Platelet Aggregation Inhibitors Review

05/08/2009

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FDA-Approved Indications

Drug	Manufacturer	FDA-Approved Indication(s)
aspirin/ dipyridamole ER (Aggrenox®)[1]	Boehringer-Ingelheim	• Risk reduction of stroke in patients who have had transient ischemia of the brain or completed ischemic thrombotic stroke due to thrombosis

clopidogrel (Plavix®)[2]	Bristol-Myers Squibb	• Secondary prevention of atherosclerotic events (fatal or nonfatal myocardial infarction (MI), fatal or nonfatal ischemic stroke, and vascular death) in patients with recent MI, recent stroke or established peripheral arterial disease
		• Acute coronary syndrome:
		  • Non-Q-wave acute MI or unstable angina during medical management or percutaneous intervention (with or without stenting) or coronary artery bypass graft (CABG) to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia
		  • For ST-segment elevation acute MI to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke; this benefit is not known to pertain to patients who receive primary angioplasty

dipyridamole (Persantine®)[3]	generic	• Adjunctive therapy to coumarin anticoagulants in the prevention of postoperative thromboembolic complications of cardiac valve replacement
ticlopidine (Ticlid)[4]	generic	• Secondary prevention of thrombotic stroke (fatal or nonfatal); second-line therapy • Adjunct to aspirin to reduce the incidence of subacute stent thrombosis for patients undergoing coronary stent placement

Aspirin is available over the counter and is indicated for primary and secondary prevention of MI, stable and unstable angina including coronary artery disease (CAD), arterial thromboembolism prophylaxis for patients with prosthetic heart valves in combination with warfarin, secondary prevention of stroke/transient ischemic attack (TIA), and acute treatment of stroke in patients not eligible for thrombolysis.

Overview

The 2009 Heart Disease and Stroke Statistics update cites cardiovascular disease as the cause of death in 864,480 people in the United States based on 2005 data.[5] Stroke causes significant morbidity and mortality in the United States, and stroke is the third leading cause of death, behind heart disease and cancer, when considered independently from other cardiovascular diseases.[6]

Inhibitory effects on the aggregation of platelets have led to a significant decrease in the rate of vascular events for both primary and secondary cardiovascular prevention trials.[7,8] Aspirin has been shown to reduce cardiovascular morbidity and mortality in both primary and secondary prevention trials.[9,10,11,12,13] For secondary prevention of CAD, as well as in patients who have had MI, ACS, or PCI, indefinite aspirin 75 mg to 100 mg daily is recommended (Grade 1A) by the 2008 American College of Chest Physicians (ACCP) evidence-based practice guidelines.[14] For primary prevention in patients with moderate risk for a coronary event, aspirin 75 mg to 100 mg daily is recommended, over the use of antithrombotic therapy or a vitamin K antagonist (Grade 1A).

Aspirin failure is most commonly described in situations when aspirin has failed to prevent a thrombotic event. Aspirin failure may be due to the inability of aspirin to produce the desired pharmacological effect or may be related to poor adherence. The definition of aspirin resistance is quite variable in the literature and has been described as the failure to prevent a thrombotic event, the inability of aspirin to inhibit platelet thromboxane formation, or the inability of the drug to cause prolongation of bleeding time. A lack of any effect on *in vivo* tests of platelet activity, including no prolongation of the bleeding time, may also be defined as aspirin resistance.[15] Several different methods to assess platelet aggregation and aspirin resistance have been described. Some of the testing methods identify those patients that are aspirin nonresponders, but the relationship to clinical events has not been fully evaluated.[16,17]

Studies have identified that inter-patient variability of response to the antiplatelet agents does exist. A small percentage of patients with cardiovascular disease have aspirin resistance and are at higher risk for cardiovascular events.[18] Variability in responsiveness to clopidogrel (Plavix) has also been documented.[19,20,21,22] Dual aspirin and clopidogrel non-responsiveness has also been documented and linked to patients at a very high risk of drug-eluting stent thrombosis or death.[23] Variability in response to clopidogrel may be due to pre-existing variability in platelet response to adenosine diphosphate (ADP), genetic variability (polymorphisms in the hepatic enzymes involved in clopidogrel metabolism or within the platelet P2Y12 receptor), or drug interactions (e.g. proton pump inhibitors).[24,25,26,27,28,29] There appears to be an association between a CYP2C19 variant, and recurrent thrombotic coronary events in patients taking clopidogrel.[30,31,32,33] The genetic variant is common, occurring in 30, 40, and over 50 percent of patients with European, African, and Asian ancestry, respectively.[34]

Recommendations to manage aspirin resistance are not currently available. At this time, much of the published literature with aspirin resistance is in small populations with study design flaws or incomplete data.[35,36,37,38,39] Until good quality clinical trials are completed and management guidelines developed, it is unknown if aspirin resistance can be overcome by increasing the dose of aspirin or adding another agent.[40,41] In addition, diagnostic testing using unvalidated methods are premature at this time.[42,43]

Other antithrombotic drugs have been developed to improve the platelet aggregation inhibition and to improve the safety profile of platelet aggregation inhibitor therapy. Clopidogrel (Plavix), aspirin/dipyridamole ER (Aggrenox), and ticlopidine (Ticlid) are platelet aggregation inhibitors and are useful in the treatment and prevention of cardiovascular and cerebrovascular thrombotic events. For the aspirin allergic patient, ticlopidine or clopidogrel are alternative therapies, however clopidogrel is preferred to ticlodipine since it is associated with less serious adverse events.

