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Aspirin, ticlopidine, and clopidogrel in acute coronary syndromes: Underused treatments could save thousands of lives

ABSTRACT

Aspirin is the cornerstone of therapy for unstable angina and acute myocardial infarction and the foundation on which other therapies are added, both in the short term and the long term. Yet, despite clear data, aspirin is woefully underused or is often used late. Prompt administration of aspirin could save thousands of lives each year. Ticlopidine and clopidogrel have a synergistic effect when used with aspirin, and can also have a role in treating patients who are aspirin-resistant or have diffuse atherosclerosis.

KEY POINTS

The benefits of antiplatelet drugs in the treatment and prevention of acute coronary syndromes outweigh the risks, although a few precautions are advisable.

Patients with aspirin resistance may be more vulnerable to adverse vascular events.

Ticlopidine and clopidogrel have been proved to be effective as adjuncts to aspirin for preventing subacute stent thrombosis.

Timely administration of these agents during acute coronary syndromes is critical.

THE ORAL ANTIPLATELET AGENTS, aspirin in particular, have the best benefit-to-risk ratio and the best cost-benefit ratio of any of the therapies for acute coronary syndromes, and have become the cornerstone of therapy.[1,2] The ISIS-2 trial[3] showed that aspirin and streptokinase were approximately equally beneficial, with approximately 24 lives saved per 1,000 patients treated. This translates into less than $20 spent for each premature death prevented by aspirin, vs about $2,000 for streptokinase.

Yet a sizable number of patients who should receive aspirin do not receive it. While physician adherence to guidelines is improving,[4] as recently as 1995 the Health Care Financing Administration reported that 39% of patients 65 years or older did not receive aspirin within 2 days of an acute MI.[5]

Aspirin (or another antiplatelet drug) should be given promptly. Eisenberg and Topol[6] showed a time gradient for deaths prevented by aspirin even within the first 12 hours of presentation for chest pain related to myocardial infarction (MI). This is not surprising given the rapid pharmacokinetics of these agents, and in light of the large body of evidence demonstrating greater myocardial salvage with prompt therapy in acute coronary syndromes. Yet a 1994 study[7] found that only 45% of patients presenting to four hospital emergency departments with acute MIs received aspirin at all, and of these, 78% received it more than 30 minutes after arrival and 54% received it after 1 hour.

With approximately 2 million patients admitted each year for acute coronary syn-

dromes, by simply giving aspirin to virtually all candidates promptly, potentially 10,000 premature deaths a year could be prevented in the United States alone. It is incumbent upon caregivers to maximize this opportunity to decrease the mortality rate in this common and frequently fatal condition.

In this paper we review the utility, risks, and optimal use of currently available oral antiplatelet agents: aspirin, ticlopidine, and clopidogrel. The glycoprotein IIb/IIIa inhibitors and other classes of agents used in treating acute coronary syndromes will be covered in future issues.

ROLE OF PLATELETS IN ACUTE CORONARY SYNDROMES

Basic and clinical research has firmly established that platelets play a central role in triggering and perpetuating acute coronary syndromes.[8–17] The cascade of events that leads to the formation of a coronary thrombus typically begins when an atherosclerotic plaque ruptures or is otherwise disrupted, exposing the subendothelium to the circulating blood (FIGURE 1).[17] When dormant platelets come into contact with factors present in the subendothelial matrix and the lipid-rich core of the plaque, they adhere to the vessel wall and become "activated," ie, they:

- Change their shape from smooth and disc-shaped to irregular with pseudopods
- Release a number of prothrombotic substances from their granules that activate and recruit neighboring platelets
- Up-regulate a number of different cell surface receptors.

If enough platelets are involved, they coalesce with thrombin and fibrin to form a hemostatic plug, resulting in myocardial ischemia or infarction.

