The use of Anti-Platelet Agents in Coronary Heart Disease

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INTRODUCTION

Intracoronary thrombosis plays an important role in the pathogenesis of acute coronary syndrome. It occurs due to a rupture of an atherosclerotic plaque, which may be spontaneous, as in the case of acute coronary syndrome, or due to procedures such as percutaneous intervention (PCI). Atherosclerotic plaque rupture causes exposure of thrombogenic subendothelial components and initiates platelet aggregation, which then initiates the coagulation cascade. In stable angina, the formation of platelet thrombus is the most important thing to occur on plaque progressiveness as a result of rupture and episodic formation of thrombi.[1] Arterial thrombi contain many platelets. Anti-platelet agents are greatly beneficial in acute and chronic coronary heart disease. This paper discusses the use of anti-platelet agents in coronary heart disease.

THE PATHOGENESIS OF INTRA-CORONARY THROMBOSIS

Intra-coronary thrombosis is initiated as a disruption of an atherosclerotic plaque, which may be either spontaneous or due to percutaneous intervention (PCI). It causes platelet adhesion on the subendothelial layer. Platelets would adhere to subendothelial gluco-proteins such as von Willebrand's factor, fibronectin, and collagen (Figure 1). Exposed collagen would then activate platelets to produce thromboxane A_2. Active platelets also secrete granules containing ADP, serotonin, fibrinogen, and other substances which then further activate platelets. Platelet activation causes the activation of platelet G IIb/IIIa, which is the last pathway of platelet aggregation.

Thromboxane A_2 and ADP secreted by activated platelets then activate surrounding platelets, thus enhancing the process of thrombosis. Active platelets increase thrombin production through the coagulation cascade, which then stabilizes thrombus through the conversion of fibrinogen into fibrin. Thrombin can also activate platelet further.[2]

The mechanism of action of anti-platelet agents [3,4,5] (Figure 2):

1. Aspirin (acetylsalicylic acid) inhibits the synthesis of thromboxane A_2 through an irreversible inhibition of the platelet cyclooxygenase enzyme. Aside from this anti-platelet effect, aspirin also has an inflammatory effect. Aspirin inhibition on cyclooxygenase I (COX I) activity, is approximately 200 times stronger than its inhibition of the inflammatory inhibitor COX_2.
2. Ticlopidine and clopidogrel. Ticlopidine and clopidogrel are both thienopyridine derivatives that irreversibly inhibit ADP linkage to receptors on platelets, thus inhibiting the actiation of the G IIb/IIIa receptors.
3. Platelet G IIb/IIIa receptor antagonist. The last pathway for platelet aggregation is the linkage between fibrinogen and G IIb/IIIa receptors on platelet surface. Inhibition of these receptors blocks the last pathway for platetet aggregation. The effect of thrombine, thromboxane A_2, collagen, ADP, and cathecolamine in inducing platelet aggregation may be prevented by blocking this receptor (Figure 2).
4. Dipyridamol inhibits platelet adhesion on patches on the blood vessel walls, increases the formation of CAMP, and reduces platelet calcium, thus inhibiting platelet aggregation. Dipyridamol also increases the anti-aggregation effects of prostacycline.
5. Sulfin pyrazone inhibits cyclooxygenase, just as aspirin.

