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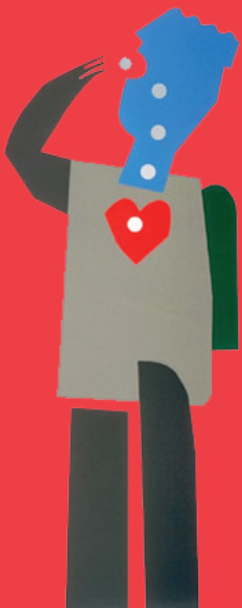
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COMMONLY USED ANTIPLATELET DRUGS

ASPIRIN :

Aspirin has been thoroughly evaluated as an antiplatelet drug, and it has been found to prevent vascular death by approximately 15% and to prevent nonfatal vascular events by about 30% in a meta-analysis of 100 randomized trials in high-risk patients.

MECHANISM OF ACTION OF ASPIRIN

Aspirin inactivates permanently the COX activity of prostaglandin (PG)H-synthase-1 and PGH-synthase-2 (also referred to as COX-1 and COX-2). These isozymes catalyze the first committed step in prostanoid biosynthesis (ie, the conversion of arachidonic acid to PGH₂). PGH₂ is the immediate precursor of PGD₂, PGE₂, PGF_{2α}, PGI₂ and thromboxane (TX)-A₂. Because aspirin has a short half-life (15 to 20 min) in the human circulation and is approximately 50-fold to 100-fold more potent in inhibiting platelet COX-1 than monocyte COX-2, it is ideally suited to act on anucleate platelets, inducing a permanent defect in TXA₂-dependent platelet function. Moreover, since aspirin probably also inactivates COX-1 in relatively mature megakaryocytes, and since only 10% of the platelet pool is replenished each day (as lifespan of platelet is 10 days), once-a-day dosing of aspirin is able to maintain virtually complete inhibition of platelet TXA₂ production. In contrast, the inhibition of COX-2-dependent pathophysiologic processes (eg, hyperalgesia and inflammation) requires larger doses of aspirin (because of decreased sensitivity of COX-2 to aspirin) and a much shorter dosing interval (because nucleated cells rapidly resynthesize the enzyme).

Human platelets and vascular endothelial cells process PGH₂ to produce primarily TXA₂ and prostacyclin (ie, PGI₂), respectively. TXA₂ induces platelet aggregation and vasoconstriction, while PGI₂ inhibits platelet aggregation and induces vasodilation. Aspirin is antithrombotic in a wide range of doses. While TXA₂ is largely a COX-1-derived product (mostly from platelets) and thus is highly sensitive to aspirin inhibition under

physiologic conditions, vascular PGI₂ can derive from both COX-1 (short-term changes in response to agonist stimulation [eg, bradykinin], which is sensitive to transient aspirin inhibition) and to a greater extent, even under physiologic conditions, from COX-2 (long-term changes in response to laminar shear stress, which is largely insensitive to aspirin inhibition at conventional antiplatelet doses). This may account for the substantial residual COX-2-dependent PGI₂ biosynthesis in vivo at daily doses of aspirin in the range of 30 to 100 mg, despite transient suppression of COX-1-dependent PGI₂ release.

PHARMACOKINETICS

Aspirin is rapidly absorbed in the stomach and upper intestine. Peak plasma levels occur 30 to 40 min after aspirin ingestion, and the inhibition of platelet function is evident by 1 h. In contrast, it can take up to 3 to 4 h to reach peak plasma levels after the administration of enteric-coated aspirin. If only enteric-coated tablets are available, and a rapid effect is required, the tablets should be chewed. The oral bioavailability of regular aspirin tablets is approximately 40 to 50% over a wide range of doses.

Because platelet COX-1 is acetylated in the presystemic circulation, the antiplatelet effect of aspirin is largely independent of systemic bioavailability.

THE OPTIMAL DOSE OF ASPIRIN

Well-designed randomized trials have shown that aspirin is an effective antithrombotic agent when used in doses ranging between 50 and 100 mg/d, and there has been a suggestion that it is effective in doses as low as 30 mg/d. Aspirin in a dose of 75 mg/d was shown to be effective in reducing the risk of acute myocardial infarction (MI) or death in patients with unstable angina and chronic stable angina, as well as in reducing the incidence of stroke or death in patients with transient cerebral ischemia and in reducing the number of postoperative strokes after carotid endarterectomy. In the European Stroke Prevention Study (ESPS)-2 trial, aspirin (25 mg twice daily) was effective in reducing the risks of stroke and of stroke or death in patients who had experienced prior stroke or transient ischemic attack (TIA). The lowest



effective dose of aspirin for these various indications is shown in Table 1. The clinical effectiveness of different doses of aspirin has been compared directly in a small number of randomized trials. In the United Kingdom-TIA study, no difference in efficacy was found between doses of 300 and 1,200 mg/d aspirin (see below). In a study of 3,131 patients after they had experienced a TIA or minor ischemic stroke, aspirin in a dose of 30 mg/d was compared with a dose of 283 mg/d, and the hazard ratio for the group receiving the lower dose was 0.91 (95% confidence interval [CI], 0.76 to 1.09). The Acetylsalicylic Acid and Carotid Endarterectomy trial reported that the risk of stroke, MI, or death within 3 months of undergoing a carotid endarterectomy is significantly lower for patients receiving 81 or 325 mg aspirin daily than for those receiving 650 or 1,300 mg (6.2% vs 8.4%, respectively; p 0.03).

