Use of oral antiplatelet agents in acute coronary syndromes

Dharam J. Kumbhani[1], Deepak L. Bhatt[2]

[1]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH, USA
[2]Department of Cardiology, VA Boston Healthcare System, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

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Corresponding author:
Deepak L Bhatt, MD, FACC, FSCAI, FESC, FACP
Cardiology, VA Boston Healthcare System
Integrated Interventional Cardiovascular Program
Brigham and Women's Hospital and the VA Boston Healthcare System
Senior Investigator
TIMI Study Group
Harvard Medical School
Boston, MA 02115, USA
Phone: 857-203-6840
Fax: 857-203-5550
E-mail: dlbhattmd@alum.mit.edu

Abstract

Platelets play a central role in the pathophysiology of acute coronary syndromes. Based on a large body of evidence from clinical trials, antiplatelet agents have become the mainstay in the management of these patients. This review details oral antiplatelet agents currently in use in acute coronary syndromes, their mechanisms of action, as well as current recommendations regarding their use. Antiplatelet drug resistance, an increasingly recognized problem, is also discussed. Finally, novel antiplatelet agents that have shown promising results in initial studies are also briefly discussed.

Key words: acute coronary syndromes, antiplatelet therapy, drugs, aspirin, thrombosis.

Introduction

Acute coronary syndromes (ACS) include unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI), and are a major source of mortality and morbidity in the general population, accounting for more than 1.4 million hospitalizations annually in the United States alone [1]. Platelet activation and aggregation plays a pivotal role in the pathophysiology of ACS, and antiplatelet agents are one of the cornerstones in the management of these patients. Indeed, the Antithrombotic Trialists' collaborative meta-analysis of 19,288 patients with acute coronary syndromes from 15 clinical trials demonstrated that one month of antiplatelet therapy resulted in 38 fewer serious vascular events per 1,000 treated patients, including 13 fewer non-fatal myocardial infarctions ($p < 0.0001$), 23 fewer vascular deaths ($p < 0.0001$), and 2 fewer strokes ($p = 0.02$) per 1,000 treated patients [2].

Pathophysiology

The primary mechanism for the development of acute coronary syndromes appears to be fissuring or rupturing of an atherosclerotic plaque, with subsequent thrombus formation, with resultant reduction or complete obliteration of epicardial coronary blood flow. Following the initial arterial injury, there is near-instantaneous deposition of platelets, with adherence of platelets to the subendothelial collagen. This is mediated primarily by the von Willebrand factor (vWF) [3, 4]. The platelet glycoprotein

(GP) Ib/IX receptor binds vWF and is the initial protein involved in the initial contact between platelets and the vessel wall [5]. Following adhesion, platelet activation occurs, with release of platelet contents including serotonin, adenosine diphosphate (ADP), and thromboxane A2, which are capable of activating further platelets. Further platelet recruitment and aggregation depends on the expression of a second platelet receptor, the GP IIb/IIIa receptor complex. The GP IIb/IIIa receptor has to be first converted from an "inactive" conformation to an "active" conformation, which is influenced by several agonists, including ADP, thrombin, vWF, fibrinogen, and a host of other adhesive proteins in the extracellular matrix including collagen [3, 6]. ADP in particular exerts its influence on platelets by at least three separate receptors, including $P2Y_{12}$ (inhibits adenylylcyclase and induced platelet aggregation), $P2Y_1$ (mediates mobilization of calcium from intracellular stores and change in platelet shape), and a third ligand-gated ion channel (permits rapid calcium influx into platelets) [7]. The activated GP IIb/IIIa receptor complex then avidly binds multivalent ligands including vWF and soluble fibrinogen, and cross-links nearby activated platelets [8]. In addition, conversion of fibrinogen to insoluble fibrin by generated thrombin consolidates and stabilizes the platelet-rich thrombus.