ASPIRIN

Hippocrates used willow bark, which contains salicylates, for its analgesic properties circa 400 BC. Native Americans used willow bark as well.[18] Acetylsalicylic acid was synthesized by Hoffman in the late 1800s, and introduced for treating rheumatism and fever by the Farbenfabriken Bayer company under the name aspirin in 1899. It is no small irony that the company had to give the public assurances that the compound had no adverse effects on the heart.[19]

Aspirin was first noted to cause a bleeding tendency in 1891. Its use in coronary artery disease was first reported in 1953 by Craven.[20] Today, aspirin is the most widely used drug for ischemic vascular diseases.[18]

Aspirin reaches its peak effect in 30 minutes

Aspirin's mechanism of action

Aspirin prevents conversion of arachidonic acid to prostaglandin H_2, which is the first step in prostaglandin synthesis and the subsequent production of thromboxane A_2 (a potent vasoconstrictor and inducer of platelet aggregation) and prostacyclin (which has the opposite effects).[21] Aspirin does this by acetylating the serine residue of the enzyme prostaglandin H_2 synthase (PGHS, also known as cyclooxygenase), irreversibly inactivating it.[22] Since platelets, unlike endothelial cells, have no nucleus, they cannot regenerate PGHS, and their ability to aggregate is impaired for the duration of their lifespan.[23] Approximately 10% to 15% of circulating platelets are replaced each day; therefore, platelet aggregation takes several days to recover as new platelets are supplied by the bone marrow.[24] However, during the interval, platelets can still be activated by substances other than thromboxane A_2, notably adenosine diphosphate, thrombin, and epinephrine.

Aspirin has other effects that may be salutary: it attenuates leukocyte rolling, cytokine production, monocyte adhesion, thrombogenicity of atherosclerotic plaques, oxidant stress, nicotine-induced endothelial cell activation, hypoxia-induced vasoconstriction, activity of nitric oxide inhibitors, activation of fibroblastic cells, and vascular smooth muscle cell proliferation.

Aspirin is rapidly absorbed in the stomach and upper intestine, achieving detectable plasma levels as early as 15 minutes after ingestion, with onset of platelet inhibition evident within minutes thereafter.[23]

Trials of aspirin in unstable angina or non–Q-wave MI

Aspirin is a cornerstone of therapy for unstable angina or non–Q-wave MI. Several studies

Blocking the cascade of platelet aggregation

When vascular endothelial cells are damaged, platelets bind to the vessel wall and undergo activation and degranulation, releasing a number of substances that activate and recruit other platelets. Aspirin, ticlopidine, clopidogrel, and glycoprotein IIb/IIIa inhibitors block the process in different ways.

