ASA on rates for bleeding, and also an effect of age in clopidogrel-treated patients.[10] In the TRITON TIMI38 study, bleeding rates with prasugrel were markedly higher than with clopidogrel (Tables 2 and 3).[11]

Clopidogrel: Also among clopidogrel-treated subjects in TRITON-TIMI 38, carriers of the CYP 2C19 variant had a relative increase of 53% in the risk of death from cardiovascular causes, MI, or stroke compared with noncarriers (12.1% vs. 8.0%); and an increase by a factor of 3 in the risk of stent thrombosis (2.6% vs. 8%).[12] A parallel study of prasugrel found no effect of this polymorphism on pharmacodynamic or clinical outcomes.[13]

Prasugrel: is contraindicated in (1) patients with a history of prior TIA or stroke, (2) for patients 75 years of age or older due to an increased incidence of fatal and intracranial bleeding. and (3) in patients weighing less than 60 kg (although not absolutely contraindicated, a higher rate of bleeding is noted because the active metabolite of prasugrel is 30-

Table 3: Duration of Antiplatelet Therapy in Subsets of CAD[8]

Subset of CAD	Recommendation
In all CAD patients	Aspirin therapy 75 – 100 mg daily. Continued Indefinitely; unless there are contraindications like bleeding or hypersensitivity
Stable ischemic hert disease after PTCA:	
After Drug –eluting stent (DES)	DAPT with Aspirin and Clopidogrel should be given for at least 6 months (Class I)
After Bare-Metasl Stent (BMS)	DAPT with Aspirin and Clopidogrel should be given for at least 1 month (Class I)
After DES / BMS who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk	DAPT may be continued for longer if tolerated well. (Class IIb)•
Acute Coronary Syndrome (ACS) after PCI	
After BMS or DES implantation	DAPT with P2Y12 inhibitors (Clopidogrel, Prasugrel or Ticagrelor) should be given for at least 12 months (Class I).
After DES / BMS who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk	Continuation of DAPT with P2Y12 inhibitors (Clopidogrel, Prasugrel or Ticagrelor) for longer than 12 months, for 18-24 months may be reasonable (Class IIb).
ACS# after PCI with DES / BMS	Reasonable to use Ticagrelor in preference to Clopidogrel for maintenance P2Y12 inhibitor therapy (Class IIa)
or	
UA / NSTEMI on Medical management (without PCI)	Reasonable to choose Prasugrel over Clopidogrel for maintenance P2Y12 inhibitor therapy (Class IIa), if not at high risk of bleeding and no prior stroke
ACS# - Post coronary Artery Bypass Grafting (CABG)	P2Y12 inhibitor therapy should be resumed after CABG to complete 12 months of DAPT therapy after ACS (Class I).
Elective Noncardiac Surgery	Delayed 30 days after BMS implantation Delayed 6 months after DES implantation

#ACS include unstable angina (UA), Non-ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI); •A new risk score (the "DAPT score"), derived from the Dual Antiplatelet Therapy study, may be useful to decide about prolonged DAPT in patients treated post PCI

40% higher in these patients. Prasugrel can be used in a dose of 5 mg daily).[14]

Ticagrelor - In the PLATO study[15], the two treatment groups did not differ significantly in the rates of CABG-related major bleeding (11.6% and 11.2%). However, there was a higher rate of non–CABG-related major bleeding.

b. Adenosine Related Side Effects of Ticagrelor - Ticagrelor is metabolized to adenosine and administration is associated with related effects like of

- Dyspnea (10%-20%), but led to its withdrawal in only 1% of cases, and
- Sinus Pauses lasting more than 3 seconds (6%) were noted on holter but were asymptomatic and did not require pacemaker implantation.

ANTI-PLATELET RESISTANCE

Aspirin Resistance: Patients developing recurrent ischemic inspite being on adequate doses of aspirin can be attributed to aspirin resistance, that encompasses a wide variety of factors that contribute to this phenomenon (Figure 3).[16]

One systematic review of 15 studies revealed a wide range in estimates of the prevalence of laboratory aspirin resistance (5% to 65%). Studies have shown increasing urinary thromboxane levels in aspirin resistance patients and was associated with combined endpoint of MI, stroke and death.