Antiplatelet agents

Currently available antiplatelet agents include aspirin, thienopyridines, GP IIb/IIIa inhibitors, and others such as cilostazol and dipyridamole. Several newer agents are also currently being investigated (Table I). While a number of oral GP IIb/IIIa inhibitors have been investigated in ACS, only intravenous preparations are approved for use in the United States as of today, owing to a lack of demonstrable efficacy and a higher risk of bleeding with oral agents [9]. For the purpose of this article, we will restrict our discussion to oral antiplatelet agents only in acute coronary syndromes.

Aspirin

Aspirin, or acetyl salicylic acid (ASA), is the most widely used and cost-effective drug in the prevention of platelet aggregation. It exerts its antiplatelet action mainly by irreversibly acetylating a serine residue of platelet cyclo-oxygenase (COX)-1 [10], thus inhibiting the formation of thromboxane A2, which is a potent stimulator of platelets. Data regarding the utility of aspirin in STEMI was first outlined by the Second International Study of Infarct Survival (ISIS-2) trial, in which aspirin 160 mg daily was associated with a 23% significant reduction in mortality five weeks after MI, compared with placebo [11]. Similarly, aspirin 324 mg daily was associated with a significant 51% reduction in mortality compared with placebo in patients presenting with NSTEMI in the VA Cooperative study [12].

Current ACC/AHA recommendations

In order to ensure rapid and complete inhibition of thromboxane mediated platelet aggregation, a loading dose of 162 mg (class I, level of evidence: A) to 325 mg (class I, level of evidence: C) of aspirin is currently recommended in all patients presenting with ACS [2, 13-15]. Current guidelines also recommend the use of 75 to 162 mg of aspirin daily lifelong thereafter for long-term prevention of serious vascular events in these patients (class I, level of evidence: A). This dose achieves an efficacy that is comparable to higher doses, but without a significant increase in bleeding or gastro-intestinal toxicity [2, 14, 15].

Thienopyridines

Thienopyridines exert their antiplatelet effects by irreversibly blocking the $P2Y_{12}$ receptor, thereby inhibiting platelet activation through ADP, and thus limit ADP-mediated conversion of glycoprotein IIb/IIIa to its active form [3, 6, 7]. Although some studies have demonstrated an incremental benefit of thienopyridine monotherapy over aspirin alone, dual therapy with aspirin and a thienopyridine is highly efficacious in ACS, especially in reducing the incidence of stent thrombosis, and is one of the mainstays in the management of these patients.

Table I. Classes of oral antiplatelet agents

1) Thromboxane A2 inhibitors: • Aspirin
2) Thienopyridines (irreversibly platelet $P2Y_{12}$ receptor inhibitor): • Clopidogrel • Ticlopidine • Prasugrel (awaiting FDA approval)
3) Glycoprotein IIb/IIIa inhibitors: • Sibrafiban (failed to show benefit)
4) Phosphodiesterase inhibitors: • Cilostazol (data unavailable) • Dipyridamole (data unavailable)
5) Newer agents (awaiting further data): • Reversible $P2Y_{12}$ receptor inhibitors: o Ticagrelor (AZD6140) o PRT060128 • Thrombin receptor antagonists: o SCH 530348 o E5555 • Miscellaneous: o NCX-4016 (aspirin + NO) o S18886 (direct thromboxane receptor antagonist) o CTRP (C1qTNF-related protein)-1 (collagen /platelet adhesion inhibitor)

Currently, clopidogrel is the most widely used thienopyridine.