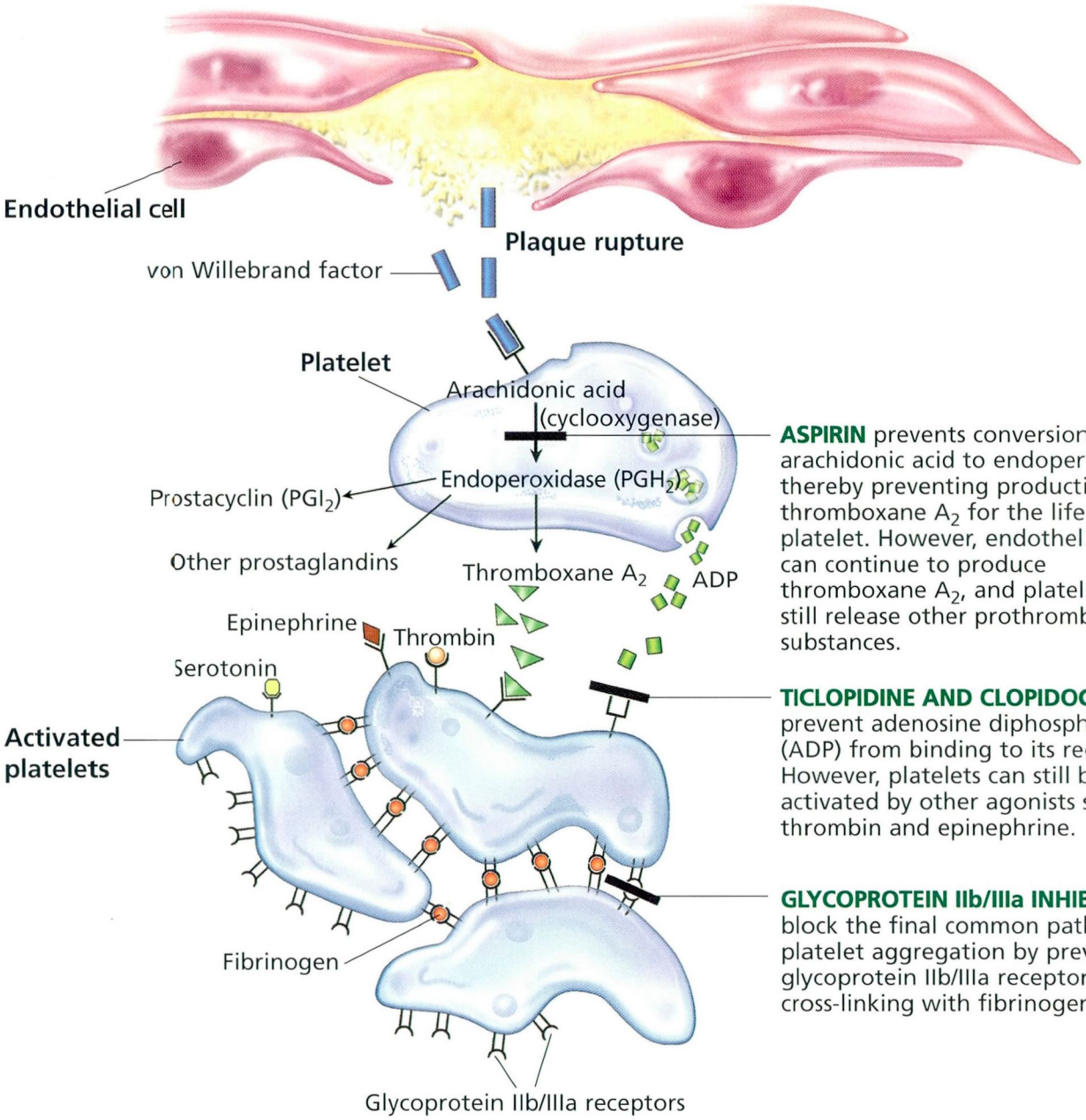

FIGURE 1 ADAPTED FROM SHARIS PJ, CANNON CP, LOSCALZO J. THE ANTIPLATELET EFFECTS OF TICLOPIDINE AND CLOPIDOGREL. ANN INTERN MED 1998; 129:394–405.

TABLE 1

Selected studies of oral antiplatelet agents in acute coronary syndromes

AGENT	STUDY	POPULATION	TIMING OF BENEFIT	NUMBER NEEDED TO TREAT*
Aspirin	Théroux et al[25]	Unstable angina	1 week	12
	RISC[26]	Unstable angina or non–Q-wave MI	3 months	10
	ISIS-2[3]	Acute MI	5 weeks	42
Ticlopidine	Balsano et al[54]	Unstable angina	6 months	16
Clopidogrel	CAPRIE[28]	History of stroke, MI, or peripheral vascular disease	2 years	200†

*To prevent one death or MI, except for the CAPRIE study (which included cerebrovascular accidents) and ISIS-2 (vascular deaths only)
†Compared with aspirin

In unstable angina, aspirin reduces death or MI by half

have shown that it can reduce the incidence of death or MI by approximately half in these conditions. For example:

- Théroux et al[25] conducted a randomized trial in patients admitted to the hospital with unstable angina. At 1 week, the incidence of fatal or nonfatal MI was 11.9% in patients who received placebo, compared with 3.3% in those who received aspirin ($P = .012$) and 1.6% for those who received both aspirin and heparin ($P = .001$). At 30 days, the rates were 16.1%, 5.8%, and 3.3%, respectively.

Another useful way to look at the data is the "number needed to treat" (NNT)—the number of patients that need to be treated to prevent one event. In this study, the NNT with aspirin for the 1-week data was only 12 (TABLE 1).

- The Research Group on Instability in Coronary Artery Disease in Southeast Sweden (RISC) showed a similar benefit for aspirin in up to 90 days of follow-up of men with unstable angina or non–Q-wave MI.[26]

Trials of aspirin in acute myocardial infarction

Aspirin serves as the linchpin of therapy for acute MI and the foundation on which other therapies are added, both in the short term and the long term. For example, the Antiplatelet Trialists' Collaboration performed a meta-analysis of eight randomized clinical trials of aspirin in acute MI involving nearly 16,000 patients.[27] In aggregate, these trials demonstrated that aspirin reduced the incidence of reinfarction by one third and the composite endpoint of MI, stroke, or vascular death by one fourth, translating into 36 major cardiovascular events prevented over 2 years per 1,000 treated patients (NNT = 28).