Prevention of Stroke and TIAs

Several scientific statements and guidelines have been published on the prevention and treatment of ischemic stroke.[44,45,46]

The 2008 ACCP evidence-based practice guidelines recommend early aspirin therapy (initial dose 150 mg to 325 mg) for acute ischemic stroke patients who are not receiving thrombolysis treatment (Grade 1A).[47] For long-term stroke prevention in patients with noncardioembolic stroke or transient ischemic attack (TIA), aspirin (50 mg to 100 mg daily), aspirin/dipyridamole ER (Aggrenox) (25 mg/200 mg twice daily), or clopidogrel (75 mg daily) are all acceptable options for initial therapy. In these patients, aspirin/dipyridamole ER is recommended over aspirin (Grade 1A), clopidogrel suggested over aspirin (Grade 2B), and long-term use of the combination of aspirin and clopidogrel is not recommended (Grade 1B). For patients who are allergic to aspirin, clopidogrel may be used (Grade 1A). Recently in PRoFESS, a large secondary stoke prevention study, aspirin/dipyridamole ER (Aggrenox) did not meet its prespecified criteria for non-inferiority versus clopidogrel (Plavix).[48] For patients with noncardioembolic stroke and TIAs, antiplatelet agents are recommended over oral anticoagulants (Grade 1A). In patients with atrial fibrillation who have suffered a recent stroke or TIA, long-term oral anticoagulation [target international normalized ratio (INR), 2.5; range: 2.0 to 3.0] is recommended (Grade 1A).

The American Heart Association/American Stroke Association (AHA/ASA) Stroke and TIA Guidelines published in 2008 state that aspirin 50 to 325 mg daily, aspirin/dipyridamole ER (Aggrenox), and clopidogrel (Plavix) all remain initial treatment options for the prevention of secondary noncardioembolic ischemic stroke and TIA.[49] There is little information regarding the treatment of patients who have an ischemic stroke while on aspirin. The combination of aspirin/dipyridamole ER is recommended over aspirin monotherapy. Clopidogrel may be considered over aspirin monotherapy on the basis of direct-comparison trials (Class II recommendation, Level of Evidence B). In a patient unable to take aspirin who requires treatment for secondary prevention of stroke, clopidogrel is a reasonable option. The addition of aspirin to clopidogrel increases the risk of hemorrhage, therefore combination therapy is not routinely recommended for ischemic stroke or TIA patients in the absence of a specific indication for use (e.g. ACS or coronary stent).

The AHA/ASA 2007 guidelines for the early management of ischemic stroke recommend aspirin (initial dose 325 mg daily) within 24 to 48 hours of stroke onset.[50] These guidelines do not recommend the administration of clopidogrel (Plavix) alone or in combination with aspirin for treatment of acute ischemic stroke.

The 2009 US Preventative Services Task Force updated the recommendations for aspirin for the primary prevention of CV disease.[51] Aspirin is recommended in men ages 45 to 79 years to prevent MIs. Aspirin is recommended in women ages 55 to 79 years to prevent ischemic stroke. There is not enough information regarding benefit versus risk to recommend aspirin in patients 80 years or older. Optimal aspirin dose is unknown, but a dose of approximately 75 mg/day seems as effective as higher doses which can increase GI bleeding.

Cardiac Uses

The 2007 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI) recommend the use of antiplatelet agents in all patients with UA/NSTEMI, in the absence of an absolute contraindication. Aspirin should be given upon presentation and given indefinitely.[52] For patients intolerant of aspirin due to hypersensitivity or major GI disturbance, clopidogrel

(Plavix) may be administered as a loading dose and then continued daily. For patients with NSTEMI in whom noninvasive treatment is selected, clopidogrel should be added to aspirin and inpatient anticoagulation. Aspirin and clopidogrel therapy should continue for at least one month and ideally up to one year. Serious hematologic adverse effects limit the use of ticlopidine.

The 2004 ACC guidelines for patients with acute ST segment myocardial infarction (STEMI) recommend aspirin 75 to 162 mg daily indefinitely.[53] Clopidogrel (Plavix), preferred over ticlopidine, should be administered to patients who are unable to tolerate aspirin due to hypersensitivity or major GI intolerance. The COMMIT trial confirms that clopidogrel plus aspirin should be utilized in the hospital for patients with STEMI to reduce the risk of all-cause mortality, reinfarction, or stroke.[54] The 2007 update to the 2004 ACC/AHA STEMI guidelines recommend clopidogrel 75 mg and aspirin in STEMI patients regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy.[55] Treatment with clopidogrel should continue for at least 14 days. It is reasonable to administer a 300 mg clopidogrel loading dose in patients less than 75 years old who receive fibrinolytic therapy or who do not receive reperfusion therapy. [56,57] Although there are no data available from clinical trials regarding long-term clopidogrel therapy in STEMI patients, as a result of experience with UA/NSTEMI and coronary transplant patients, long-term maintenance therapy (e.g. one year) with clopidogrel 75 mg daily is reasonable in STEMI patients.

The 2008 ACCP evidence-based practice guidelines recommend both aspirin and clopidogrel for patients with acute STEMI regardless of whether they receive fibrinolytic therapy.[58] Aspirin (75 mg to 162 mg daily) is recommended indefinitely and clopidogrel 75 mg daily up to 28 days in patients receiving fibrinolytic therapy without reperfusion and up to one year in acute STEMI patients without coronary stents.

