
ANTIPLATELET THERAPY

Oral antiplatelet therapy is the cornerstone of pharmacotherapy during percutaneous coronary intervention (Table 34.14). Aspirin alone (PTCA, laser, atherectomy) and aspirin plus clopidogrel (stents) are the standard regimens in the interventional setting.

A. ASPIRIN. Aspirin blocks the formation of prostaglandin endoperoxides and thromboxane A₂ by inhibiting prostaglandin G/H synthase and the cyclooxygenase pathway. This effect is transient in nucleated cells but is permanent for the life of anucleate platelets. Aspirin also exerts antiplatelet effects which are independent of its effects on thromboxane.^{83,84} Preprocedural aspirin reduces the risk of abrupt coronary occlusion by 50-75% and is standard therapy for all coronary interventional procedures.^{85,86} Other beneficial effects include prevention of coronary artery disease and stroke, improved outcome in chronic stable angina, unstable angina, and acute MI,⁸⁷⁻⁹² and maintenance of saphenous vein graft patency after coronary bypass surgery.⁹³ Aspirin increases the risk of bleeding complications^{94,95} and has no impact on restenosis.⁹⁶

1. Dosage. The optimal dose, timing, and duration of administration of aspirin are unknown, but it is customary to administer 325 mg at least one day before elective PTCA and continue it indefinitely. If urgent PTCA is required, 4 chewable baby aspirins (81 mg each) are given prior to the case. For the aspirin-allergic patient, clopidogrel (75 mg daily starting 3-5 days prior to intervention) can be substituted; dipyridamole, sulfapyrazone, and dextran have not been studied and are not routinely recommended. Patients with acute coronary syndromes may be resistant to aspirin,⁹⁷ but the impact of higher doses has not been studied. New slow-release oral and transdermal aspirin preparations may selectively inhibit platelet aggregation without inhibiting the synthesis of prostacyclin (PGI₂), which is a potent vasodilator and platelet inhibitor. Whether these preparations offer any advantage over conventional aspirin is unknown.

2. Limitations. Aspirin does not prevent platelet aggregation caused by thrombin, catecholamines, ADP, serotonin, or shear-stress. These deficiencies may partially explain persistent thrombin generation and platelet activation in some patients despite “therapeutic” aspirin and heparin; unfortunately, these prothrombotic conditions are difficult to detect in routine clinical settings. Recent studies also suggest that 8-12% of patients with coronary artery disease may be unresponsive to the antiplatelet effects of aspirin;⁹⁸⁻¹⁰⁰ bedside platelet function testing may soon facilitate the identification of such aspirin nonresponders.

B. TICLOPIDINE. Ticlopidine is a thienopyridine that blocks ADP-induced platelet activation by interfering with the signaling between the low-affinity platelet ADP receptor (P2T) and the subsequent processes of platelet activation, including activation of the platelet glycoprotein (GP) IIb/IIIa receptor.¹⁰¹⁻¹⁰³ Ticlopidine inhibits platelet aggregation in response to collagen, thrombin, and shear-stress by inhibiting ADP amplification mechanisms for platelet activation;¹⁰⁴ it also enhances the antiaggregatory effects of prostacyclin¹⁰⁵ and promotes deaggregation of thrombin-activated platelets.¹⁰⁶

Thienopyridines such as ticlopidine and clopidogrel are much more effective than aspirin in inhibiting shear-induced platelet activation, an important mechanism for endovascular thrombosis in coronary artery disease. In a randomized PTCA trial, ticlopidine (250 mg BID) resulted in fewer ischemic complications than aspirin plus dipyridamole (2% vs. 5%).⁹⁶ Several other trials have demonstrated superiority of aspirin plus ticlopidine vs. aspirin plus warfarin in reducing ischemic and hemorrhagic complications after stenting (STARS,¹⁰⁷ ISAR,^{108,109} FANTASTIC,¹¹⁰ MATTIS¹¹¹) (Chapter 26). Ticlopidine has also been shown to reduce the risk of death and nonfatal MI in unstable angina,¹¹² prevent stroke in patients with TIAs,¹¹³ and has been used for aspirin-allergic or intolerant patients. In patients with coronary artery disease, the combination of aspirin (50 mg/day) plus ticlopidine (250 mg twice daily) demonstrated synergistic platelet inhibition.¹¹⁴

