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Antiplatelet Therapy in Patients with Acute Coronary Syndrome: An Update

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Abstract:

Antiplatelet therapy is the cornerstone in the treatment of acute coronary syndrome. Aspirin is the most widely used antiplatelet agent followed by $P2Y_{12}$ inhibitors. Glycoprotein (GP) IIb-IIIa antagonists are also gaining popularity as an antiplatelet agents during peri-PCI period. This review article summarizes the indications, duration of dual antiplatelet therapy (DAPT) in ACS setting. Antiplatelet therapy in special situations like atrial fibrillation and thrombocytopenia are discussed here. Issues like switching between $P2Y_{12}$ inhibitors and genetic testing of antiplatelet agents are also mentioned in this article

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Introduction:

Cardiovascular disease (MI, stroke) are the major cause of morbidity and mortality in current era. Approximately 15 million deaths occur per year due cardiovascular disease worldwide. One of the main pathology behind this cardiovascular disease is atherothrombosis in vessel.[1]For prevention and treatment of this atherothombosis, antiplatelet agents are the cornerstone. Oral antiplatelet agents have been documented to decrease vascular death by 15% and serious cardiovascular events by 20% in high risk patients.[2]

The idea of using aspirin to prevent clotting diseases (such as MI and strokes) was revived in the 1960s. There are many antiplatelet agents available now a days. Among them, aspirin is the most popular and efficient antiplatelet agent in both primary and secondary prevention of ischemic events.[3]

In 1996, Schwomig et al. first described the role of dual antiplatelet therapy (DAPT) in patients undergoing intracoronary stent placement.[4] Ticlopidine was used as a part of DAPT along with aspirin at that time. Currently as part of DAPT, ticagrelor, prasugrel and clopidogrel are preferred agents.

Type of antiplatelet agents:

There are many types of antiplatelet agents available and they are classified on the basis of mechanism of action, route of administration. Table 1 shows the approved antiplatelet agents used in cardiovascular disease.[5]

Aspirin

Aspirin exerts its inhibitory effect by irreversible acetylation of a serine residue of cyclooxygenase-1 and -2, ultimately blocking thromboxane A2 generation.[6] ISIS-2 (Second International Study of Infarct Survival) trial showed aspirin when used in post-thrombolysis patients significantly reduced early vascular mortality and also has long term benefit.[7] The antiplatelet effect of aspirin is at the dose range of 50–325 mg/day.[8] CURRENT OASIS-7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes) trial proved that 75 mg of aspirin is optimum dose for antiplatelet activity.[9] So, aspirin is the backbone of DAPT therapy and guideline also recommends it.[10]

$P2Y_{12}$ inhibitors:

Five $P2Y_{12}$inhibitors have been approved. These are ticlopidine, clopidogrel, prasugrel, ticagrelor and cangralor. Except ticlopidine, all are being used now a days in ACS patients.

Clopidogrel: The most extensively and commonly used $P2Y_{12}$ inhibitor is clopidogrel. It is a thienopiridine class $P2Y_{12}$ inhibitor which irreversibly inhibits platelet. CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial revealed, loading dose of clopidogrel followed by long term clopidogrel with aspirin has significantly reduced primary end point outcome (Death

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Table-I

List of approved antiplatelet agents along with their mechanism and indications[5]

Agent	Administration	Mechanism	Indication
Aspirin	Oral	COX-1 inhibition	CAD, PAD, CVD, CABG, coronary and peripheral stents
Clopidogrel	Oral	P2Y12 inhibition	Prior MI, stroke or symptomatic PAD, as monotherapy; ACS or coronary stenting,in combination with aspirin
Prasugrel	Oral	P2Y12 inhibition	ACS patients undergoing PCI with stenting, in combination with aspirin
Ticagrelor	Oral	P2Y12 inhibition	ACS patients, in combination with aspirin
Cangrelor	Intravenous	P2Y12 inhibition	P2Y12 inhibitor naïve PCI patients
Abciximab	Intravenous	GPIIb-IIIa	PCI
Tirofiban	Intravenous	Inhibition	ACS, PCI
Eptifibatide	Intravenous	GPIIb-IIIa	ACS, PCI
Vorapaxar	Oral	PAR-1 inhibition	Prior MI, PAD