The combination of clopidogrel 75 mg daily and indefinite aspirin 75 mg to 100 mg daily is recommended for patients experiencing ST-segment elevation (STE) and NSTE ACS (Grade 1A) according to ACCP.[59] In the STE ACS population, clopidogrel is recommended for duration of two to four weeks with the suggestion of continuing up to 12 months post hospital discharge. In the NSTE ACS patient population, clopidogrel is recommended for 12 months. Clopidogrel as monotherapy is recommended for patients with contraindications to aspirin (Grade 1A).

Both clopidogrel (Plavix) and ticlopidine, with the addition of aspirin, are efficacious in reducing major cardiac adverse events following successful coronary stent implantation. Clopidogrel may be better tolerated than ticlopidine and have a faster onset of action.[60,61,62,63] After the placement of a drug-eluting stent, the 2007 ACC/AHA guidelines recommend dual antiplatelet therapy with aspirin indefinitely and a thienopyridine for 12 months.[64] Early discontinuation of dual antiplatelet therapy (aspirin and clopidogrel) greatly increases the risk of stent thrombosis, MI, and death.[65] The 2007 ACC/AHA guidelines recommend and the PCI-CLARITY study supports clopidogrel pre-treatment and long-term therapy following PCI.[66] Poor adherence to clopidogrel in post-drug-eluting stent patients within the first 30 days of therapy has been shown to reduce the beneficial effects on mortality.[67] The 2008 ACCP evidence-based clinical practice guidelines recommend the combination of aspirin and clopidogrel for at least 12 months in patients who undergo bare metal stent or drug-eluting stent placement (Grade 1A).[68] In patients with drug-eluting stents who do not have bleeding or tolerability issues, the indefinite combination of aspirin and clopidogrel is suggested (Grade 2C). Serious hematologic adverse effects limit the use of ticlopidine.

Use in Peripheral Arterial Disease (PAD)

For the treatment of peripheral arterial disease (PAD), the 2005 ACC/AHA guidelines state that aspirin is preferred over clopidogrel (Plavix) to reduce the risk of MI, stroke, and vascular death in patients with PAD.[69] Currently, there are no data to support the use of the combination of clopidogrel and aspirin in patients with severe lower limb PAD.

Other Uses

Per the 2008 ACCP evidence-based clinical practice guidelines anticoagulation recommendations, for the management of rheumatic mitral valve disease and atrial fibrillation or previous systemic embolism, warfarin with a target INR of 2.5 (INR range: 2.0 to 3.0) is recommended.[70] For patients with rheumatic mitral valve disease and atrial fibrillation who have a systemic embolism while on warfarin with a therapeutic INR, warfarin and aspirin 50 mg to 100 mg daily should be administered, after consideration of the additional hemorrhagic risks. An alternative strategy might be the adjustment of warfarin dosing to achieve a higher target INR (target INR, 3.0; range: 2.5 to 3.5). These guidelines state that until there are further clinical studies supporting the use of dipyridamole in the setting of valvular heart disease, its role will remain unclear and data are insufficient to recommend dipyridamole in combination with warfarin. The 2007 ACC/AHA STEMI guidelines recommend a target INR of 2.0 to 2.5 in patients requiring warfarin and clopidogrel and aspirin.[71] In this case, low dose (75 mg to 81 mg) aspirin and clopidogrel 75 mg daily are recommended as there is an increase risk of bleeding. Both the ACCP and the ACC/AHA NSTEMI guidelines recommend low dose aspirin with warfarin in patients with an indication for warfarin therapy (e.g. atrial fibrillation).

The 2008 American College of Cardiology Foundation (ACCF)/American College of Gastroenterology (ACG), and AHA have released an expert consensus document regarding gastrointestinal (GI) risk of antiplatelet and nonsteroidal inflammatory (NSAID) agents.[72] The guidelines highlight the increased risk of upper-GI events with aspirin dose escalation, therefore they recommend against routine use of doses greater than 81 mg daily for chronic therapy. The combination of aspirin and warfarin should only be used in patients with an established indication. The guidelines state that clopidogrel (Plavix) should not be substituted for aspirin as a strategy to reduce GI ulcer bleeding and the combination of warfarin and clopidogrel should only be considered when the benefits outweigh the risks. Gastroprotection with proton pump inhibitors (PPIs) is recommended for both the prevention and treatment of aspirin and NSAID-associated GI injury. These 2008 guidelines recognize *in vitro* data suggesting a drug interaction between PPIs and clopidogrel due to metabolism by the cytochrome P450 pathway. They find relatively little evidence of any clinically significant interaction between clopidogrel and PPIs.

In January 2009, the FDA issued an Early Communication about an Ongoing Safety Review for clopidogrel and its effectiveness when used in combination with PPIs.[73] Several studies have reported increased risk of CV events including MI, and death or greater platelet reactivity associated with concurrent use of clopidogrel and a PPI.[74,75,76] There is conflicting data regarding reduced antiplatelet activity when omeprazole, lansoprazole, or pantoprazole are given with clopidogrel.[77,78,79] Currently, the FDA does not have evidence that histamine-2 (H2) blockers or antacids interfere with the antiplatelet activity of clopidogrel. The FDA recommends that healthcare providers continue to prescribe clopidogrel while re-evaluating the need for prescription or over-the-counter (OTC) PPIs in patients taking clopidogrel.

In May 2009, the Society for Cardiovascular Angiography and Interventions (SCAI) warned health care providers who are treating post-stent patients on dual antiplatelet therapy to consider alternative therapy with histamine-2 (H2) blockers or antacids instead of a PPI, when appropriate.[80] This is in response to the high risk of CV adverse events and stroke in the Clopidogrel Medco Outcomes Study presented during the SCAI's Annual Scientific Sessions.