The antithrombotic effects of a range of doses of aspirin also have been compared with an untreated control group in a number of thrombotic vascular disorders. The doses have varied between 50 and 1,500 mg/d. Aspirin has been shown to be effective treatment for patients with the following conditions: unstable angina in which the incidence of acute MI or death was significantly reduced to a similar degree in four separate studies using daily doses of 75 mg, 325 mg, 650 mg, and 1,300 mg; stable angina in which a dose of 75 mg daily reduced the incidence of acute MI or sudden death; aortocoronary bypass surgery in which the incidence of early occlusion was similarly reduced with daily doses of 100 mg, 325 mg, 975 mg and 1,200 mg; thromboprophylaxis of patients with prosthetic heart valves who also received warfarin in whom the incidence of systemic embolism was reduced with daily doses of 100 mg, 500 mg, and 1,500 mg; thromboprophylaxis of patients with arterial venous shunts undergoing long-term hemodialysis in whom a dose of 160 mg/d was shown to be effective; acute MI in which a dose of 162.5 mg/d reduced early mortality (ie, 35 day) as well as nonfatal reinfarction and stroke; transient cerebral ischemia in which doses between 50 and 1,200 mg/d were effective; and acute ischemic stroke in which doses of 160 to 300 mg/d were effective in reducing early mortality and stroke recurrence. Thus, aspirin is an effective antithrombotic agent in doses between 50 and

Table 1 - Vascular Disorders for Which Aspirin Has Been Shown to be Effective and Minimum Effective Dose

Disorder	Minimum Effective Daily Dose, mg
Men at high cardiovascular risk	75
Hypertension	75
Stable angina	75
Unstable angina*	75
Acute MI	160
TIA and ischemic stroke*	50
Severe carotid artery stenosis*	75
Acute ischemic stroke*	160

*Higher doses have been tested in other trials and not found to confer any greater risk reduction.

1,500 mg/d. It is also possible from the results of the Dutch TIA study that 30 mg/d is effective. There is no evidence that low doses (50 to 100 mg/d) are less effective than high doses (650 to 1,500 mg/d), and, in fact, the opposite may be true. The data from the Antithrombotic Trialists Collaboration overview are consistent with this conclusion (Table 2).

There is evidence, however, that doses of approximately 300 mg/d produce fewer GI side effects than those of approximately 1,200 mg/d. There is also some evidence that a dose of 30 mg/d produces fewer side effects than a dose of 283 mg/d. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) investigators have retrospectively investigated the relationship between the aspirin dose (CURE protocol recommendation, 75 to 325 mg daily) and the risk of major bleeding. In this trial bleeding risks increased with increasing aspirin dose, with or without clopidogrel, without any increase in efficacy.

Table 2 - Indirect Comparison of Aspirin Doses Reducing Vascular Events in High-Risk Patients*

Aspirin Dose, mg/d	Trials, No	Patients, No	Odds Reduction, † %
500-1500	34	22,451	19 ± 3
160-325	19	26,513	26 ± 3
75-150	12	6,776	32 ± 6

* Data are from Antithrombotic Trialists Collaboration.

† Values given as mean ± SD.

In summary, the results of biochemical studies on its mechanism of action, the lack of dose-response relationship in clinical studies evaluating its antithrombotic effects, and the dose dependence of its side effects all support the use of as low a dose of aspirin as has been found to be effective in the treatment of various thromboembolic disorders (Table 1). Use of the lowest effective dose of aspirin (ie, 50 to 100 mg daily for long-term treatment) is probably the most rational strategy to maximize its efficacy and to minimize its toxicity.

EFFECTS OF ASPIRIN NOT RELATED TO TXA₂

Aspirin has been reported to have effects on hemostasis that are unrelated to its ability to inactivate platelet COX-1. These effects include the dose-dependent inhibition of platelet function, the enhancement of fibrinolysis, and the suppression of plasma coagulation.

ASPIRIN RESISTANCE

The term aspirin resistance has been used to describe a number of different phenomena, including the inability of aspirin to accomplish the following: (1) to protect individuals from thrombotic complications; (2) to cause a prolongation of the bleeding time; (3) to reduce TXA₂ production; or (4) to produce an anticipated effect on one or more in vitro tests of platelet function.