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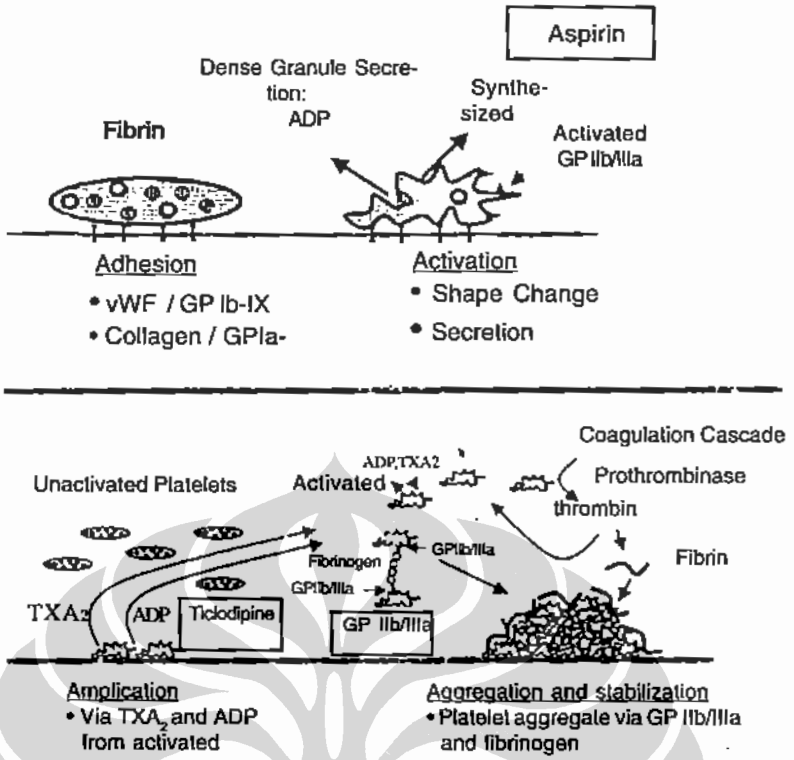

Figure 1. Steps Involved in Intracoronary Thrombus Formation. Antiplatelet Agents Are Shown in Gray Boxes by the Spesific Process They Inhibit.

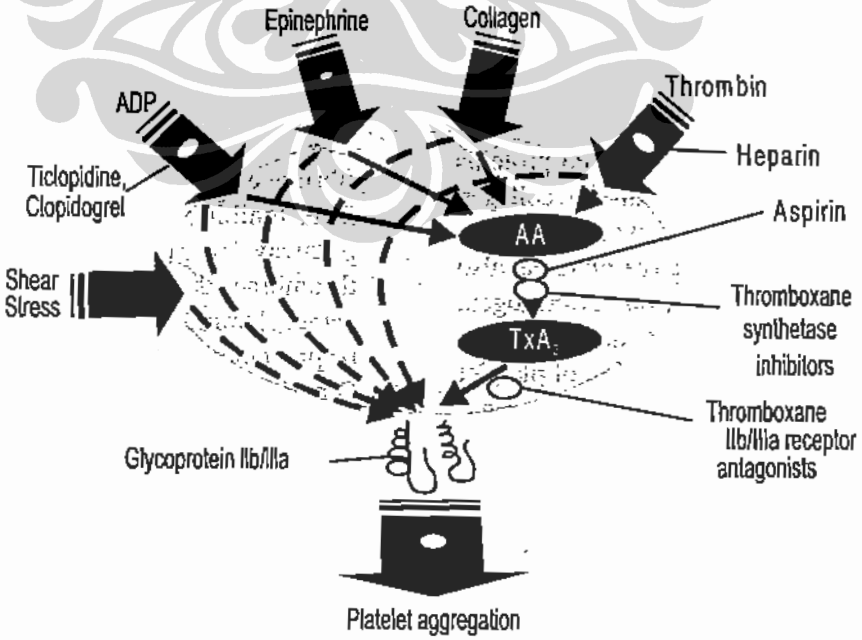

Figure 2.

CLINICAL TRIALS

Aspirin

A report from the Antiplatelet Trialists Collaboration demonstrated that the administration of anti-platelet agents reduces the incindence of cardiovascular conditions. Out of 2000 patients with acute myocardial infarct, there was a reduced incidence of cardiovascular conditions, with a rate of 14% in the control group and 10% in the group receiving anti-platelet agents. There is also a reduction in the incidence of cardiovascular conditions in patients with a history of myocardiac infarction, unstable angina, stable angina, and post-angioplasty. This benefit is still noticeable up to the third year. Long-term administration of anti-platelet agents is recommended. The most widely use anti-platelet agent is aspirin, with a dose ranging from 75 to 325 mg per day.[6]

A meta-analysis reported that the administration of anti-platelet agents in high-risk patients can reduce the incidence rate of cardiovascular incidence by one fourths, non-fatal myocardiac infarct by one third, non-fatal stroke by one fourths, and vascular mortality by one sixth. A dose of 75 to 150 mg of aspirin daily is sufficiently effective for long-term treatment, while an initial dose of 150 mg is needed for acute conditions.