Additional studies are needed to determine the degree to which individual PPIs may differ in their potential for interacting with clopidogrel.

Pharmacology[81,82]

Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclooxygenase and thus inhibits the generation of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction.

Dipyridamole inhibits cyclic nucleotide phosphodiesterase which degrades cyclic-3',5'-adenosine monophosphate (cAMP) to 5'AMP; this results in intraplatelet accumulation of cAMP, a platelet inhibitor.[83] Dipyridamole also blocks uptake of adenosine which leads to increased cAMP. This inhibition results in an increase in local concentrations of adenosine that acts on the platelet A2 receptor, thereby stimulating platelet adenylate cyclase and increasing platelet cAMP levels. Dipyridamole presumably inhibits adenosine deaminase as well as phosphodiesterase, allowing levels of cAMP to remain increased.

Aspirin/dipyridamole ER (Aggrenox) provides two mechanisms of anti-aggregation effects on platelets by administration of aspirin and dipyridamole together.[84]

Clopidogrel (Plavix) selectively inhibits the binding of adenosine diphosphate (ADP) to the platelet receptor that blocks the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex, thereby inhibiting platelet aggregation.[85] Clopidogrel irreversibly inhibits platelet aggregation.

Platelet aggregation is central in healing through the release of various platelet-derived growth factors that promote angiogenesis.[86] Angiogenesis is critical for repair of GI mucosal disruptions. In addition, adenosine diphosphate-receptor antagonists impair the healing of gastric ulcers by inhibiting platelet release of pro-angiogenic growth factors, such as vascular endothelial growth factor, which promotes endothelial proliferation and accelerates the healing of ulcers. Clopidogrel impairs angiogenesis but this may not be a primary cause of gastroduodenal ulcers; the anti-angiogenic effects may impair healing of gastric erosions or small ulcerations that develop because of other medications or *Helicobacter pylori* infection. In presence of acid, this can lead to clinically significant ulceration and related complications. PPIs inhibit the parietal cell proton pump, thereby exerting a suppressive effect on gastric acid.[87] Combining a PPI with clopidogrel appears to result in less GI bleeding.[88,89] However clopidogrel effectiveness can be decreased in the presence of PPIs.[90,91,92, 93,94]

Ticlopidine interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions.[95] The effect on platelet function is irreversible for the life of the platelet.

Pharmacokinetics

Drug	Half-Life (hr)	Metabolites	Excretion (%)
aspirin	0.33	metabolites	Renal: pH dependent Feces: varies
dipyridamole (Aggrenox)[96]	13.6	monoglucuronide metabolite (low activity)	Renal: <5 Feces: 95
clopidogrel (Plavix)[97]	nr	carboxylic acid derivative is inactive; parent is inactive	Renal: 50 Feces: 46
dipyridamole (Persantine)[98]	10	inactive glucuronide metabolite	Predominately feces
ticlopidine (Ticlid)[99]	At steady state, 4-5 days	>20 inactive metabolites	Renal: 60 Feces: 23

nr = not reported

Aspirin/dipyridamole ER (Aggrenox): The pharmacokinetics of the individual agents are not affected by concurrent administration.[100]

Contraindications/Warnings

Clopidogrel (Plavix) is contraindicated in patients with active pathological bleeding such as bleeding peptic ulcer or intracranial hemorrhage as well as those patients with hypersensitivity to clopidogrel or any of the excipients.[101]

Aspirin/dipyridamole ER (Aggrenox) is contraindicated in patients with hypersensitivity to dipyridamole, aspirin, or any excipients.[102] Aspirin/dipyridamole ER should not be administered to patients with known allergy to NSAIDs or to patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin/dipyridamole ER, due to the aspirin component, should not be given to children or teenagers with viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

Ticlopidine is contraindicated in patients with a presence of neutropenia and thrombocytopenia, or a history of thrombotic thrombocytopenic purpura (TTP) or aplastic anemia.[103] Ticlopidine should not be used in patients with a hemostatic disorder, active bleeding (including intracranial or peptic ulcer bleeding), or in patients with severe liver impairment.

Ticlopidine has a black box warning stating that ticlopidine has been associated with life-threatening hematologic adverse reactions, including neutropenia, agranulocytosis, TTP, and aplastic anemia. Periodic monitoring of complete blood count is recommended, especially during the first three months of therapy.[104]

Clopidogrel (Plavix) has been rarely associated with TTP.[105] Onset of TTP is generally within the first two weeks of therapy.[106] Clopidogrel should be discontinued five days prior to surgery, if possible, to reduce the risk of bleeding. Very little experience with clopidogrel is available for

use in patients with severe hepatic or renal impairment.

Aspirin/dipyridamole ER (Aggrenox) has several warnings in the package labeling.[107] Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic heavy alcohol use while taking aspirin. Due to the aspirin component, the increase in bleeding time may adversely affect patients with inherited or acquired (liver disease or vitamin K deficiency) bleeding disorders. Aspirin has known gastrointestinal (GI) adverse effects that include stomach pain, heartburn, nausea, vomiting, and GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, it is important to monitor for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Patients with a history of active peptic ulcer disease should avoid using aspirin due to the potential for gastric mucosal irritation and bleeding.