Clopidogrel Resistance

Clopidogrel is a prodrug and requires its conversion to active metabolite through CYP2C19 isoenzyme. Among healthy volunteers, Mega and colleagues129 demonstrated a 30% prevalence of the CYP2C19 allele, a genetic polymorphism that confers loss of function and

hence a reduction of the active metabolite of clopidogrel. In retrospective analysis of TRITON-TIMI 38 trial, there was a 54% increase in the risk of the composite endpoint of myocardial infarction, cardiovascular death, or stroke among carriers of at least one CYP2C19 allele over that of noncarriers. Presence of the CYP2C19 allele was also associated with a threefold increase in the risk of stent thrombosis.

Optimal management of patients with clopidogrel resistance is not known. Ongoing GRAVITAS study may add important information in such patients.

INTRAVENOUS ANTI-PLATELET AGENTS:

Glycoprotein IIB/IIIA antagonists (Table 4)

GpIIb/IIIa is a member of a family of adhesive receptors (integrins) composed of α and β transmembrane proteins and an estimated 50,000 to 80,000 GpIIb/IIIa receptors on the surface of each platelet. Platelet activation results in a change in the shape of the receptor, which greatly increases its normal low affinity for fibrinogen and vWF.

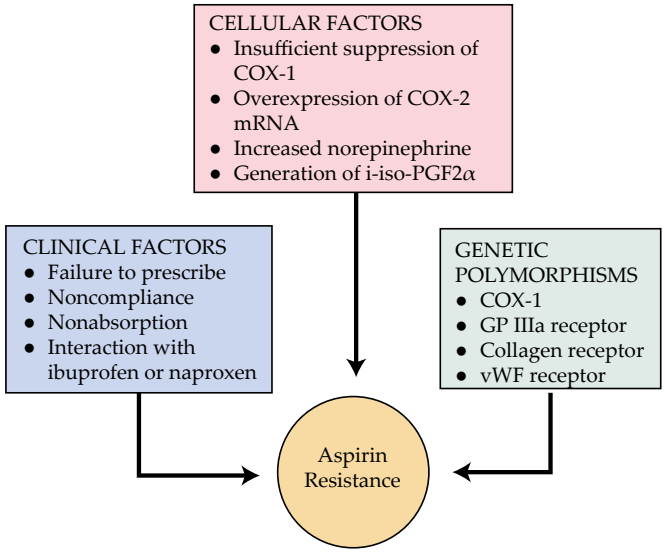

Fig. 3: Factors contributing to Aspirin Resistance

Two types of GpIIb/IIIa receptor antagonists are available[17,18]: noncompetitive (monoclonal antibodies) and competitive (a peptide and a peptidomimetic).

Clinical Use

Platelet GpIIb/IIIa antagonist should be used in patients with moderate-to high-risk ACS in whom catheterization and PCI are planned (ACC/AHA guideline - class I, level A).[19]

Abxicimab has been found to superior to tirofiban and eptifibatide as shown in TARGET, IMACT II and RESTORE trials and it has also been found to superior in diabetic patients and safer in renal failure pateients.[20-22]

Side Effects

a. Bleeding – most common site is vascular access site.

b. Thrombocytopenia – Incidence is 1.1-5.6% and is immune mediated.

EMERGING DEVELOPMENT IN ANTI-PLATELET THERAPY

Protease Activated Receptor 1 (Thrombin receptor) – Compounds have been developed that inhibit the ligand-binding site on PAR-1, which is a G protein–coupled receptor known as protease activated receptor-1 (PAR-1) receptor for thrombin. Two compounds which are in development are Atopaxar and Voropaxar which achieve 90% and 80% platelet inhibition respectively.[23,24]

Table 4: Basic Pharmacokinetics of GPIIb/IIIa antagonists

Drug	Dosage	Chemistry	Plasma Half Life	Biologic Half Life	Clearance Mechanism	% Inhibition of platelet aggregation
Abxicimab	Bolus: 0.25 mg/kg IV Maintenance: 0.125 mcg/mkg/min (max 10 mcg/min for 12 hours	Monoclonal antibody	10 min	12-24 hr	Reticulo-endothelial system	>80%
Tirofiban	Bolus: 0.25 mcg / kg IV in 5 min Maintenance: 0.15 mcg/kg/min infusion for 18 hours	Peptidomimetic	2 hr	4-8 hr	Renal	>90%
Eptifibatide	Bolus: 180 mcg/kg IV Maintenance: 2 mcg/kg/min infusion for 72 hours	Polypeptide	2.5 hr	4-6 hr	Renal	85% after bolus, >90% during steady state infusion

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CHAPTER

198 Combined Oral Anticoagulation and Antiplatelet Therapy - Management of a Difficult Situation

Jamshed J Dalal

The combination of atrial fibrillation (AF) and coronary artery disease (CAD), is not only an uncommon clinical setting, but also a complex setting associated with significantly higher mortality rates[1] that requires doctors to deal with using a combination of anticoagulation (OAC) and antiplatelet therapy. The benefit of the combination has to be balanced with the increased bleeding risk.