Prevalence of aspirin resistance

Variability of platelet response has been shown with



aspirin, where as many as 43% of patients do not fully respond to therapy as measured by ex-vivo parameters like prolongation of bleeding time, platelet function tests, platelet aggregometry, and the surrogate marker urinary thromboxane.

Mechanism of aspirin resistance (Table-3)

Table - 3

Clinical factors	Cellular factors	Genetic factors
<ul style="list-style-type: none"> ● Failure to prescribe ● Non-compliance ● Non-absorption ● Interaction with ibuprofen ● Acute coronary syndrome ● Congestive heart failure ● Hyperglycaemia ● Catecholamine surge 	<ul style="list-style-type: none"> ● Insufficient suppression of COX- 1 ● Over-expression of COX-2 mRNA ● Erythrocyte-induced platelet activation ● Increased norepinephrine ● Generation of 8-iso-PGF₂ ● Resolvins 	<ul style="list-style-type: none"> ● COX-1 ● GP IIb/IIIa receptor polymorphism ● Collagen receptor polymorphism ● vWF receptor polymorphism ● P.Y, single nucleotide polymorphism

Consequences of aspirin resistance

Eikelboom et al. measured urinary 11-dehydro thromboxane B2 levels in patients on aspirin from the Heart Outcomes Prevention Evaluation (HOPE) study. Patients in the highest quartile of urinary 11-dehydro thromboxane B2 levels had a 1.8 times higher risk of myocardial infarction, stroke, or cardiovascular death than patients in the lowest quartile (P= 0.009). Gum et al. performed a randomized prospective trial of 326 patients on aspirin and no other anti-platelet agents. Aspirin sensitivity was tested by optical platelet aggregation, considered the gold standard in determining platelet response. Of those studies, 17(5%) patients were found to be aspirin-resistant and in follow-up had a nearly three-fold increased risk of death, myocardial infarction, or CVA (P= 0.03).

More recently, Chen et al. investigated the effect of aspirin resistance on myonecrosis after non-urgent percutaneous coronary intervention (PCI) among 151 patients pretreated with 300 mg of clopidogrel >12h prior to PCI and 75 mg the morning of the PCI. The point-of-care VerifyNow RPFA test was utilized to determine therapeutic responsiveness. Twenty-nine patients (19.2%) were found to be aspirin-resistant with an increased risk of myonecrosis (51.7% vs. 24.6% as assessed by troponin elevation, P= 0.006) following non-urgent PCI, despite pretreatment with aspirin.

Treating aspirin resistance

The treatment for failed antiplatelet therapy is as yet undefined. An initial approach would be to correct the clinical factors that may cause therapeutic resistance. Physicians must ensure proper patient compliance while also minimizing drug-drug interactions. In addition, optimal control of glucose levels and cholesterol levels can reduce platelet reactivity.

Currently, there is no good evidence that increasing aspirin dose would be useful. Data from Blockage of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial and the CURE trial actually indicate an

increased risk of serious bleeding associated with high aspirin doses. However, it remains possible, though unproven, that increased doses of aspirin may overcome aspirin resistance in an individual patient. The addition of clopidogrel to aspirin is logical given its distinct mechanism of action. The Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study revealed modest superiority of clopidogrel monotherapy over aspirin monotherapy, while also showing an increased benefit in high-risk patients. In terms of dual antiplatelet therapy, aspirin resistant patients have platelets that are more sensitive to ADP. The CURE and CREDO trials support this notion as they revealed the additive clinical benefit of clopidogrel to aspirin.

THE ANTITHROMBOTIC EFFECT OF ASPIRIN

Prevention of atherothrombosis in different clinical settings

The efficacy and safety of aspirin are documented from analysis of approximately 70 randomized clinical trials that included 115,000 patients who were at variable risk of thrombotic complications from atherosclerosis. In the Second International Study of Infarct Survival, a single tablet of aspirin, 162.5 mg, administered within 24 h of the onset of symptoms of a suspected MI and continued daily for 5 weeks produced highly significant reductions in the risk of vascular mortality (by 23%), nonfatal reinfarction (by 49%), and nonfatal stroke (by 46%). There was no increase in the risk of hemorrhagic stroke or GI bleeding in the aspirin-treated patients, and only a small increase in minor bleeding. The treatment of 1,000 patients with suspected acute MI with aspirin for 5 weeks will result in approximately 40 patients in whom a vascular event is prevented, with a proportional odds reduction of 30%.

Two separate trials with a similar protocol, the International Stroke Trial and the Chinese Acute Stroke Trial, tested the efficacy and safety of early aspirin use in patients with acute ischemic stroke. Approximately 40,000 patients were randomized within 48 h of the onset of symptoms to 2 to 4 weeks of daily aspirin therapy (300 and 160 mg, respectively) or placebo. An overview of the results of both trials suggests an absolute benefit of about 10 fewer deaths or nonfatal strokes per 1,000 patients in the first month of aspirin therapy plus an extra 10 patients per 1,000 who experienced a complete recovery. The proportional odds reduction in fatal or nonfatal vascular events is only 10% in this setting. Although the background risk of hemorrhagic stroke was threefold higher in the Chinese Acute Stroke Trial than in the International Stroke Trial, the small absolute increase in this risk associated with the early use of aspirin was similar in the two studies (an excess of 2 strokes per 1,000 patients).