The benefits of aspirin administration in patients receiving thrombolytic treatment were found in the ISIS 2 study. Administration of 160 mg of aspirin for 1 month produces a 23% reduction in mortality, while the administration of streptokinase produces a reduction of 25%, and the administration of both aspirin and streptokinase produces a mortality reduction of 42%.[8]

In RISC, the administration of aspirin to patients with unstable angina and non-Q infarct demonstrated a reduction in mortality risk and myocardiac infarct. Administration of aspirin in unstable angina reduces the risk of acute myocardiac infarct, stroke, and cardiovascular mortality.[9]

In SAPAT, the administration of 75 mg of aspirin to for stable angina demonstrated a 34% reduction of myocardiac infarct and sudden death compared to placebo. All patients in this study received sotalol.10 In stable angina, the administration of aspirin reduces vascular death, re-infarct, and stroke up to 25%. The administration of anti-platelet agents (particularly aspirin or aspirin plus dipyridamole) reduces the incidence of reocclusion in patients with a history of PTCA or CABG. Patients with CABG receiving anti-platelet agents demonstrated a 21% incidence of reocclusion compared to 30% in the control group. Patients with PTCA receiving anti-platelet agents had a 4% incidence rate of reocclusion, compared to 8% in the control group.[7]

Ticlopidine

Ticlopidine is used for secondary prevention of stroke, myocardiac infarct, thrombosis in stent and graft occlusion. Due to its many side effects, ticlopidine has limited use. Neutropenia may occur in approximately 2.4% of patients, severe neutropenia in 0.8%. Neutropenia usually disappears after 1-3 weeks of drug termination. The administration of ticlopidine necessitates a blood check every 2 weeks in the first 3 months of treatment.[12] In a study of 652 patients with unstable angina who were randomized to take 250 mg of ticlopidine twice daily or standard therapy, ticlopidine was proven to have reduced vascular death and non-fatal myocardiac infarct (13.6% in those receiving placebo, 7.3% in the ticlopidine p=0.009). The effect of the administration of ticlopidine was achieved after 2 weeks of administration, and its maximum effect is achieved at the same point.[13] In another study, the effect of ticlopidine was not better than that of aspirin in preventing myocardiac infarct, stroke, and vascular death. Ticlopidine is indicated when aspirin use is contraindicated or failed to produce results.[6]

In the STARS trial, the effects of a daily 325 mg of aspirin, a combination between aspirine and 500 mg ticlopidine daily, and aspirin plus warfarin were compared in preventing thrombosis in patients with stent. The incidence of stent thrombosis in those receiving aspirin alone was 3.6%, 2.7% in those receiving aspirin and warfarin, and 0.5% in those receiving aspirin and ticlopidine ($p < 0.014$). Thus, the administration of aspirin plus ticlopidine achieved better results than the administration of aspirin alone or aspirin plus warfarin in preventing the occurrence of stent thrombosis.[14]

Administration of ticlopidine in patients undergoing coronary arterial bypass graft (CABG) demonstrated a better graft acceptance compared to those receiving placebo.[15]

Clopidogrel

The mechanism of action of clopidogrel is just like ticlopidine, but there is less incidence of neutropenia, compared to in the use of ticlopidine. The CAPRIE trial compared the efficacy of clopidogrel and aspirin in preventing ischemic stroke, infarct myocard, and cardiovascular death in patients with recent ischemic stroke, recent myocardiac infarct, or symptomatic peripheral arterial disease. Patients underwent follow-up for 1-3 years. Clopidogrel was significantly more effective than aspirin in preventing ischemic vascular conditions (myocardiac infarct, ischemic stroke, and vascular death). The reduced relative risk is 8.7% (95% CI 0.3-16.5, $p = 0.0043$). The incidence rate of vascular ischemia was 5.8% in aspirin and 5.0% in clopidogrel.