A common clinical dilemma regarding treatment of patients with AF is the need to use concomitant antiplatelet agents for a variety of reasons including, primary prevention of CAD, or for secondary prevention after a diagnosis of coronary disease, or for maintenance therapy after percutaneous coronary intervention (PCI). In some of these situations, dual antiplatelet therapy may be utilized, for example after an acute myocardial infarction or after PCI. While the combination of OAC and antiplatelet therapy carry the potential of additive benefits, they also carry the danger of increased risk of bleeding.[2]

Fortunately, we have subgroup data available from the various novel oral anticoagulant (NOAC) trials looking at concomitant antiplatelet use with NOACs. In ARISTOTLE trial, concomitant aspirin was used in around 20–25% of patients with AF treated with an anticoagulant and was associated with a higher risk of bleeding. Similar effects of apixaban, compared with warfarin, on stroke or systemic embolism, major bleeding, or mortality were observed irrespective of concomitant aspirin use. Clopidogrel use was an exclusion criterion at randomization and only started in a small proportion of patients included in the ARISTOTLE trial thus limiting ability to assess the outcomes associated with concomitant apixaban or warfarin and either clopidogrel or dual antiplatelet therapy.[3]

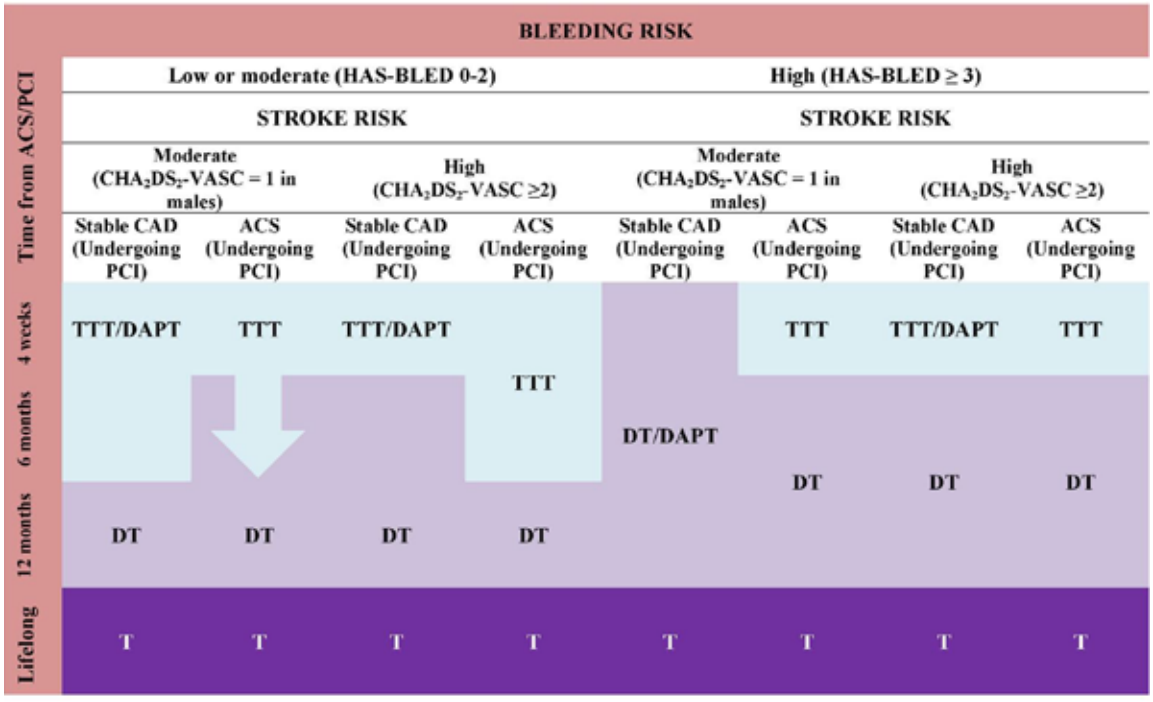
In RE-LY trial, concomitant antiplatelet use led to a significant rise in the overall risk of major bleeding when dabigatran was combined with any OAC. The risk appeared to increase by 50% with a single antiplatelet, and doubled when dual antiplatelet was used at any time. The relative increase in risk was similar with dabigatran 110mg, 150mg or warfarin.[2]