- 1. Dosage.** Ticlopidine should be administered at a dose of 250 mg PO BID for at least 3 days prior to intervention to maximize antiplatelet effect. Onset of action is 48-72 hours, and full antiplatelet effects are evident in 5-7 days. An oral loading dose of 500 mg PO BID for 48 hours may accelerate antiplatelet effects¹¹⁵ and confer some benefit in emergency situations. After ticlopidine is stopped, the antiplatelet effects subside over 1-2 weeks.¹⁰⁶ Although ticlopidine was routinely administered for 2-4 weeks after stenting, the benefit of therapy beyond 2 weeks has been questioned.¹¹⁶
- 2. Limitations.** An important side effect of ticlopidine is reversible neutropenia, which occurs in 0.5-2% of patients after 4 weeks of use,^{117,118} complete blood counts are recommended every 2-4 weeks during the first few months of therapy. Sporadic cases of thrombotic thrombocytopenic purpura (TTP) have also been reported, with an estimated incidence of 0.02%; most cases occur in the third or fourth week of therapy (Chapter 25). Nausea, vomiting, and diarrhea are common and can be minimized by taking ticlopidine with food; skin rash and elevated transaminases are rare. Long-term administration of ticlopidine lowers plasma fibrinogen and increases cholesterol, but the clinical consequences of these effects are unknown.

C. CLOPIDOGREL. Clopidogrel is another thienopyridine derivative, analogous to ticlopidine,¹¹⁹ which blocks ADP-induced platelet activation by irreversibly modifying the platelet ADP receptor. Compared to ticlopidine, clopidogrel has a longer duration of action, a faster onset of action, and is associated with fewer adverse hematologic effects.¹¹⁹⁻¹²² In more than 19,000 patients randomized to clopidogrel vs. aspirin in CAPRIE,¹²² there was no difference in neutropenia. In the randomized CLASSICS trial of 1020 patients undergoing elective stenting,¹²³ clopidogrel was better tolerated than ticlopidine without compromising clinical efficacy (Chapter 26). Clopidogrel has largely replaced ticlopidine in the United States because of its superior safety profile. The combined use of aspirin plus clopidogrel vs. aspirin alone for acute coronary syndromes was recently evaluated in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial.²²⁹ In this study, 12,562 patients with unstable angina or non-Q-wave MI were randomized to aspirin (75-325 mg/day) alone or aspirin plus clopidogrel (300 mg loading dose followed by 75 mg/day) for 3-12 months (average 9 months). Patients treated with IIb/IIIa inhibitors within 3 days or revascularization within 3 months were excluded from this study. As shown in Table 34.32 (below), clopidogrel resulted in a highly significant 20% relative reduction in the primary composite endpoint of cardiovascular death, MI, or stroke (9.3% vs. 11.5%, $p = 0.00005$). Benefits were evident within the first 30 days, and increased further beyond 30 days, demonstrating the

importance of long-term therapy. Although there was a 1% absolute increase in major bleeding with clopidogrel, these cases were effectively managed by blood transfusions, and there was no increase in fatal bleeding. These compelling data suggest that patients with acute coronary syndromes should be considered for antiplatelet therapy with aspirin plus clopidogrel.

- 1. Dosage.** The oral dose of clopidogrel is 75 mg daily; full antiplatelet effect is achieved in 5 days. A loading dose of 300 mg was employed in CLASSICS, CREDO, and CURE, and a 375 mg loading dose produced 60% inhibition of ADP-induced platelet aggregation in normal volunteers.¹²⁴ Higher loading doses may produce more rapid platelet inhibition. The ongoing CREDO trial will define the ideal dose and duration of clopidogrel when used with aspirin following stent implantation.
- 2. Limitations.** Clopidogrel may be better tolerated than aspirin. The most frequent side effects¹²² include purpura (5%), diarrhea (4%), rash (4%), and pruritus (3%). Clopidogrel is not associated with an increased risk of neutropenia, so routine hematologic monitoring is not necessary for patients on chronic therapy. A recent report¹²⁵ documented 11 cases of suspected TTP among 3 million patients exposed to clopidogrel, although the incidence of TTP is substantially lower than that associated with ticlopidine.¹²⁶ Some patients on combined aspirin and clopidogrel therapy may develop severe platelet inhibition, which could be clinically important if CABG is needed; the rapid platelet aggregation assay can be used to assess the degree of antiplatelet activity in this instance. Clopidogrel is metabolized in the liver but has little impact on hepatic enzyme induction or drug metabolism. Although clopidogrel may interfere with metabolism of fluvastatin, the significance of this interaction is unknown. Caution is recommended when clopidogrel is used in combination with nonsteroidal anti-inflammatory drugs or warfarin due to the increased risk of bleeding.