Clopidogrel

Clopidogrel is a prodrug, and is converted to its active metabolite, a carboxylic acid derivative, SR 26334, in the liver [16]. The benefit of clopidogrel in non-ST-elevation acute coronary syndromes was demonstrated in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, in which 300 mg of clopidogrel as a loading dose, followed by 75 mg daily in addition to aspirin 75-325 mg daily was associated with a significant 20% reduction in the incidence of nonfatal myocardial infarction (MI), stroke or cardiovascular death, and a 23% reduction in the incidence of MI, compared with placebo, over a mean duration of follow-up of 9 months. Clopidogrel was however associated with a 38% higher risk of major bleeding [17]. Similarly, the benefit of clopidogrel in patients presenting within 12 h of STEMI was demonstrated in the Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 trial, in which 300 mg of clopidogrel as a loading dose, followed by 75 mg daily in addition to aspirin 75-162 mg daily was associated with a significant 36% reduction in the incidence of death, recurrent MI or TIMI flow grade of 0 or 1 on angiography, compared with placebo. The largest benefit was noted in the rate of an occluded infarct-related artery (41% reduction), and there was also a trend towards a reduction in the incidence of recurrent MI ($p = 0.08$). While both major and minor bleeding seemed higher with clopidogrel, this difference was not statistically significant [18]. Subsequent studies have confirmed the utility of clopidogrel in acute coronary syndromes [19].

Some uncertainty exists about the optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg [17-19]. Platelet inhibition studies indicate that the incidence of clopidogrel hypo- or non-responsiveness may be as high as 27-30% with this dose, and higher oral loading doses such as 600 or 900 mg of clopidogrel which inhibit platelet aggregation more rapidly and achieve a higher absolute level of inhibition of platelet aggregation may be beneficial in clopidogrel naïve patients [20-22]. Moreover, recent data seems to indicate that even in patients with acute coronary syndromes who are already on clopidogrel, reloading with 900 mg of clopidogrel achieves significantly higher platelet inhibition than 300 mg or 600 mg [22]. However, the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established but is being studied in a large ongoing ACS trial which is comparing the 600 mg and 300 mg loading doses.

Current ACC/AHA recommendations

ST-elevation myocardial infarction

In patients presenting with STEMI who have undergone diagnostic cardiac catheterization and for whom PCI is planned, current guidelines recommend the initiation and continuation of clopidogrel for at least 1 month after bare metal stent implantation, for several months after drug-eluting stent implantation (3 months for sirolimus, 6 months for paclitaxel), and for up to 12 months in patients who are not at high risk for bleeding (class I, level of evidence: B) [14]. Given an increased risk of late stent thrombosis with drug-eluting stents [23], future guidelines will likely mirror current practice, where clopidogrel is continued for at least 1 year following drug-eluting stent implantation. Current STEMI guidelines also recommend the addition of clopidogrel 75 mg daily to aspirin in patients with STEMI even if they do not undergo primary PCI (class I, level of evidence: A), for a period of at least 14 days (class I, level of evidence: B) or up to 1 year (class IIa, level of evidence: C). In addition, patients who are intolerant to aspirin should receive a thienopyridine, preferably clopidogrel 300 mg as a bolus followed by 75 mg daily indefinitely (class I, level of evidence: C) [14].

Non-ST-elevation acute coronary syndromes

For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography ("upstream" use) with either clopidogrel (loading dose followed by daily maintenance dose) or an intravenous GP IIb/IIIa inhibitor (class I, level of evidence: A). In patients undergoing PCI, the preferred loading dose of clopidogrel is 600 mg. Guidelines regarding the optimal duration of clopidogrel therapy post-PCI are same as for STEMI. For UA/NSTEMI patients in whom an initial conservative strategy is selected, clopidogrel loading dose followed by daily maintenance dose should be added to ASA and anticoagulant therapy as soon as possible after admission and administered for at least 1 month (class I, level of evidence: A) and ideally up to 1 year (class I, level of evidence: B) [15].