Of interest, one of the trials in this analysis, the Second International Study of Infarct Survival (ISIS-2),[3] found aspirin nearly as effective as streptokinase in reducing vascular mortality in patients with suspected MI. At 35 days, aspirin had reduced the rate of vascular mortality by 23%, compared with 25% for streptokinase (FIGURE 2). Combining the two agents yielded a 42% reduction in mortality compared with placebo. Similarly, a study in 11,630 patients with recent MIs[28] found aspirin approximately as effective as clopidogrel: at 1.9 years the rate of ischemic stroke, MI, or vascular death was 4.84% in the clopidogrel group vs 5.03% in the aspirin group ($P = .66$). (TABLE 2 lists the relative advantages, disadvantages, and costs of aspirin, ticlopidine, and clopidogrel.)

Trials of aspirin in angioplasty

In a trial in patients undergoing percutaneous

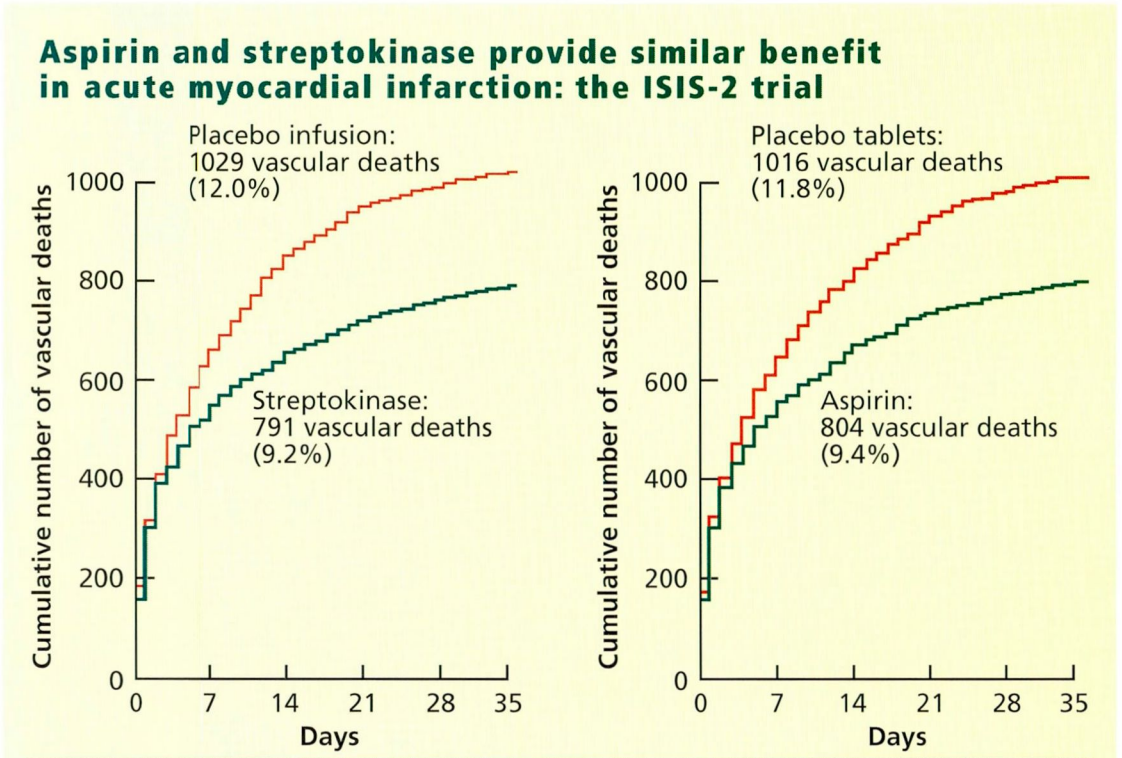

FIGURE 2. Cumulative vascular mortality in days 0 through 35 after myocardial infarction in patients treated with placebo, streptokinase, or aspirin. Note the similar benefit with aspirin compared with streptokinase.

FROM ISIS-2 INVESTIGATORS. RANDOMISED TRIAL OF INTRAVENOUS STREPTOKINASE, ORAL ASPIRIN, BOTH, OR NEITHER AMONG 17,187 CASES OF SUSPECTED ACUTE MYOCARDIAL INFARCTION: ISIS-2 (SECOND INTERNATIONAL STUDY OF INFARCT SURVIVAL) COLLABORATIVE GROUP. LANCET 1988; 2:349–360.

transluminal coronary angioplasty, half of whom had unstable angina, Barnathan and colleagues[29] reported an incidence of clinically significant coronary thrombosis of 10.7% in patients who received placebo compared with 1.8% in those who received aspirin (P = .005).