Drug Interactions

Drug	theophylline	warfarin	Comment
aspirin/ dipyridamole ER (Aggrenox)[108]	-	May be at higher risk for bleeding	Dipyridamole may increase the cardiovascular effects of adenosine
clopidogrel (Plavix)[109]	-	May be at higher risk for bleeding	-
dipyridamole (Persantine)[110]	-	-	Dipyridamole may increase the cardiovascular effects of adenosine
ticlopidine (Ticlid)[111]	Increased theophylline level	-	Monitor theophylline level

Clopidogrel is a prodrug which requires hepatic conversion via CYP2C19 to its active metabolite.[112] Impaired clopidogrel conversion to its active metabolite may be due to either CYP450 polymorphisms or drug interactions (e.g. PPIs) resulting in suboptimal antiplatelet activity.[113] PPIs are CYP2C19 isoenzymes substrates so it is possible that any PPI may decrease the conversion of clopidogrel to its active metabolite thereby reducing its effectiveness.[114]

Several studies have been performed to assess the effects of PPIs on platelet inhibition by clopidogrel.[115,116,117,118] These studies are limited by small population size and study design flaws. Large randomized trials are needed to evaluate the interaction and estimate its severity on clinical outcomes.

The OCLA study was a double-blind placebo-controlled trial, which included 124 consecutive patients undergoing coronary artery stent implantation and receiving aspirin (75 mg/day) and clopidogrel (loading dose, followed by 75 mg/day).[119] Patients were randomized to omeprazole (20 mg/day) or placebo for seven days. Clopidogrel effectiveness was tested on days one and seven in both groups by measuring platelet phosphorylated-VASP expressed as a platelet reactivity index (PRI); the higher the PRI, the more frequently thrombosis occurs. The main end

point compared PRI value at the seven-day treatment period in the two groups. On day one, mean PRI was 83.2 percent and 83.9 percent, respectively, in the placebo and omeprazole groups (p=NS). On day seven, mean PRI was 39.8 percent and 51.4 percent, in the placebo and omeprazole groups respectively (p<0.0001). This study did not exclude clopidogrel nonresponders, was ex vivo, and had a small sample size.

A retrospective cohort study of 8,205 patients with ACS taking clopidogrel after discharge from 127 Veterans Affairs hospitals between 2003, and 2006, included 63.9 percent who were prescribed a PPI at discharge, during follow-up, or both and 36.1 percent who were not prescribed a PPI.[120] Death or rehospitalization for ACS occurred in 20.8 percent of patients taking clopidogrel without a PPI and 29.8 percent of patients taking clopidogrel plus a PPI. In multivariable analyses, use of clopidogrel plus a PPI was associated with an increased risk of death or rehospitalization for ACS compared with use of clopidogrel without a PPI (adjusted odds ratio [AOR], 1.25; 95% CI, 1.11-1.41). Among patients taking clopidogrel after hospital discharge and prescribed PPI at any point during follow-up (n=5244), periods of use of clopidogrel plus a PPI (compared with periods of use of clopidogrel without a PPI) were associated with a higher risk of death or rehospitalization for ACS (adjusted hazard ratio, 1.27; 95% CI, 1.10-1.46). In analyses of secondary outcomes, patients taking clopidogrel plus a PPI had a higher risk of hospitalizations for recurrent ACS compared with patients taking clopidogrel without a PPI (14.6 percent versus 6.9 percent; AOR, 1.86 [95% CI, 1.57-2.20]) and revascularization procedures (15.5 percent versus 11.9 percent; AOR, 1.49 [95% CI, 1.30-1.71]), but not for all-cause mortality (19.9 percent versus 16.6 percent; AOR, 0.91 [95% CI, 0.80-1.05]).

Recently, the preliminary results of the Clopidogrel Medco Outcomes Study were released. This is a retrospective cohort study of 16,690 patients taking clopidogrel for 12 months following coronary stenting.[121] The study compared major adverse cardiovascular (CV) events among members in the pharmacy and medical claims database. One year risk of major CV events was significantly higher in PPI-treated patients (25.1 percent) compared to patients without PPIs (17.9 percent), HR 1.51, 95% CI, 1.39-1.64, p<0.0001.The use of individual PPIs was associated with a significantly higher risk of major CV events compared to no PPI use, 25.1 (p<0.0001), 24.9 (p<0.0001), 29.2 (p<0.0001), and 24.3 percent (p<0.0004), for omeprazole, esomeprazole, pantoprazole, and lansoprazole, respectively.

Adverse Effects

Drug	Dyspepsia	Nausea	Rash	Dizziness	Headache	Diarrhea	Discontinuation Rate	Hemorrhage
aspirin/ dipyridamole ER (Aggrenox)[122] n=1,650	18.4	16	nr	nr	39.2	12.7	25	Not specified 3.3
dipyridamole ER 200 mg twice daily n=1,654	17.4	15.4			38.3	15.5	25	1.5
aspirin 25mg twice daily n=1,649	18.1	12.7			33.8	6.8	19	2.8
placebo n=1,649 ESPS2 data	16.7	14.1			32.9	9.8	21	1.5
clopidogrel (Plavix)[123] n=9,599	5.2	3.4	4.2	6.2	7.6	4.5	13	GI 2
aspirin 325 mg daily n=9,586 CAPRIE data	6.1	3.8	3.5	6.7	7.2	3.4	13	2.7
clopidogrel (Plavix) + aspirin n=6,259	2	nr	4	2.4	nr	2.1	21.1	Major bleeding 3.7
aspirin[124] n=6,303 CURE data	1.9		3.5	2		2.2	18.8	2.7 (p=0.001)
dipyridamole[125] n=147	reported	reported	2.3 (1.1)	13.6 (8.2)	2.3 (0)	reported	nr	reported with concurrent warfarin
ticlopidine (Ticlid)[126] n=2,048	7	7	5.1	1.1	nr	12.5	21	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and therefore, should not be considered comparative. nr = not reported

A meta-analysis evaluated the risk of bleeding complications associated with antiplatelet agents in 51 randomized trials with 338,191 patients.[127] Low-dose aspirin (less than 100 mg daily) and dipyridamole have the lowest risk of bleeding (3.6 and 6.7 percent, respectively). Aspirin doses exceeding 100 mg daily had a similar risk for bleeding as clopidogrel (Plavix) and ticlopidine.