Prasugrel

Despite the remarkable benefit noted with clopidogrel in patients with acute coronary syndromes, considerable individual variability of response exists, and suboptimal platelet inhibition may occur in as many as 30% of patients, which has been associated with stent thrombosis and adverse cardiovascular events [24, 25]. Prasugrel is a newer generation thienopyridine that, like clopi-

dogrel, is a prodrug that gets converted to an active metabolite *in vivo*. However, it results in more complete platelet inhibition than clopidogrel, with significantly less variation in individual response [24]. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, prasugrel 60 mg loading dose followed by 10 mg daily was associated with a 24% reduction in nonfatal MI, a 34% reduction in urgent target-vessel revascularization (TVR), and a 52% reduction in stent thrombosis, compared with 300 mg loading dose followed by 75 mg daily of clopidogrel in patients presenting with acute coronary syndromes. Life-threatening bleeding was 52% more likely with prasugrel compared with clopidogrel, and the bleeding risk increased in elderly patients, patients with history of cerebrovascular disease, and body weight < 60 kg [26].

Current ACC/AHA recommendations

Prasugrel is currently undergoing FDA review, and is likely to figure prominently in future acute coronary syndrome management guidelines.

Ticlopidine

Ticlopidine is also converted to an active metabolite *in vivo*. Data from as early as 1990 demonstrated that ticlopidine 250 mg twice daily was associated with a 46% reduction in nonfatal MI, and a 47% reduction in vascular mortality in patients with unstable angina, compared with conventional therapy [27]. However, the association of ticlopidine with neutropenia, often severe (reported rate of occurrence is 2.4% for neutrophils $< 1.2 \times 10^9$/l and 0.8% for neutrophils $< 0.45 \times 10^9$/l), and its comparative expense, have led to a virtual abandonment of this therapy as an alternative to aspirin in most situations. Moreover, ticlopidine has also been associated with a variety of other hematological dyscrasias, such as thrombocytopenia, aplastic anemia, and thrombotic thrombocytopenic purpura [28].

Current ACC/AHA recommendations

Given its significant toxicities, ticlopidine is current recommended only in patients who are allergic to clopidogrel or aspirin (in the absence of contraindications) [14, 15].

Cilostazol

Cilostazol exerts its antiplatelet action by selective antagonism of the phosphodiesterase (PDE) 3A enzyme. In addition, it also inhibits the uptake of adenosine, and has been shown to inhibit platelet aggregation. Most, if not all, of its actions are mediated by cyclic adenosine monophosphate (cAMP) [29]. Although its efficacy has been demonstrated in preventing restenosis following PCI in some small studies [30], similar studies in ACS are lacking at this point, and cilostazol is not currently approved for use in this situation.

Dipyridamole

Dipyridamole has a number of different actions on platelets, and has been primarily used in patients with ischemic strokes in combination with aspirin [31]. Its most important action is probably to inhibit the cyclic guanosine monophosphate (cGMP) PDE V enzyme, thereby enhancing the antiplatelet effects of the NO/cyclic GMP signaling pathway [32]. It is also known to inhibit adenosine uptake, and has the ability to increase the release of prostanoids from the endothelium [33]. Its efficacy in secondary prevention in post-MI patients is doubtful [34, 35], and it is currently not approved for use in ACS.

Antiplatelet drug resistance

Antiplatelet drug resistance refers to the development of a thrombotic event while on antiplatelet agents due to ineffective or incomplete platelet inhibition. Low levels of platelet inhibition have also been associated with an elevated risk of ischemic events [36]. Although probably best characterized for aspirin, "resistance" or "hyporesponsiveness" has been described for clopidogrel and GP IIb/IIIa inhibitors [37].

While "resistance" may in fact result from patient non-compliance, a number of mechanisms for true antiplatelet resistance have been elucidated. Patients with diabetes and obesity may be more likely to develop clopidogrel resistance, possibly due to elevated plasma fibrinogen [38, 39]. Other well-described mechanisms include incomplete suppression of thromboxane A2 generation with aspirin, accelerated turnover with introduction of newly formed, drug-unaffected platelets into the bloodstream, increased platelet sensitivity to collagen and ADP, and stress-induced COX-2 generation in platelets. Interference from other medications such as atorvastatin causing a decrease in bioavailability, or poor absorption of enteric-coated aspirin in certain patients can also contribute to antiplatelet resistance. In addition, single nucleotide polymorphisms conferring resistance to antiplatelet agents have also been described. For example, the $P2Y_{12}$ H2 haplotype has been shown to be associated with thienopyridine resistance [37, 40].