In another study,[30] the incidence of periprocedural Q-wave MIs was 6.9% in patients receiving placebo compared with 1.6% in patients randomized to receive aspirin and dipyridamole combined before the procedure (P = .01).

Safety issues with aspirin

While the benefits of aspirin in the treatment and secondary prevention of acute coronary syndromes far outweigh the risks, a few precautions are in order, especially since this treatment is lifelong.

Bleeding. Aspirin increases the risk of gastric bleeding in a dose-related manner. A slight excess risk has been observed even at a low dose (75 mg/day), which is doubled with a daily dose of 300 mg, and is increased fivefold at doses of 1,800 mg or more.[23,31] The risk appears to be greatest during the first week, after which most patients may develop gastric adaptation.[32,33]

Of note: no excess in gastric complications was seen in the Physician's Health Study,[34] in which healthy subjects took 325 mg of aspirin every other day as primary prevention. However, this was in the context of a relatively healthy population cohort.

If necessary, one can consider prophylactic therapy with misoprostol or a proton pump inhibitor (eg, omeprazole, lansoprazole) for patients at increased risk of gastrointestinal bleeding.

The Physician's Health Study found no excess GI bleeding with aspirin

TABLE 2

Advantages, disadvantages, and costs of oral antiplatelet agents

AGENT	ADVANTAGES	DISADVANTAGES	COST (30-DAY SUPPLY)*
Aspirin	Well established Safe Inexpensive	Weak antiplatelet effect Allergy Gastrointestinal intolerance Gastrointestinal upset (main side effect) Bleeding Nonresponders	$1
Ticlopidine	Decreases stent thrombosis (with aspirin)	Rare but life-threatening neutropenia and thrombotic thrombocytopenia purpura Expensive	$130
Clopidogrel	To date, safer than aspirin Proven for peripheral vascular disease Effective for secondary prevention and for stenting	Relatively new Gastrointestinal upset Expensive	$100

*Average wholesale price

Some people may become resistant to aspirin

Aspirin resistance. An emerging body of evidence suggests that people differ widely in their response to aspirin. Valettas et al[35] gave aspirin 325 mg/day to 29 healthy subjects for a week and then used flow cytometry to measure platelet activation in response to in vitro stimulation. The mean value was 30% platelet activation, compared with 92% at baseline prior to aspirin intake. However, the investigators observed a wide distribution of response: 13 subjects had less than 25% platelet activation, but 12 had between 25% and 50%, and 4 had more than 50%.

Moreover, some people may become resistant to aspirin with treatment. Helgason[36] followed 306 stroke patients who were taking aspirin over 33 months with serial aggregation studies. Seventy four percent of these patients had complete platelet inhibition initially, but 33% lost some degree of platelet inhibition over time. Eight percent remained aspirin-resistant even when doses were increased to 1,300 mg/day.

Patients with aspirin resistance may be more vulnerable to adverse vascular events.[37,38] It is possible that aspirin resistance is a marker of proclivity to thrombotic events and may not be amenable to a simple increase in aspirin dose.

At present there are no recommendations about monitoring platelet inhibition in patients on long-term aspirin therapy. However, if a patient has diffuse atherosclerosis or recurrent events, most physicians would reduce the dose of aspirin and add clopidogrel, or switch to clopidogrel alone.

Aspirin dosage recommendations

The dose of aspirin required to suppress platelet function is lower than that needed for analgesia. Indeed, the RISC study,[26] discussed above, used doses of 75 mg/day. However, only one randomized study has compared aspirin doses in acute coronary syndromes: the Duke University Clinical Cardiology Study II (DUCCS-II).[39] In this study, 162 thrombolytic-eligible MI patients received either 81 or 325 mg of aspirin daily. There were no differ-

TABLE 3

Effect and dosage of antiplatelet agents

AGENT	ONSET OF ACTION	PEAK EFFECT	% INHIBITION OF PLATELET AGGREGATION*	DURATION OF ANTIPLATELET EFFECT (DAYS)	RECOMMENDED DOSAGE
Aspirin	Minutes	< 30 min[43]	20	5–7	Loading dose: 325 mg chewed, then 150–325 mg daily in the hospital, then 80–325 mg daily at home
Ticlopidine	1–2 hours	5 days[66]	40[67]	5–7[49]	Loading dose: 500 mg, then 250 mg twice a day for 2 weeks†
Clopidogrel	1–2 hours[68]	5 days	40	5–7	Loading dose: 300 mg, then 75 mg daily

*With 5 µmol/L ADP stimulation
†As adjunct for intracoronary stenting

ences between the outcomes of the two groups with regard to death, stroke, shock, vessel patency, or global left ventricular function. However, the study's small sample size precludes any definitive conclusions.