Long-term aspirin therapy confers a conclusive net benefit on the risk of subsequent MI, stroke, or vascular death among subjects with an intermediate-to-high risk of vascular complications. These include patients with chronic stable angina, patients with prior MI, patients with unstable angina, and patients with TIA or minor stroke, as



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well as other high-risk categories.

In terms of absolute benefit, these protective effects of aspirin translate into avoidance of a major vascular event in 50 patients per 1,000 patients with unstable angina who had been treated for 6 months and in 36 patients per 1,000 patients with prior MI, stroke, or TIA who had been treated for approximately 30 months.

For patients with different manifestations of ischemic heart or brain disease, a widespread consensus exists in defining a rather narrow range of recommended daily doses (ie, 75 to 160 mg) for the prevention of MI, stroke, or vascular death. This is supported by separate trial data in patients who were randomized to treatment with low dose aspirin or placebo as well as by an overview of all antiplatelet trials showing no obvious dose dependence, from indirect comparisons, for the protective effects of aspirin (Table 2).

In terms of primary prevention, aspirin has been evaluated in six randomized trials. The Physicians Health Study showed a 44% risk reduction in first myocardial infarction among physicians treated with aspirin. The Thrombosis Prevention Trial (TPT) revealed the utility of aspirin in men at high-risk for coronary disease, whereas the Hypertension Optimal Treatment (HOT) trial demonstrated a 36% reduction of myocardial infarction in hypertensive patients treated with aspirin. The Primary Prevention Project (PPP) extended the findings of these trials by showing a 56% relative reduction in cardiovascular death in men and women with one or more major cardiovascular risk factors treated with aspirin. Interestingly, the underpowered British Doctors' Study found no significant benefit to aspirin therapy. A meta-analysis of these five trials evaluated a combined 55,580 patients and found a 32% relative risk reduction of having a first myocardial infarction in treated patients. The Women's Health Study randomized 39,876 females to low-dose aspirin therapy and showed no significant reduction in myocardial infarction though there was a significant relative risk reduction in total and ischaemic stroke. However, a subgroup analysis revealed a significant benefit in women older than 65 years of age.

ATRIAL FIBRILLATION

Moderate-dose warfarin alone (international normalized ratio [INR], 2.0 to 3.0) is very effective in reducing the risk of stroke in patients with nonvalvular atrial fibrillation. The effectiveness of aspirin therapy in doses between 75 and 325 mg has been compared with therapy with warfarin and placebo in three randomized trials of patients with nonvalvular atrial fibrillation. In one study, therapy with aspirin was significantly more effective than that with placebo, whereas in the other two studies there was a nonsignificant trend in favor of aspirin therapy. A pooled analysis of the three studies shows a reduction in relative risk (RR) of about 25% (range, 14 to 44%), which is in favor of therapy with aspirin over that with placebo. Aspirin therapy was significantly less effective than that with

warfarin in two studies on an intention-to-treat analysis, and in the third study with an efficacy analysis. Thus, therapy with aspirin appears to be effective in preventing stroke in patients with atrial fibrillation but is substantially less effective than therapy with warfarin. However, aspirin is less expensive, safer, and more convenient than warfarin, and may be considered for patients who are unable to receive anticoagulation therapy or those with lone atrial fibrillation who have a low risk of stroke.

DEEP VENOUS THROMBOSIS

The Pulmonary Embolism Prevention trial has established that aspirin is effective in preventing venous thromboembolism after surgery for hip fracture. Among the 13,356 patients with hip fracture, aspirin produced a 36% reduction in symptomatic deep venous thrombosis or pulmonary embolism (PE) [absolute risk reduction, 0.9%; p 0.0003]. A similar RR reduction in patients who were assigned to received aspirin was observed in patients who also received heparin. However, the indirect comparisons are supported by the results of three randomized studies in patients undergoing major orthopedic surgery comparing therapy with aspirin with either warfarin or a low-molecular-weight heparin. In all three studies, the incidence of venous thrombosis was significantly higher in the aspirin group.

PLACENTAL INSUFFICIENCY

The pathogenesis of preeclampsia and fetal growth retardation is related to reduced placental blood flow, which is believed to be caused by constriction and/or thrombosis of small placental arteries. The initial reports that low-dose aspirin therapy reduces the risk of severe low birth weight among newborns and the risk of cesarean section in mothers with pregnancy-induced hypertension led to the widespread use of prophylactic aspirin therapy to prevent preeclampsia. A systematic review of data from 39 trials in 30,000 women showed that antiplatelet therapy (mostly aspirin, 60 mg daily) is associated with a 15% decrease in the risk of preeclampsia. This effect was consistent, regardless of risk status (ie, moderate or high risk), dose of aspirin, or gestation at trial entry.