The incidence of neutropenia in clopidogrel was not any higher than that of aspirin.[16] The CURE trial evaluated the efficacy and safety of the administration of clopidogrel plus aspirin in patients with acute coronary syndrome without ST elevation. Patients were randomized to receive aspirin alone (75-325 mg) or aspirin plus clopidogrel (initial dose of 300 mg continued with 75 mg daily) for 3-12 months. On the 9th month, the incidence of cardiovascular death, non-fatal myocardiac infarct, and stroke in patients using clopidogrel plus aspirin group was 9.3%, while in the aspirin only group it was 11.4% (relative risk 0.80; 95% CI 0.72-0.9; $p < 0.001$). Refractory ischemia in the clopidogrel plus aspirin group was 16.5%, while in the aspirin group was 18.8% (rr 0.86 $p < 0.001$). There was more bleeding in clopidogrel plus aspirin group compared to the aspirin only group (3.7% and 2.7% $p = 0.001$). However, there was no significant difference in the incidence of severe bleeding or hemorrhagic stroke.[17]

In the double-blind PCI-CURE study, 2658 patients with acute coronary syndrome without ST elevation undergoing PCI received clopidogrel plus aspirin or aspirin alone. In the clopidogrel plus aspirin group, the incidence of cardiovascular death, myocardiac infarct, or target vessel revascularization was 4.5% compared to 6.4% in the aspirin group (OR 0.70, 95% CI 0.5-0.97, $p = 0.03$). Long-term administration of clopidogrel following PCI reduces the incidence of cardiovascular death, myocardiac infarct, and revascularization ($p = 0.003$). Pre-treatment with clopidogrel plus aspirin in acute cardiovascular syndrome patients undergoing PCI reduces cardiovascular conditions. Long-term administration for an average period of 8 months following PCI reduces the cardiovascular death or myocardiac infarct.[18] The CLASSICS study compared the efficacy of the administration of ticlopidine plus aspirin and clopidogrel plus aspirin in stent patients. Clopidogrel has less side effects with the same efficacy.[19] In a meta-analysis comparing the efficacy of clopidogrel plus aspirin and ticlopidine plus aspirin following stent insertion demonstrated that the administration of clopidogrel plus aspirin is better than the administration of ticlopidine plus aspirin. Cardiovascular conditions (death, myocardiac infarct, target vessel revascularization, or sub-acute stent thrombosis) was 2.1% in the clopidogrel group as supposed to 4.4% in the ticlopidine group OR 0.72 (95%, CI 0.55-0.8) $p = 0.002$. The mortality rate was also lower in the clopidogrel group compared to the ticlopidine group (0.4% vs 1.09%, OR 0.55 95% 0.37-0.82) $p = 0.003$. Such results might have been achieved due to the rapid effect of the administration of clopidogrel loading dose. Clopidogrel plus aspirin as standard treatment replacing ticlopidine plus aspirin in patients with unstable angina undergoing stent insertion.[20]

Platelet G IIb/IIIa Receptor Antagonist

Thromboxane A2 is inhibitied by aspirin. ADP is inhibited by ticlopidine and clopidogrel. Thromboxane A2 and ADP are two out of many agonist (over 90) that can stimulate platelet aggregation. GIIb/IIIa receptor antagonist could prevent platelet aggregation irrespective of the type of agonist by blocking the final pathway of platelet aggregation (Figure 2).

At this moment, there are three types of GIIb/IIIa receptor antagonist approved by FDA for use in PCI, unstable angina, and intravenous use. These drugs are abciximab, eptifibatide, and tirofiban.