ACS-Acute coronary syndrome, PDA-Peripheral arterial disease, CVD-Cardiovascular disease, CABG- Coronary artery bypass graft, PCI- Percutaneous coronary inervention

from cardiovascular cause, nonfatal MI, stroke) than aspirin monotherapy in non-ST elevation acute myocardial infarction.[11]Among the patients who underwent angioplasty in CURE trial (PCI-CURE trial) was found to have benefit with DAPT consisting of clopidogrel with aspirin then aspirin monotherapy.[12] CLARITY TIMI-28 trial [The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)- Thrombolysis in Myocardial Infarction (TIMI)] among the STEMI patients showed 6.7% absolute reduction in the primary efficacy end points in the study group (15% in clopidogrel arm vs. 21.7% in placebo-arm).[13] In this study, angioplasty subgroup revealed46% relative risk reduction in the 30-day composite of CV death, MI, or stroke.[14] COMMIT trial (The Clopidogrel and Metoprolol in Myocardial Infarction Trial).10 There was 9% relative risk reduction in the DAPT arm (aspirin plus clopidogrel) compared to placebo arm (aspirin monotherapy) among the medically managed STEMI patients.[15]

Prasugrel: Another thienopyridine is prasugrel, which is more potent and consistently inhibit platelet aggregation than clopidogrel.The TRITON-TIMI 38 trial compared prasugrel with clopidogrel in 13,608 moderate- to high-risk ACS patients undergoing PCI. the primary efficacy end point occurred significantly less often in patients treated with prasugrel (9.9 versus 12.1 percent) at 15 month follow up.[16]TRILOGY ACS[17] and ACCOAST study[18] failed to demonstrate benefit from treatment with medically managed ACS and NSTEMI patients underwent angioplasty respectively over clopidogrel.

Ticagrelor: It is a nonthienopyridine$P2Y_{12}$ inhibitor which reversibly inhibits platelet. Its onset of action is faster than other oral antiplatelet agents. PLATO study showed ticagrelor with aspirin combination is superior to aspirin and clopidogrel combination in reducing thrombotic events (CV death, MI or Stroke)[absolute risk reduction 1.9% and relative risk reduction 16% at 1 year follow up] among ACS patients.[19] ticagrelor is the most preferred $P2Y_{12}$ inhibitor in DAPT regimen as because it is most potent, has least side effect exceptmild dyspnea and can be used in both medical and interventional management of ACS. Recently, ticagrelor has been proven to have antibacterial activity, which will give extra benefit in patients who are undergoing PCI to combat nosocomial infection.[20]

Cangrelor: Cangrelor is an I/V $P2Y_{12}$ inhibitor using as an adjunct to percutaneous coronary intervention (PCI) to decrease the incidence of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients who did not get any $P2Y_{12}$ platelet inhibitor previously and were not being given a glycoprotein IIb/IIIa inhibitor.[21] Cangrelor can also be used as a bridge therapy for patients receiving oral antiplatelet agents during surgery and for patients who are unable to receive oral medications.[22]

Glycoprotein (GP) IIb-IIIa antagonists:

Abciximab, tirofiban and eptifibatide are glycoprotein (GP) IIb-IIIa antagonists usually used intravenously during the peri-interventional setting.[23] Commonly used agent is eptifibatide. ESC guideline recommends GP IIb/IIIa inhibitors to use in bailout situation if there is evidence of no-reflow or a thrombotic complication.[24]

PAR-1 inhibitor:

Lastly, vorapaxar, the thrombin receptor inhibitor prevents platelet activation by thrombin via protease-activated receptor (PAR)-1 on human platelets.[6] Vorapaxar can be used in addition to standard antiplatelet therapy in the secondary prevention of ischemic coronary events in patients with a history of MI or symptomatic peripheral artery disease on the basis of information obtained from TRA 2P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events – Thrombolysis in Myocardial Infarction) trial in patients with stable atherosclerotic disease.[25]

Duration of antiplatelet therapy:

In ACS setting, antiplatelet agents are used for a long term to prevent ischemic events particularly in patients who undergoes PCI. Many studies were done to find out the optimum duration of DAPT in ACS patients. Among them DAPT study and PEGASUS-TIMI 54 trial are two landmark trial. DAPT study showed the benefit (reduced stent thrombosis and all causes mortality, MI, stroke) of long duration (30 months) of DAPT but with the increased risk of moderate to severe bleeding in comparison to standard DAPT therapy for 12 months.[26] In the PEGASUS-TIMI (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction) 54 trial compared aspirinwith placebo and aspirin with standard and low dose ticagrelor in prior MI patients. The primary efficacy end point was the composite of MI, stroke, or cardiovascular death were significantly reduced in ticagrelor arm then placebo with aspirin but there was increased major TIMI bleeding in 33 months median follow up.[27]

Current guidelines recommend DAPT with aspirin and clopidogrel for 6 months following elective PCI with stent implantation, and DAPT with aspirin and prasugrel or ticagrelor for 12 months in ACS patients undergoing PCI and stenting.[10]Clopidogrel is an alternative in ACS patients who have PCI if intolerant to prasugrel and ticagrelor. The patients who are medically managed after ACS should have DAPT(aspirin and ticagrelor) for 1 year. If intolerant to ticagrelor, then clopidogrel is an alternative.[10]

DAPT score and PRECISE-DAPT score may be used to determine whether the patient will get standard DAPT, short DAPT or long DAPT.[10]

DAPT in special situations:

- Dual or triple antithrombotic therapy in patients with AF and having PCI: Oral anticoagulant (OAC) an essential part of treatment of AF in patients with stroke and systemic embolism who have CHA_2DS_2-VAS_c score ≥2.[28]The RE-DUAL PCI study showed that dual therapy with a $P2Y_{12}$ inhibitor and dabigatran has lower risk of bleeding than triple therapy with aspirin, $P2Y_{12}$ inhibitor and warfarin.[29]

  Current guideline recommends to give triple therapy with aspirin, clopidogrel and OAC for 6 months followed by dual therapy consisting of OAC with aspirin or clopidogrel in ischemic risk patients for 6 months in PCI patients with AF.[10] In high bleeding risk patients, initial dual therapy consisting of OAC with clopidogrel can be given.[10] In both cases, after 12 months, treatment with OAC only is sufficient.[10]

- ACS patients with thrombocytopenia:There is no clear cut guideline for management of ACS patients with thrombocytopenia. Recently McCarthy et al.[30] described not to give any antiplatelet agent and also to avoid PCI in patientswith ACS having platelet count below $50x10^9$/L. If platelet count more then $50x10^9$/L, then PCI can be done and DAPT may be given for 1 month then clopidogrel only. If PCI is not done, then colpidogrel monotherapy is sufficient[29]

- Switching between $P2Y_{12}$ inhibitors:In ACS setting current ESC guideline suggests to give loading dose during switching from one $P2Y_{12}$ inhibitor to another.[10] During the escalation in acute setting loading dose should be given immediately but during de-escalation loading dose should be given 24 hours later from previous dose of $P2Y_{12}$ inhibitor.[10]

In chronic setting, during switching from ticagrelor to prasugrel or clopidogrel loading dose should be given. During other situations, maintenance dose is sufficient after 24 hours of previous $P2Y_{12}$ inhibitor dose.[10]

Resistance to antiplatelet agents:

Many patients develop ischemic events during the course of DAPT despite having adequate dose and compliance. Main reason is thought to be aspirin or clopidogrel resistance. Aspirin resistance prevalence varies from 5 to

45% in different population.[8] Clopidogrel resistance is another alarming condition making the drug ineffective in many patients.

So, in developed countries, genetic testing to find out the resistance to aspirin or clopidogrel is being carried out. Due to availability issue and cost, this is not popular in third world country

Conclusion:

Antiplatelet therapy are the cornerstone of the treatment of ACS patients. Aspirin is the backbone of all antiplatelet agents and major part of DAPT. Different $P2Y_{12}$ inhibitors are being used in different situations of ACS as an adjunct to aspirin. Intravenous antiplatelet are using during the time of peri-PCI period. Finally, researchers are also trying to invent newer and more potent antiplatelet agents like $P2Y_1$ inhibitor, PAR-4 inhibitor, glycoprotein IV inhibitor and lipoxygenase inhibitor to prevent ischemic risk without any increased risk of bleeding.

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