Given the central role of antiplatelet therapy as demonstrated by the large-scale platelet glycoprotein IIb/IIIa drug trials,[40–42] and the recognition that individual responses to low aspirin doses may vary considerably, we recommend giving 325 mg of chewable (regular) aspirin for acute coronary syndromes followed by 150 to 325 mg/day during the hospital stay (TABLE 3).[43,44] A maintenance dose of 80 to 325 mg daily should be prescribed indefinitely for secondary prevention, unless there are compelling contraindications such as proven aspirin allergy, aspirin-induced asthma, or bleeding ulcers. This is similar to the recommendation from the Agency for Health Care Policy and Research that patients with unstable angina receive a loading dose of 325 mg initially followed by a daily dose of 150 to 325 mg.[45]

One possible but uncommon condition in which aspirin may not be mandatory is dilated cardiomyopathy with angiographically normal coronary arteries. The reason: some retrospective data suggest that aspirin might interfere with the action of angiotensin-converting enzyme inhibitors.[46–48]

ADENOSINE DIPHOSPHATE ANTAGONISTS

Ticlopidine (Ticlid) and clopidogrel (Plavix) are thienopyridine derivatives that block adenosine diphosphate (ADP)-mediated platelet aggregation without affecting the cyclooxygenase pathway.[49] This blockade is thought to inhibit fibrinogen from binding to the glycoprotein IIb/IIIa receptor.[50] In addition, ticlopidine may interfere with binding of von Willebrand factor to platelet receptors.[51,52] The end effect is an irreversible and noncompetitive inhibition of platelet function. Both of these agents have a synergistic effect when used with aspirin and are typically added to aspirin (although this combination remains to be proven in a clinical trial for clopidogrel). Maximal bioavailability is achieved when they are taken after meals.

Ticlopidine

Ticlopidine was first used extensively for cerebrovascular disease, in which it was shown to be superior to aspirin in specific patient subsets in the Ticlopidine Aspirin Stroke Study (TASS).[53] At 3 years, 17% of patients taking ticlopidine had died or suffered a second stroke, compared with 19% of those taking aspirin ($P = .048$).

In the only randomized trial of ticlopidine

Obtain a CBC 10 days after starting ticlopidine to look for neutropenia

in acute coronary syndromes, Balsano et al[54] randomized 652 patients with unstable angina to receive either ticlopidine or conventional therapy (which did not include aspirin at that time—only beta blockers, calcium antagonists, and nitrates). At 6 months, 7.3% of patients taking ticlopidine had died of a vascular cause or suffered a nonfatal MI, compared with 13.6% of those receiving conventional therapy alone, a 46% risk reduction ($P = .009$).

Ticlopidine came into wide use in cardiovascular medicine as an adjunct to aspirin to prevent stent thrombosis in coronary interventions. Schomig and coworkers[55,56] found the combination of ticlopidine and aspirin better than aspirin plus anticoagulant therapy in preventing acute stent thrombosis, MI, and repeat interventions. Registry data also show that giving ticlopidine before percutaneous coronary angioplasty improves the short-term outcomes.[57] A widely-used regimen is ticlopidine 500 mg as an oral loading dose followed by 250 mg twice a day. If possible, the loading dose should be given 3 days before the procedure, because ticlopidine achieves its maximal effect in 4 days.[58] If the patient receives an intracoronary stent, the maintenance dose is 250 mg twice a day for 2 to 4 weeks, along with lifelong aspirin.

Stop ticlopidine or clopidogrel 1 week before elective surgery

Clopidogrel

Clopidogrel, a congener of ticlopidine, is increasingly being used as an alternative to ticlopidine. Currently, it is used in acute coronary syndromes if the patient has aspirin resistance, allergy, or intolerance, or following intracoronary stent placement.