Up to now, there have been many studies involving over 35,000 patients to evaluate the role of the administration of GIIb/IIIa receptor antagonist in patients with acute coronary syndrome or those undergoing PCI.

Administration of platelet G IIb/IIIa receptor antagonist in patients with acute coronary syndrome

In acute coronary syndrome, additional administration of GIIb/IIIa receptor antagonist reduces the risk of death or myocardiac infarct compared to standard therapy (Table 1).[21]

There is a reduction of death and myocardiac infarct of 1.4 to 3% in 30 days. The PURSUIT trial demonstrated the advantage of the administration of eptifibate in preventing initial ischemia. The benefit is still observable on the 30th day (the absolute risk reduction of vascular incidence is 15-20/1000 patients).

A meta-analysis of 6 trials involving 31,402 patients demonstrated a significant reduction of death and

Table 1. Unstable Angina Pectoris/Non Q Myocardial Infarction

		Rate of MI and Death at 30-days (%)				
Trial	Drug	Drug	vs	Placebo	p value	RR (%)**
PRISM	Tirofiban	5.8		7.1	0.11	18
PRISM PLUS	Tirofiban	8.7		11.9	0.03	27
PURSUIT	Eptifibatide	14.2		15.7	0.04	10
PARAGON	Lamifiban	10.6		11.7	0.48	9

** Relative reduction

myocardiac infract in the GIIb/IIIa inhibitor group compared to control (10.8% vs 11.8%) OR 0.91 (95% CI 0.84-0.98) p = 0.015. Treatment produced better results in patients with higher risks. The complication of major bleeding was significantly increased in the GIIb/IIIa receptor antagonist group, but there was no significant difference in the complication of intra-cranial bleeding.[22]

PERCUTANEOUS INTERVENTION (PCI)

PCI could cause damage of the blood vessel wall, which could cause acute reocclusion due to acute thrombosis. This could occur in 4-8% of cases. Acute thrombosis may result in death, myocardiac infarct or CABG emergency. GIIb/IIIc has been evaluated in over 15,000 patients undergoing PCI. The first large-scale study on the use of GIIb/IIIc antagonist in patients undergoing PCI is the EPIC trial using abciximab, which demonstrated a 35% reduction of death, myocardiac infarct, and urgent revascularization (Table 2).[23] On follow-up at 6 months, the benefits of abciximab administration was still observable, and remained up to 3 years.[24] The most common complication is bleeding, which could be reduced with reduced dosage of heparin.[25] Abciximab is particularly used in high risk patients, such as unstable angina evolving into myocardiac infarct.

In patients with acute myocardiac infarct undergoing primary angioplasty (without the administration of thrombolytic pre-treatment) , abciximab could prevent the incidence of ischemia immediately after the procedure, thus reducing the incidence of death, re-infarct, as well as urgent revascularization.[26] The combination of abciximab and coronary stent is the new standard in preventing ischemia in PCI. In the EPISTENT trial, abciximab was able to reduce restenosis up to 50%, particularly in patients with diabetes mellitus.[27] It could be combined with fibrolytics in acute myocardiac infarct.

The TIMI 14 trial demonstrated that the administration of abciximab along with a partial dose of plasminogen could achieve the same rate of angiographic reperfusion as in primary angioplasty. Perfusion was not only higher, but was also achieved earlier, thus saving more myocardium. There needs to be further studies to evaluate new approaches in the management of acute myocardiac infarct.[28]

Oral G IIb/IIIa Receptor Antagonist

Studies on long-term administration of oral GIIb/IIIa antagonist to prevent re-thrombosis in acute coronary syndrome or acute myocardiac infarct are still underway. Initial results demonstrate a high rate of bleeding complications.[29]

COMPLICATIONS

The down side of the use of GIIb/IIIa receptor antagonist is increased risk of bleeding. This can be reduced by reducing the dose of heparin.