ADVERSE EFFECTS OF ASPIRIN

Aspirin does not cause a generalized bleeding abnormality unless it is given to patients with an underlying hemostatic defect, such as hemophilia, uremia, or that induced by anticoagulant therapy. Aspirin-induced impairment of primary hemostasis cannot be separated from its antithrombotic effect and is similar at all doses 75 mg/d.

The balance between preventing vascular occlusion and causing excess bleeding with aspirin depends critically on the absolute thrombotic risk vs hemorrhagic risk of the patient. Thus, in individuals who are at low risk for vascular occlusion (eg, 1% per year), a very small absolute benefit is offset by exposure of a large number of healthy subjects to undue bleeding complications. In contrast, in patients who are at high risk of cardiovascular or cerebrovascular complications (eg, 3% per year), the substantial absolute benefit of aspirin prophylaxis clearly



outweighs the risk. For example, the absolute excess of major bleeds (ie, those requiring transfusion) in patients who have experienced acute MI is approximately one hundred the absolute number of major vascular events avoided by aspirin therapy.

Hypertension often has been considered a contraindication to aspirin because of the concern that possible benefits in the prevention of cardiovascular events may be counterbalanced by an increased risk of cerebral bleeding. The results of the aspirin component of the HOT study are reassuring in this regard, since hypertensive patients whose BP was well-controlled were protected from MI by aspirin therapy without an increase in the number of cerebral hemorrhage or strokes.

Aspirin-induced GI toxicity, as detected in randomized clinical trials, appears to be dose-dependent in the range of 30 to 1,300 mg daily.

A case-control study with hospital and community control subjects has examined the risks of hospitalization for bleeding peptic ulcer associated with three different regimens of aspirin prophylaxis. ORs were raised for all doses of aspirin taken (75 mg: OR, 2.3; 95% CI, 1.2 to 4.4; 150 mg: OR, 3.2; 95% CI, 1.7 to 6.5; 300 mg: OR, 3.9; 95% CI, 2.5 to 6.3). Additional epidemiologic studies have found a dose-response relationship between aspirin prescription and upper GI complications, as reviewed by Garcya Rodrı́guez et al. Similarly, the incidence of major bleeding was 1.9%, 2.8%, and 3.7%, respectively, in patients with acute coronary syndromes who were prescribed doses of aspirin of \leq 100 mg, 101 mg to 199 mg, and 200 mg to 325 mg in the CURE Trial. It has been calculated that each year in England and Wales approximately 900 of the 10,000 episodes of ulcer bleeding occurring in people aged \geq 60 years could be associated with, and ascribed to, prophylactic aspirin use. A general change to lower doses of aspirin (ie, 75 mg) would not eliminate risks but would reduce risk by about 40% compared with doses of 300 mg and by 30% compared with doses of 150 mg, if the assumptions from indirect comparisons are correct. Given that the mortality rate among patients who are hospitalized for NSAID-induced upper GI bleeding is about 5 to 10%, 149 such a strategy could save a significant number of lives. absolute risk in an elderly population exposed to "primary" prevention.

The widely held belief that enteric-coated and buffered varieties of aspirin are less likely to occasion major upper GI bleeding than plain tablets was tested in data from a multicenter case-control study. The RRs of upper GI bleeding for plain, enteric-coated, and buffered aspirin at average daily doses of \leq 325 mg were 2.6, 2.7, and 3.1, respectively. Thus, physicians who recommend aspirin in an enteric-coated or buffered form should not assume that these formulations are less likely to cause GI tract bleeding than plain aspirin.

Suppressing acid secretion is thought to reduce the risk of ulcers associated with the regular use of NSAIDs.

Omeprazole is better than ranitidine in this respect. In high-risk patients (ie, those with a history of previous ulcer bleeding) receiving low-dose aspirin therapy for 6 months, omeprazole and *H.pylori* eradication were associated with similar rates of recurrent bleeding (0.9% vs 1.9%), although the small sample size of the study (250 patients) does not allow the exclusion of clinically important differences between the two preventive strategies.

In the overview of the Antithrombotic Trialists' Collaboration, the absolute excess of intracranial hemorrhage due to aspirin therapy is less than one hemorrhage per 1,000 patients per year in high-risk trials, with somewhat higher risks in patients with cerebrovascular disease.

Low-dose aspirin therapy has not been reported to affect renal function or BP control, which is consistent with its lack of effect on renal PGs that derive primarily from constitutively expressed COX-2 in the human kidney. Moreover, aspirin therapy, 75 mg daily, did not affect BP or the need for antihypertensive therapy in intensively treated hypertensive patients. The ACE Inhibitors Collaborative Group has carried out a systematic overview of data for 22,060 patients from six long-term randomized trials of ACE inhibitors to assess whether aspirin altered the effects of ACE inhibitor therapy on major clinical outcomes. Even though results from these analyses cannot rule out the possibility of some sort of interaction, they show unequivocally that even if aspirin is administered, the addition of ACE inhibitor therapy produced substantial additional benefit in all major vascular outcomes. Therefore, in the absence of clear contraindications, the concomitant use of aspirin and ACE inhibitors should be considered in all patients who are at high risk for major vascular events.