A systematic review of 22 clinical trials evaluated the adverse events with aspirin (75 to 325 mg daily) and clopidogrel (Plavix) associated with therapy for primary or secondary prophylaxis for cardiovascular events.[128] Aspirin was associated with an increased risk of major bleeding,

major GI bleeding, and intracranial bleeding compared to placebo. The increased risk with low-dose aspirin was 1.7 to 2.1-fold; however, the absolute increased risk was only a 0.13 percent per year increase. A dose-related effect was not observed when dividing the aspirin doses into two groups of 75-162.5 mg daily doses versus 162.5 to 325 mg daily doses in the analysis, which conflicts with other available data. Of the studies included, clopidogrel was not compared to placebo. One study included in the analysis had increased major GI bleeding with aspirin 325 mg compared to clopidogrel (RR=1.45; 95% CI, 1.0-2.1) with an absolute increase in risk of 0.12 percent per year associated with aspirin use (95% CI, 0.00-0.28).

Special Populations[129,130,131,132]

Pediatrics

Safety and effectiveness have not been established for clopidogrel (Plavix), ticlopidine, dipyridamole and aspirin/dipyridamole ER (Aggrenox) in pediatric patients. The use of aspirin in children should be avoided due to the risk of Reye's syndrome with aspirin usage in certain viral illnesses.

The 2008 ACCP evidence-based clinical guidelines state that aspirin remains the most common antiplatelet agent used in pediatrics.[133] The dose of aspirin for optimal inhibition of platelet aggregation is not known, although empiric low doses of 1 to 5 mg/kg/day have been proposed. Dipyridamole has also been used in pediatrics.

Pregnancy

Clopidogrel (Plavix), dipyridamole, and ticlopidine are Pregnancy Category B. Aspirin should not be used within one week preceding or during labor and delivery, as the risk of hemorrhage is increased.

Aspirin/dipyridamole ER (Aggrenox) is classified as Pregnancy Category D. Aggrenox labeling states that aspirin may cause low birth weight, increased incidence for intracranial hemorrhage in premature infants, stillbirths, and neonatal death. Due to the risk of these harmful effects and because of the known effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the fetal cardiovascular system (closure of the ductus arteriosus), aspirin/dipyridamole ER (Aggrenox) should be avoided in the third trimester of pregnancy.

Japanese

A randomized double-blind study of 1,151 Japanese patients with noncardioembolic cerebral infarction compared clopidogrel (Plavix) 75 mg to ticlodipine 200 mg once daily for 52 weeks.[134] In these stroke patients, clopidogrel was associated with significantly fewer safety events compared to ticlodipine (7 versus 15.1 percent respectively, $p<0.001$) in the primary endpoint of safety. There was no significant difference in the major secondary endpoint of incidence of vascular events (HR 0.977, 95% CI, 0.488-1.957).

A randomized, prospective, multicenter, open-label, blinded, end-point trial which enrolled 2,539 Japanese patients with type 2 diabetes without a history of atherosclerotic disease with a median follow-up of 4.37 years examined the efficacy of low-dose aspirin (81 or 100 mg/day) for the primary prevention of atherosclerotic events to a non-aspirin group.[135] A total of 154 atherosclerotic events occurred: 68 in the aspirin group (13.6 per 1000 person-years) and 86 in the non-aspirin group (17.0 per 1000 person-years) (HR, 0.80; 95% CI, 0.58-1.10; p=0.16). The

combined end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal MIs and 5 fatal strokes) in the non-aspirin group (HR, 0.10; 95% CI, 0.01-0.79; p=0.0037). A total of 34 patients in the aspirin group and 38 patients in the non-aspirin group died from any cause (HR, 0.90; 95% CI, 0.57-1.14, p=0.67). The composite of hemorrhagic stroke and significant gastrointestinal bleeding was not significantly different between the aspirin and non-aspirin groups.

Dosages

Drug	Dose	Availability
aspirin 25 mg/ dipyridamole ER 200 mg (Aggrenox)[136]	1 capsule twice daily Alternative regimen for patients with intolerable headaches: during initial treatment switch to one capsule at bedtime and low-dose aspirin in the morning. Because there are no outcome data with this regimen and headaches become less of a problem as treatment continues, patients should return to the usual regimen (capsule twice daily) as soon as possible, usually within one week.	25 mg/200 mg capsule
clopidogrel (Plavix)[137]	75 mg daily acute coronary syndrome: 300 mg for one dose then 75 mg daily plus aspirin 75 to 325 mg daily	75, 300 mg tablets
dipyridamole (Persantine)[138]	75-100 mg four times daily with concurrent coumarin anticoagulants	25, 50, and 75 mg tablets
ticlopidine (Ticlid)[139]	250 mg twice daily	250 mg tablet