Table 34.32. Combination Antiplatelet Therapy for ACS: Results of the CURE Trial²²⁹

Endpoint	Aspirin (n = 6303)	Aspirin + Clopidogrel (n = 6259)	Risk Ratio	p-Value
CV death, MI, stroke (%)*	11.5	9.3	0.80	0.00005
CV death, MI, stroke, refractory ischemia (%)	19.0	16.7	0.88	0.0004
Major bleeding (%)	2.7	3.6	1.34	0.003
Minor bleeding (%)	8.6	15.3	1.78	< 0.001

Abbreviations: ACS = acute coronary syndromes; CURE = Clopidogrel in Unstable angina to prevent Recurrent Events; CV = cardiovascular; MI = myocardial infarction

* Primary endpoint

- D. DIPYRIDAMOLE.** Dipyridamole increases platelet cAMP and causes direct release of prostacyclin from the endothelium, but its antiplatelet mechanism of action is incompletely understood. Dipyridamole has a half-life of 10 days and is primarily metabolized by the liver and excreted in the bile. When used in conjunction with aspirin, dipyridamole enhances platelet survival in patients with venous and arterial thrombosis, prosthetic valves, and prosthetic grafts. In ESPS-II,¹²⁷ high-dose dipyridamole plus low-dose aspirin (50 mg/d) was superior to aspirin alone in preventing recurrent ischemic events following stroke or TIA, but acceptance of this regimen has been hampered by prior negative studies in the same clinical scenario. In PTCA patients, two studies of parenteral dipyridamole plus aspirin reported fewer ischemic complications compared to aspirin alone,^{128,129} but a randomized trial of oral dipyridamole failed to demonstrate benefit.¹³⁰ At the present time, dipyridamole is not routinely recommended for coronary intervention. The usual oral dose of dipyridamole is 75 mg BID for 6 months. Side effects include exacerbation of angina, headaches, hypertension, hypotension, and tachycardia. Concurrent administration with aspirin increases the risk of GI bleeding.
- E. DEXTRAN.** Dextran is rarely used today in interventional cardiology. Despite its theoretical benefits, there is no proven benefit compared to placebo. Serious adverse effects include anaphylaxis, hypotension, and pulmonary hemorrhage.
- F. OTHER ANTIPLATELET INHIBITORS.** Other promising agents under investigation include thromboxane receptor and synthetase antagonists (Ridogrel), serotonin antagonists (Ketanserin), prostacyclin analogues (Ciprostene), intravenous ADP receptor antagonists, platelet glycoprotein Ib receptor antagonists, and other GP IIb/IIIa inhibitors.

Table 34.14. Major Trials of Oral Antiplatelet Therapy for Coronary Intervention

Study	Drug	Setting	Endpoint	Results
Ticlopidine trial ²⁰¹ (n = 337)	Placebo ASA/dipyridamole Ticlopidine	PTCA	Ischemic complications; restenosis	Ischemic complications (14% vs. 4% vs. 3%); no effect on restenosis
STARS ¹⁰⁷ (n = 1653)	ASA Warfarin + ASA Ticlopidine + ASA	Stent	Death, MI, TVR, or thrombosis at 30 days	Ischemic complications (3.6% vs. 2.8% vs. 0.5%, p = 0.001)
ISAR ^{109,188} (n = 517)	Warfarin + ASA Ticlopidine + ASA	High-risk stent	Cardiac death, MI, TVR at 30 days	Ischemic complications (6.2% vs. 1.6%, p < 0.01)
FANTASTIC ¹¹⁰ (n = 236)	Warfarin + ASA Ticlopidine + ASA	Elective and nonelective stent (Wiktor)	Bleeding; clinical events (death, MI, occlusion at 6 months)	Bleeding (21% vs. 13.5%, p = 0.03); clinical events (15.5% vs. 12.9%, p = NS)
MATTIS ¹¹¹ (n = 350)	Warfarin + ASA Ticlopidine + ASA	High-risk stent	Death, MI, or TVR at 30 days	Ischemic complications (11% vs. 5.6%, p = 0.07)
Albiero ²⁰² (n = 801)	ASA Ticlopidine + ASA	Successful optimized stent (usually with IVUS)	Stent thrombosis, major adverse clinical events	Stent thrombosis (1.9% vs. 1.9%); MACE (1.9% vs. 1.9%)
Moussa ²⁰³ (n = 1489)	ASA + ticlopidine ASA + clopidogrel (not randomized)	Stent	Clinical events; drug side effects	Clinical events (1.5% vs. 1.4%); drug side effects (10.6% vs. 0.3%, p = 0.006)
CLASSICS ¹²³ (n = 1020)	ASA+ ticlopidine ASA + clopidogrel ASA + clopidogrel (loaded)	Stent	1°: Safety (bleeding, neutropenia, thrombocytopenia, early drug D/C) 2°: Clinical events (death, MI, TVR at 6 months)	Safety (9.1% vs. 6.3% vs. 2.9% p = 0.005); clinical events (0.9% vs. 1.5% vs. 1.2%, p = NS)
CREDO	ASA + clopidogrel ASA + clopidogrel (loaded) Short- vs. long-term therapy	Stent	Clinical events	[Ongoing]

Abbreviations: ASA = aspirin; IVUS = intravascular ultrasound; MACE = major adverse cardiac events; MI = myocardial infarction; TVR = target vessel revascularization

Acronyms: See Table 34.31, p. 803