CLOPIDOGREL

Clopidogrel is one of the most widely used antiplatelet agents. Both clopidogrel and ticlopidine are thienopyridine analogs with similar structure and mechanism of action. In 1991, ticlopidine was the first thienopyridine approved in the United States, although its use has since been largely replaced by clopidogrel, which has a more favorable safety profile and more rapid maximal inhibition of platelet aggregation.

MECHANISM OF ACTION & PHARMACODYNAMICS

Clopidogrel is an inhibitor of platelet aggregation induced by adenosine diphosphate (ADP) that specifically and irreversibly inhibits the binding of ADP to the purinergic P2Y₁₂ receptor on the platelet surface. This action inhibits activation of the glycoprotein (GP) IIb/IIIa complex, thereby preventing fibrinogen binding to platelets. ADP-induced thromboxane A₂ generation in human platelets requires coordinated signaling through IIb/IIIa and ADP receptor activity. Clopidogrel is inactive in vitro and requires in vivo hepatic transformation to exhibit its antiaggregating activity. In the liver, clopidogrel is metabolized through a cytochrome P-dependent pathway



to form an intermediate metabolite (2-oxo-clopidogrel) that is hydrolyzed to generate the highly labile active metabolite. The reactive thiol group of the active metabolite of clopidogrel forms a disulfide bridge between one or more cysteine residues of the P2Y₁₂ receptor, resulting in irreversible modification at the ADP receptor site. Platelets exposed to the active metabolite are affected for the remainder of their lifespan, approximately 10 days. Thus, repeat daily dosing results in the cumulative inhibition of platelet function, a pharmacodynamic pattern similar to that of aspirin. The effects of clopidogrel are time and dose-dependent, with a single oral 400 mg dose producing an apparent ceiling effect in healthy volunteers of approximately 40% inhibition of platelet aggregation detectable 2 hours after dosing and remaining relatively stable as long as 48 hours. Repeat daily dosing of 75 mg (no loading dose) results in steady-state inhibition of platelet aggregation of approximately 50% to 60% after 4 to 7 days, whereas maximal inhibition of platelet aggregation is achieved within 4 to 24 hours with loading doses of 300 to 600 mg.

CLOPIDOGREL AS A THERAPEUTIC AGENT

The clinical efficacy of clopidogrel was assessed in a large, randomized, double-blind clinical trial (CAPRIE) that compared the regimen of clopidogrel (75 mg/d) to aspirin (325 mg/d) in the reduction of composite end points of fatal, nonfatal acute myocardial infarction (AMI) and ischemic stroke or vascular death with clinical follow-up of 1 to 3 years. Analysis revealed a significant 8.7% relative risk reduction of composite end points in patients treated with clopidogrel in comparison with aspirin.

Clopidogrel was again studied in 2001 in the Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE) study, a randomized, international, double-blind trial that investigated whether combination treatment with aspirin and clopidogrel for 3 to 12 months' duration would produce a benefit over aspirin alone in vascular outcomes in patients diagnosed with acute coronary syndrome without ST-segment elevation MI. Clopidogrel combined with aspirin was found to significantly reduce the risk of the first primary composite end point of nonfatal MI, stroke, and cardiovascular disease (9.3% vs. 11.4%), for a reduction of 20% compared with aspirin alone. Also, a significant risk reduction rate of 14% in the second primary composite of cardiovascular disease, stroke, nonfatal MI, and refractory ischemia was found. The superiority of the combined antiplatelet regimen also was observed for the secondary end points of severe ischemia, recurrent angina, revascularization procedures, and evidence of heart failure.

Clopidogrel also has proved useful in combination with aspirin for the prevention of subacute stent thrombosis after stenting. Large randomized clinical trials have demonstrated significantly better tolerance, less early treatment discontinuations, and fewer drug-related adverse events with the regimen of clopidogrel plus aspirin compared with that of ticlopidine plus aspirin after

coronary stenting. A recent meta-analysis of the major randomized trials and registries comparing clopidogrel and ticlopidine in coronary stenting concluded that clopidogrel plus aspirin should be the standard antiplatelet regimen after stent deployment.