Pretreatment with clopidogrel (Plavix) therapy can reduce the risks associated with PCI. A loading dose of 600 mg instead of 300 mg has been studied to shorten the time for clopidogrel to become effective and produce a greater antiplatelet effect, without an apparent adverse effect on safety.[140,141,142, 143, 144,145,146,147]

Clinical Trials

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled trials comparing agents in ambulatory patients who are at high risk or have documented vascular disease due to thrombotic episodes are considered the most relevant in this category. Studies included also reflect the FDA-approved indications. Comparative trials are the most important, but when comparative trials are not available, placebo-controlled trials were considered relevant. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

aspirin

Aspirin has been extensively studied and found to prevent vascular events, both fatal and non-fatal, by 15 to 30 percent in many trials.[148] The Physicians' Health Study with 22,071 men (age >50 years without CAD) provided the first strong support for aspirin 325 mg daily in reducing the risk of a first MI; however, the relative risk reductions for stroke and mortality due to cardiovascular causes were less clear.[149] Further study confirmed aspirin use also reduced mortality in patients at higher risk for cardiovascular disease.[150,151]

The Women's Health Study was a large randomized, double-blind, placebo-controlled trial of aspirin 100 mg daily in the primary prevention of cardiovascular disease among 39,876 healthy women with a majority of women less than age 65 years.[152] Patients were followed for a mean of ten years for the major cardiovascular events of MI, stroke, and death from cardiovascular causes. The risk of major cardiovascular events was slightly lower with aspirin; however, the risk reduction was not statistically significant (nine percent relative risk reduction, 0.91; 95% CI, 0.80 to 1.03; p=0.13). Aspirin reduced the relative risk of stroke but not of MI.

The findings from the large preventive trials - Physician's Health Study in men and Women's Health Study - are different. Aspirin doses and rate of MI are examples of the many differences between the two studies. A meta-analysis demonstrated aspirin's beneficial effects on the composite of cardiovascular outcomes in both men and women.[153]

aspirin/dipyridamole ER (Aggrenox)

The second European Stroke Prevention Study (ESPS-2) evaluated the effectiveness of dipyridamole ER plus low-dose aspirin in the secondary prevention of stroke versus monotherapy for two years.[154] The double-blind study randomized 6,602 patients who had experienced a TIA or ischemic stroke within the previous three months to placebo, aspirin 25

mg twice daily, dipyridamole ER 200 mg twice daily, or the combination of aspirin 25 mg plus dipyridamole ER 200 mg twice daily. The primary endpoints were stroke, death or the combination. The aspirin/dipyridamole ER group showed a relative risk reduction for stroke of 37 percent versus placebo (p<0.001). The combination therapy had an absolute risk reduction of fatal and nonfatal stroke of three percent versus aspirin and dipyridamole monotherapy groups. Mortality rate was not significantly affected by any treatment. Beneficial effects of antiplatelet therapy were evident regardless of age.[155] Aspirin was associated with significantly more overall and gastrointestinal bleeding compared to dipyridamole or placebo. One criticism of the ESPS-2 study was the inclusion of the placebo group.

In a randomized, placebo-controlled study of 149 patients from fibrinolytic trials who had a patent infarct-related artery three to four weeks after STEMI, quantitative coronary angiography of non-infarct arteries was performed on paired cine-angiograms at one year.[156] Patients had been randomized to either continue the daily combination of 50 mg aspirin and 400 mg dipyridamole or to placebo. There were no significant differences in these groups in changes in minimal luminal diameter (MLD) (-0.02 mm; 95% CI, -0.09 to 0.05). Progression of CAD was seen in two thirds of patients and did not independently predict long-term death and/or reinfarction.

clopidogrel (Plavix) versus aspirin

In the CAPRIE study, clopidogrel 75 mg daily and aspirin 325 mg daily were compared for relative efficacy in reducing a composite outcome cluster of ischemic stroke, MI, or vascular death in a randomized, blinded trial.[157] A total of 19,185 patients with a documented stroke, MI, or symptomatic peripheral arterial disease were enrolled in the trial and followed for one to three years. Significant findings include an 8.7 percent relative risk reduction of all endpoints (ischemic stroke, MI, or vascular death) with clopidogrel (5.32 percent annual risk) versus aspirin (5.83 percent annual risk) (95% CI, 0.3-16.5; p=0.043). The absolute risk reduction of clopidogrel over aspirin was 0.5 percent for the combined endpoints. Hemorrhagic events were similar between the groups.[158]

clopidogrel (Plavix) versus aspirin plus esomeprazole (Nexium®)

Aspirin with esomeprazole and clopidogrel were compared for the prevention of recurrent GI bleeding in patients with a history of GI bleeding.[159] Following ulcer healing and a negative *H. pylori* test, patients were randomized to clopidogrel 75 mg daily (n=161) or aspirin 80 mg daily plus esomeprazole 20 mg twice daily (n=159). Patients were followed for 12 months for the recurrence of ulcer bleeding. Recurrent bleeding occurred in 13 clopidogrel-treated patients and one patient receiving aspirin plus esomeprazole. The cumulative incidence of recurrent ulcer bleeding was 8.6 percent (95% CI, 4.1 to 13.1 percent) and 0.7 percent (95% CI, 0 to 2.0 percent) for the clopidogrel and aspirin/esomeprazole groups, respectively (difference, 7.9 percent; 95% CI for the difference, 3.4 to 12.4; p=0.001). Aspirin in combination with a proton pump inhibitor is a safe alternative to clopidogrel for patients with a history of GI ulcer bleeding.