Although not currently recommended for routine use, a number of platelet function tests are being evaluated [37, 39], and some assays have demonstrated exciting clinical results. In a recent randomized clinical trial, Bonello *et al.* demonstrated

the utility of using vasodilator-stimulated phosphoprotein (VASP) phosphorylation analysis in patients undergoing PCI. Almost 50% of eligible patients receiving 600 mg of clopidogrel as a loading dose had clopidogrel hyporesponsivess, as defined by a VASP index of > 50%. Patients in the VASP-guided group received additional loading doses of clopidogrel (as high as 2,400 mg of clopidogrel) to reduce the VASP index below 50%, with a significantly lower incidence of major adverse cardiac events (MACE) at 30 days, compared with the conventional therapy group. Major and minor bleeding was similar [41]. Further large scale randomized studies of this and other assays will help clarify their role in routine medical practice.

Newer oral antiplatelet agents

A number of novel antiplatelet agents with different mechanisms of action are being investigated, and are in various stages of development. Several agents have already shown promising results in initial studies, and the future of antiplatelet agents seems to be bright as our understanding of platelet biology and interactions evolves.

Ticagrelor (AZD6140)

AZD6140 is the first of a new class of orally active non-thienopyridines, the cyclopentyltriazolopyrimidines [42]. It binds to the platelet ADP ($P2Y_{12}$) receptor in a reversible manner. In the Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST-segment Elevation myocardial infarction-2 (DISPERSE-2), AZD6140 270 mg loading dose followed by 90 mg twice daily, and 180 mg twice daily achieved significantly better inhibition of platelet activity (IPA) than clopidogrel 300 mg followed by 75 mg daily (79 vs. 95 vs. 64%). There was a reduction in MI with the higher dose compared with clopidogrel at 4 weeks, and a trend towards a benefit at 12 weeks. Minor bleeding was more common with the higher dose, major and life-threatening bleeding were similar [43, 44]. Further phase III clinical trial evaluation is ongoing.

PRT060128

Yet another reversible, direct $P2Y_{12}$ receptor inhibitor, PRT060128 is has been developed in both oral and intravenous formulations. Its intravenous preparation has been shown to achieve dose-dependent complete inhibition of ADP-induced platelet aggregation [45]. Phase II clinical trials are currently underway.

SCH 530348

SCH 530348 belongs to a novel class of antiplatelet agents, called thrombin receptor antagonists (TRAs). Thrombin plays a major role in platelet activation, and does so through a cell surface G_p/G_i-coupled protease-activated receptor (PAR)-1, also known as the thrombin receptor [42, 46]. SCH 530348 is a PAR-1 receptor blocker that inhibits the activation and aggregation of platelets. Phase III clinical trials in patients with acute coronary syndromes as well as with stable coronary disease are ongoing.

E5555

This is a novel TRA, and has shown promising efficacy *in vitro* [47]. Phase II clinical trials are currently underway.

NCX-4016

NCX-4016 is a nitric oxide (NO) releasing preparation of aspirin. It thus combines the beneficial effects of aspirin (thromboxane A2 inhibition) with NO (vasodilatative, antiatherogenic, antithrombotic, gastroprotective) [33].

S18886

Unlike aspirin which indirectly inhibits thromboxane A2 formation, S18886 acts directly on the thromboxane receptor [33]. It thus also inhibits other eicosanoids not affected by aspirin, such as hydroxyeicosatetraenoic acids (HETEs) and isoprostanes.

CTRP (C1qTNF-related protein)-1

This is a collagen inhibitor, and acts by blocking the ability of vWF to bind to bind to collagen, thus inhibition platelet adhesion [48].

Thus, several new antiplatelet drugs are under evaluation. Depending on their particular effects on ischemic and bleeding events, these agents may have a substantial impact in the field of acute coronary syndromes.

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