Furthermore, in 2002, the Clopidogrel for the Reduction of Events During Observation (CREDO) trial demonstrated that long term (ie, 1 year) clopidogrel plus aspirin therapy can significantly reduce the risk of major vascular events after PCI compared with aspirin alone. A loading dose of clopidogrel given at least 3 hours before the procedure did not reduce events at 28 days, but recently a subgroup analysis of CREDO trial suggested that longer intervals (≥ 15 hrs) of pre treatment with clopidogrel achieved an approximately 58.6% relative risk reduction in incidence of 28-day death, MI, or urgent target vessel revascularization. In patients pre-treated for longer durations, the optimal duration seems to approach 24 h.□

In a recent analysis of the Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment (ISAR-REACT) trial, in which all patients received a 600-mg loading dose of clopidogrel between 2 and 24 h before PCI, no relationship was found between the duration of pre-treatment and clinical events. Although there was no clopidogrel-placebo arm in this study, these results suggest that unlike with a 300-mg loading dose, a 600-mg loading dose is able to achieve its maximal clinical benefit within 2 h. This faster onset of action of a 600-mg loading dose compared with 300 mg would help explain the lower event rates in a recent trial comparing these two loading regimens initiated 4 to 8 h before a PCI.

ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) Study showed that Pretreatment with a 600-mg loading dose of clopidogrel 4 to 8 hours before the procedure is safe and, as compared with the conventional 300-mg dose, significantly reduced periprocedural MI in patients undergoing percutaneous coronary intervention. These results may influence practice patterns with regard to antiplatelet therapy before percutaneous revascularization. The Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis (ALBION) trial demonstrated the clinical benefit of a 600 mg and 900 mg clopidogrel loading dose versus 300 mg without added toxicity. The Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect trial (ISAR-CHOICE) has been recently published and showed a greater and faster degree of platelet inhibition with a 600 mg versus a 300 mg loading dose of clopidogrel. On the other hand recent study published this year showed that in patients with stable angina pectoris, a 300-mg clopidogrel loading dose, when given immediately before PCI, is sufficient and 600 mg was clinically safe, it was not associated with fewer periprocedural events and improved 30-day outcomes compared with 300 mg. □□



Recently, it was shown in the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI 28) study that there was significant clinical benefit from adding clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction patients with ST-segment elevation, with an improved patency rate of the infarct-related artery and reduced ischemic complications. The CLARITY trial has now been complemented by the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT). In this mega trial, 45,000 patients with suspected myocardial infarction-ST segment changes or left bundle branch block were randomized to receive clopidogrel 75 mg daily without a loading dose or placebo. There was a 9% reduction in the composite end point of death, reinfarction, or stroke. Mortality was reduced by 7% and reinfarction by 13%, with no increase in major bleeding.

CLOPIDOGREL RESISTANCE

Like aspirin resistance in broad sense it may be define as the continued occurrence of ischaemic events despite adequate antiplatelet therapy and compliance. Several methods are available to measure platelet function and the effects of antiplatelet agents like clopidogrel, although none of these tests has been conclusively shown to predict the risk of future events in individual patients taking clopidogrel. The test most commonly used in studies is optical aggregometry, where platelet aggregation is measured by light transmittance in platelet-rich plasma in response to ADP and other inducers of platelet aggregation. Due to patient variability, results are often reported as a percentage of a baseline value. Clopidogrel nonresponse is commonly defined as a relative inhibition of ADP-induced platelet aggregation of 10%.

Prevalence of clopidogrel resistance^{III}

Variable platelet inhibition in response to clopidogrel has been well documented in numerous studies. Muller et al defined clopidogrel nonresponse as an inhibition of ADP (5 and 20 Mol/L)-induced platelet aggregation that was less than 10% of baseline values 4 hours after clopidogrel intake (600 mg single dose), semiresponse as an inhibition of 10% to 29%, and normal response as an inhibition greater than 30%. Using these definitions, the study found that 5% to 11% of the patients were nonresponders and 9% to 26% were semiresponders. All patients in this study were also taking 100 mg aspirin daily. Others studies have reported higher rates of nonresponse. Mobley et al. used the same definition for clopidogrel nonresponse and found a nonreponse rate of 30%.

Mechanisms of Clopidogrel Resistance (Table 4)

The potential for an unfavorable drug-drug interaction between clopidogrel and hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) that may contribute to the phenomenon of clopidogrel resistance has been the recent topic of debate. As both clopidogrel and several statins (atorvastatin, lovastatin, and simvastatin) are metabolized by CYP 3A4, the

Table 4 - Possible Mechanisms of Clopidogrel Resistance

1. Inadequate clopidogrel dosage
2. Noncompliance with therapy
3. Drug–drug interactions with some HMG CoA reductase inhibitors (eg, statins)
4. Polymorphisms of the P2Y₁₂ receptor
5. Interindividual differences in CYP 3A4 metabolic activity

antiplatelet effect of clopidogrel may be compromised by their coadministration. Lau et al. first described this interaction between clopidogrel and atorvastatin as a serendipitous finding while evaluating a new bedside platelet aggregometer. Analysis of the CREDO trial, found that this was not clinically significant and that the benefit of Clopidogrel was similar with all statins regardless of the metabolic mechanism. Other data, from the Plavix for Reduction of New Thrombotic Occurrences (PRONTO) study and the Interaction of Atorvastatin and Clopidogrel Study (Interaction) have shown that statins including atorvastatin do not interfere with platelet inhibition by Clopidogrel. Additional studies investigating the use of high-dose Clopidogrel (600 mg) with statins has shown a lack of interaction between the agents.