Clinical Use of Anti-platelet Agents [30-34]

1. Primary prevention

   For prevention purposes, aspirin is administered to:

   a. Males over 50 years of age with at least 1 risk factor for coronary heart disease (smoking, hypertension, diabetes mellitus, hypercholesterolemia, history of coronary heart disease in parents) without contraindications for the administration of aspirin (Grade IA).

   b. Females over 50 years of age with at least 1 risk factor (Grade 2C).

2. Stable angina pectoris

   Long-term aspirin is indicated for patients with stable angina pectoris (Grade 1A).

Table 2. GP IIb / IIIa Antagonists Trials

		Coronary Intervention Composite rate (%)*			
Trial	Drug	Drug	vs Placebo	P value	RR (%)**
EPIC	Abciximab	8.3	12.8	0.008	35
EPILOG	Abciximab	5.2	11.7	<0.001	56
CAPTURE	Abciximab	11.3	15.9	0.012	29
EPISTENT	Abciximab	5.3	10.8	<0.001	51
RESTORE	Tirofiban	8.0	10.5	0.052	24
IMPACT II	Eptifibatide	9.2	11.4	0.063	19
RAPPORT	Abciximab	5.8	11.2	0.038	48
ADMIRAL	Abciximab	10.7	20.0	0.03	47

* Composite rate of death, myocardial infarction and revascularisation at 30 days

3. Unstable angina pectoris without ST elevation
   a. Aspirin must be administered immediately and continued for long-term use (Grade 1A).
   b. Clopidogrel is administered to patients that cannot take aspirin due to allergy or severe gastrointestinal disturbance (IA).
   c. Patients scheduled for non-surgical treatment, clopidogrel is administered in addition to aspirin for at least 1 month (IA) or up to 9 months (IB).
   d. Patients scheduled for PCI are to receive clopidogrel immediately and continued for at least 1 month (IA) or up to 9 months (IB).
   e. GIIb/IIIa receptor antagonist is administered in addition to aspirin and heparin in patients scheduled for catheterization and PCI (Grade IA).
4. Acute myocardial infarct
   All patients with acute myocardiac infarct must immediately receive 165-325 mg chewed and continued as long-term treatment (Grade 1A).
5. Patients undergoing PCI
   a. Aspirin is administered 2 hours prior to PCI, continued as long-term treatment (Grade IA).
   b. Patients that cannot take aspirin are to receive 300 mg of clopidogrel loading dose followed by 75 mg daily for 14-30 days following PCI (Grade 1A) or 500 mg of Ticlopidine loading dose followed by 250 mg twice daily for 10-14 days following PCI (Grade 2A).
   c. Aspirin plus clopidogrel are to be administered to patients undergoing stent insertion.
   d. GIIb/IIIa receptor antagonist is to be given to patients undergoing PCI, particularly for unstable refractory angina or high risk patients (Grade IA).
6. Coronary arterial bypass graft (CABG)
   a. For patients undergoing saphenous vein bypass graft, 325 mg of aspirin is administered 6 hours after the operation, and continued for at least 1 year (Grade 1A). If the patient is allergic to aspirin, 300 mg of clopidogrel loading dose is administered 6 hours following the operation, continued to 75 mg daily (Grade 2C).
   b. Patients undergoing internal mammary graft are to receive aspirin following surgery (Grade 1A).

CONCLUSION

Aspirin and other anti-platelet agents are greatly beneficial for secondary prevention for patients with acute myocardiac infarct or acute ischemic stroke, unstable as well as stable angina, as well as those with history of infarct, stroke, or cerebral ischemia, and as well as those undergoing PCI. A dose of 75-150 mg of aspirin is quite effective. In acute conditions, 150 mg is required. Additional anti-platelets have additional effects. The use of aspirin for primary prevention is limited to high-risk patients. The new GIIb/IIIa receptor antagonist has promising effects for the prevention of ischemia in patients with acute coronary syndrome and those undergoing PCI.

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