Evidence of clopidogrel's safety and efficacy comes from the CAPRIE trial,[28] which included 19,185 patients with recent MI, ischemic stroke, or symptomatic peripheral vascular disease who were randomized to receive clopidogrel 75 mg daily or aspirin 325 mg daily. At 3 years, the incidence of death, MI, or cerebrovascular accident was a modest 9% lower in patients taking clopidogrel compared with aspirin. The only patient subgroup in which clopidogrel was clearly better than aspirin was the group with peripheral vascular disease.

We have only limited data about using clopidogrel during angioplasty. However, a laboratory experiment using vessels from pigs in a milieu of high shear stress indicated that clopidogrel may be more effective than aspirin in preventing stent thrombosis.[59] Recently, the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS),[60] indicated that the two drugs likely produced equivalent outcomes, but clopidogrel was more tolerable and patients complied better with taking it. (The study was not powered to compare efficacy outcomes.)

An ongoing placebo-controlled trial, Clopidogrel for Reduction of Events During Observation (CREDO), is testing the efficacy of giving clopidogrel before angioplasty. Patients receiving clopidogrel before the procedure will continue therapy for 1 year, whereas those randomized to receive placebo before the procedure will receive clopidogrel afterward for 1 month.

At the Cleveland Clinic, before angioplasty, we give a loading dose of 300 mg of clopidogrel (preferably at least 2 hours before the procedure, based on an anticipated near-maximal antiplatelet effect by 2 hours),[61] and continue with 75 mg daily for a month (along with lifelong aspirin therapy) if the patient receives a stent.

Safety issues with ticlopidine and clopidogrel

Bleeding. Although the newer agents have not been as well-studied as aspirin, the same considerations of bleeding risk apply to them.

The incidence of gastrointestinal hemorrhage may be slightly lower with ticlopidine or clopidogrel than with aspirin, because the new agents do not inhibit prostaglandin synthesis. For example, in the CAPRIE study,[28] the incidence of severe gastrointestinal hemorrhage was 0.71% with aspirin compared with 0.49% with clopidogrel ($P < .05$).

If a patient requires surgery, keep in mind that ticlopidine and clopidogrel irreversibly inhibit platelets for the lifespan of the platelet. Hence, we recommend that these drugs be stopped about a week before any elective surgery if the patient is stable from a coronary standpoint. In cases of urgent surgery, platelet transfusions can be given if significant bleed-

ing occurs. Aprotinin has been shown in an animal study to reduce the prolonged bleeding time observed with clopidogrel, but whether this can reduce bleeding in clinical practice is uncertain.

Thrombotic thrombocytopenic purpura, which may be life-threatening, has been reported at an estimated rate of 1 case per 4,814 persons exposed to ticlopidine, and can occur up to 19 days after ticlopidine is stopped.[62] Keep this condition in mind, because prompt plasmapheresis may be life-saving. On the other hand, follow-up for up to 3 years in the CAPRIE study has not uncovered any excess incidence of thrombotic thrombocytopenic purpura with clopidogrel.[28]

Neutropenia has been reported to occur in approximately 1% of patients taking ticlopidine. This condition usually resolves if the drug is stopped. We recommend obtaining a complete blood count about 10 days after starting ticlopidine specifically to look for neutropenia.

Treatment resistance. There is also emerging evidence of interindividual variability of response to ticlopidine,[63] as there is to aspirin.

A PUBLIC HEALTH NOTE ON THE IMPORTANCE OF USING ASPIRIN

Coronary artery disease is still the most common cause of death in the United States. Each year more than 1.5 million Americans suffer a myocardial infarction.[64,65]

As we have noted throughout this paper, the oral antiplatelet agents, and aspirin in particular, are the cornerstone of therapy for acute coronary syndromes, and for good reason. They are effective, reducing the rate of death or MI by one third to one half, depending on the situation. The number patients who need to be treated to prevent one event is remarkably low: as few as 10, according to some studies. The agents are inexpensive, aspirin costing only pennies per dose. And although the agents do pose risks, they have the best benefit-to-risk ratio and the best cost-benefit ratio of any of the therapies for acute coronary syndromes.

In light of this evidence, physicians should be certain that nearly every patient suspected of having unstable angina or an MI gets an aspirin tablet expeditiously and consistently.

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