In ENGAGE AF-TIMI 48 trial, the addition of a single antiplatelet drug to an anticoagulant (warfarin or edoxaban) was associated with a significantly greater risk of bleeding. However, the addition of a single drug did not modify the relative efficacy and safety of edoxaban as compared to warfarin. Notably, when compared to warfarin, both edoxaban regimens resulted in a significant reduction in all forms of bleeding, including intracranial hemorrhage and life-threatening bleeding, both in patients who were as well as those who were not, receiving a single antiplatelet therapy.[4]

There is no randomized study comparing vitamin K antagonist (VKA) and NOACs in patients with AF undergoing PCI for acute coronary syndromes (ACS) or for stable CAD, i.e. patients who have an indication to receive single or DAPT.[1] There are no large-scale randomized studies published evaluating the newer antiplatelet agents in patients with AF receiving either VKAs or NOACs, adding to the uncertainty on how to use these antithrombotic agents in combination when both CAD (ACS or stable disease) and AF converge in a given patient.[1]

There are currently three ongoing large-scale outcome studies evaluating combinations of NOAC or VKA and antiplatelets in patients with AF that undergo a PCI with stenting (elective or due to an ACS), providing hope that within the next few years there will be more evidence in this field.

1. The PIONEER AF PCI study (NCT01830543) evaluates the safety of two different rivaroxaban treatment strategies vs. VKA: (i) 15 mg rivaroxaban OD plus clopidogrel; (ii) 2.5 mg BID plus low-dose aspirin 75–100 mg plus clopidogrel, prasugrel or ticagrelor, followed by rivaroxaban 15 mg OD (or 10 mg for subjects with moderate renal impairment) plus aspirin for 12 months; or (iii) VKA treatment strategy utilizing similar combinations of antiplatelet therapy.
2. The RE-DUAL PCI study (NCT02164864) evaluates dual antithrombotic therapy regimens of (i) 110 mg dabigatran BID plus clopidogrel or ticagrelor, or (ii) 150 mg dabigatran BID plus clopidogrel or ticagrelor, with (iii) a triple antithrombotic therapy combination of warfarin plus clopidogrel or ticagrelor plus low-dose aspirin for 1–3 months.
3. The AUGUSTUS trial (NCT02415400), apixaban will be evaluated vs. VKA in AF patients with a recent ACS. All patients will be receiving a P2Y12 inhibitor and will be randomized in a 2 × 2 factorial design to 6 months of apixaban 5 mg BID vs. VKA, and aspirin vs. placebo.



TTT- triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day
DT- OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day)
T- Monotherapy with oral anticoagulants
DAPT - Dual antiplatelet therapy consisting of aspirin 75 mg/day and clopidogrel 75 mg/day

Fig. 1: Management of acute coronary syndrome in atrial fibrillation (Dalal et al IHJ; 67, 2015, s13-34)

The optimal combination, or duration of combination antithrombotic therapy for AF patients undergoing percutaneous coronary intervention is not known, but the increased bleeding risk suggests all efforts must be made to keep the duration short. Expert consensus, reviewed and reconsidered by the ESC 2016 Guidelines Task Force, suggests the following principles:[5]

AF patients at risk for stroke, patients with mechanical valves, and patients with recent or recurrent deep vein thrombosis or pulmonary embolism should continue OAC during and after stenting. In general, a short period of triple therapy (OAC, aspirin and clopidogrel) for six weeks to three months only is recommended, especially for those with less thrombotic and high bleeding risk, followed by a period of dual therapy (OAC plus a single antiplatelet) upto one year. For those with less bleeding and high thrombotic profile, triple therapy may be continued for six months and changed to single antiplatelet pus OAC for one year. At the end of one year, antiplatelet therapy may be stopped and only OAC continued. A review of the combination therapy of AF and ACS is shown in Figure 1.[7] There is data to show that VKA plus clopidogrel is preferred to VKA plus aspirin to reduce bleeding complications,[6] however no data is available whether aspirin or clopidogrel combination is better with NOACs. Newer antiplatelet agents such as prasugrel and ticagrelor are presently not recommended with NOACS or VKAs. When a NOAC is used, the consensus recommendation is that the lowest dose effective for stroke prevention in AF should be considered. Dose reduction beyond the approved dosing tested in phase III trials is not currently recommended, and awaits assessment in ongoing controlled trials.

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