Consequence of clopidogrel resistance^{III}

Clopidogrel resistance has been studied in patients with acute myocardial infarction confirming the inter-individual variability of platelet inhibition by clopidogrel. Matetzky et al. analysed 60 patients with acute ST-segment myocardial infarction who underwent primary PCI and were subsequently placed on clopidogrel. Patients were divided into quartiles of responsiveness to clopidogrel measured by the percent reduction of ADP-induced platelet aggregation. The patients who were least responsive to therapy determined by aggregometry were 25% more likely to have a recurrent cardiovascular event during a 6-month follow-up when compared with patients in the other three quartiles of platelet responsiveness (P = 0.007). In addition, clopidogrel use post-PCI for stable angina has been evaluated, with a higher rate of subacute stent thrombosis found in clopidogrel non-responders.

Treating clopidogrel resistance

Consideration can be given to increasing maintenance doses or loading doses of clopidogrel (as evident from previously mentioned trials).

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Cardiology News

Bone Marrow Transplant Shows Lasting Benefit in Heart Disease

The final results of a phase I study of autologous bone marrow cell transplantation in patients with advanced heart disease show that the technique is safe and feasible. In addition, the procedure appears to improve symptoms and the benefits are sustained at the 1-year follow-up point. Patients in the study were classified as "no option." They were on maximal medical therapy, with refractory angina and myocardial ischemia, and were not candidates for surgery. Researchers injected 27 patients with nucleated bone marrow cells containing 2.2% CD34+ cells directed into infarcted heart muscle. The procedure was successful and caused no adverse events in any of the patients. At 3 months follow-up, Canadian Cardiovascular Society angina score, treadmill exercise duration and stress-induced ischemia scores also improved in the injected territories. Improvements were sustained at 1 year. Five patients were able to undergo revascularization.

Am J Cardiol 2006;97:823-829.

High Aldosterone Levels Tied to Resistant Hypertension

Patients with high plasma aldosterone, but who do not meet diagnostic criteria for primary aldosteronism, are more likely to have resistant hypertension than patients with low aldosterone levels. The clinical course of these patients is indistinguishable from that of hypertensives with clinically diagnosed IHA (Idiopathic High Aldosteronism). The data cast doubts on the diagnosis of IHA based on the currently accepted criteria and suggest that primary aldosteronism is part of a large continuum, spanning from low renin essential hypertension to adrenal hyperplasia. Thirty percent of hypertensive patients are treatment-resistant, meaning treatment with at least three classes of antihypertensive drugs has failed to bring their blood pressure below 140/90 mm Hg. The researchers analyzed 149 patients with aldosterone-renin-ratios (ARRs) of 25 (ng/dL)/(ng/ml/h) or greater and plasma aldosterone of 12 ng/dL or above. Results showed that the role of relative aldosterone excess in causing treatment resistance beyond classic primary aldosteronism, suggest the need of clinical trials with aldosterone antagonists, possibly with less antiandrogenic and antiprogesteronic effects than spironolactone, such as eplerenone, even in patients with high aldosterone levels but without confirmed primary aldosteronism.

Am J Hypertens 2006;19:373-379.

Phenotypic, Demographic Factors Affect Simvastatin Response

Whites, women, older individuals, and nonsmokers are more likely than others to experience significant lipid changes with statin therapy. Statins have been proven to be beneficial lipid-lowering drugs across all subgroups of at-risk persons, but their effectiveness in lowering LDL is affected by phenotypic and genetic characteristics. Data from 944 participants in the Cholesterol and Pharmacogenetics Study was examined. In a multivariate analysis, race/ethnicity, age, and smoking status were significant predictors of the LDL response to simvastatin. Compared with whites, African Americans had a 3-mg/dL smaller decrease in LDL cholesterol and a 1-mg/dL smaller increase in HDL cholesterol, and older participants had a more robust decline in LDL than did younger participants. Smokers had a 4-mg/dL smaller decrease in LDL compared with nonsmokers. The mean increase in HDL cholesterol was higher in women (2 mg/dL) than in men (1 mg/dL), the results indicate. The only factors independently associated with a change in triglyceride levels were waist circumference and smoking, with leaner participants and nonsmokers showing a more robust triglyceride lowering response with simvastatin.

Am J Cardiol 2006;97:843-850.

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Editorial Note

Dear Doctor

We are happy to present the 4th issue of "Insight Heart". It is a small endeavor to provide you compiled & updated information on cardiovascular diseases and its management. This issue is focused on "Commonly Used Antiplatelet Drugs". We will appreciate your thoughtful comments to enrich the publication.

Thanks and regards.

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