In a double-blind, randomized trial, esomeprazole with aspirin was compared to clopidogrel in patients with a history of ulcer bleeding while on low-dose aspirin.[160] Patients (n=170), after ulcer healing and eradication of *H. pylori*, if necessary, were given esomeprazole 20 mg daily plus aspirin 100 mg daily or clopidogrel 75 mg daily for one year. Recurrent ulcer complications developed in nine patients (13.6 percent) in the clopidogrel group and none in the esomeprazole/aspirin group (95% CI, 6.3-20.9; p=0.00019).

clopidogrel (Plavix) plus aspirin

The CURE study evaluated the efficacy and safety of clopidogrel when given with aspirin in 12,562 acute coronary syndrome patients.[161] Patients were randomized within 24 hours of onset of angina symptoms to clopidogrel 300 mg for one dose then 75 mg daily or placebo, and all patients received aspirin (75 to 325 mg daily) for three to 12 months. The composite primary endpoint was cardiovascular death, nonfatal MI, or stroke, which occurred in 9.3 percent of the clopidogrel group and 11.4 percent in the placebo group (relative risk with clopidogrel as compared with placebo, 0.80; 95% CI, 0.72 to 0.90; p<0.001). Clopidogrel reduced the risk of the second primary endpoint defined as cardiovascular death, nonfatal MI, or stroke plus occurrence of refractory ischemia compared to the placebo group (16.5 percent clopidogrel group compared to 18.8 percent in the placebo group; relative risk, 0.86; 95% CI, 0.79 to 0.94; p<0.001). Rates of the individual outcome endpoints of cardiovascular death, stroke, and refractory ischemia showed numerical improvement with clopidogrel but did not achieve statistical significance. Significantly more major bleeding episodes were observed in the clopidogrel group (3.7 percent in the clopidogrel group versus 2.7 percent in the placebo group, relative risk 1.38; p=0.001). Hemorrhagic strokes and life-threatening bleeding episodes were similar in both groups. Higher doses of aspirin with or without clopidogrel were associated with a higher risk of major bleeding.[162] Minor bleeding episodes were significantly higher in the clopidogrel group (5.1 percent versus 2.4 percent in the placebo group, p<0.001). Benefits of the combination of clopidogrel and aspirin are seen at all doses of aspirin; however, bleeding risk increased with higher doses of aspirin.[163]

In an evaluation of the 2,658 patients that underwent percutaneous coronary intervention (PCI) after randomization in the CURE study (PCI-CURE study), clopidogrel and placebo in addition to aspirin were compared for safety and efficacy.[164] Patients received aspirin and the study drug [clopidogrel or placebo] for a median of ten days prior to PCI. Open-label use of ticlopidine or clopidogrel in addition to aspirin 75 to 325 mg daily was permitted for two to four weeks after stent placement and then the randomly assigned medication resumed. The primary endpoint was the composite of cardiovascular death, MI, or urgent revascularization within 30 days of the PCI. Despite the open-label use of antiplatelet agents, the rate of composite endpoint in the clopidogrel group was 4.5 percent compared to 6.4 percent in the placebo group within the first 30 days (relative risk 0.70; 95% CI, 0.50-0.97; p=0.03). As seen in the CURE study, clopidogrel patients had a lower incidence of cardiovascular death and MI or any revascularization compared to placebo (p=0.03) and a lower rate of cardiovascular death or MI (p=0.047). Bleeding rates between the groups did not differ significantly.

The COURAGE trial was a randomized, multicenter, 4.6-year study of 2,287 patients with stable coronary artery disease.[165] Patients were randomized to PCI plus optimal medical therapy (PCI group) or optimal medical therapy alone. All patients received aspirin 81 to 325 mg per day or clopidogrel 75 mg per day, if patients were intolerant to aspirin. Patients undergoing PCI received both aspirin and clopidogrel. Both groups received beta blockers, statins, ACE inhibitors, as well as made lifestyle modifications of diet, exercise, and smoking cessation. The primary outcome of death from any cause and nonfatal MI occurred in 19 percent of the PCI group versus 18.5 percent of the optimal medical therapy group (hazard ratio 1.05, 95% CI, 0.87 to 1.27, p=0.62). More patients in the optimal medical therapy group required revascularization (32.6 percent) versus the PCI group (21.1 percent; p<0.001). PCI had the initial advantage of relieving angina; however, 74 percent of the PCI group versus 72 percent of the optimal medical therapy group did not experience angina at five years (p=0.35). PCI did not reduce the risk of

death, MI, or other major cardiovascular events in comparison to optimal medical therapy in patients with stable CAD.

In the CREDO study, 2,116 patients who planned to have angioplasty were randomized to clopidogrel or placebo and followed for one year for the combined event rate of death, MI, or stroke.[166] In the double-blind, placebo-controlled trial, patients randomized to clopidogrel received 300 mg prior to the revascularization or placebo. All patients received aspirin 325 mg daily and clopidogrel 75 mg daily for 28 days following stent placement. On day 29, patients then received clopidogrel or placebo in addition to aspirin. At one year, 8.5 percent of the clopidogrel group had reached the composite endpoint compared to 11.5 percent in the placebo group (26.9 percent relative risk reduction; 95% CI, 3.9 - 44.4 percent; p=0.02). Clopidogrel was not associated with a significant reduction in the combined event rate of death, MI, or urgent target vessel revascularization at 28 days. No significant difference was seen in the individual endpoints (death, MI, or death/MI) or bleeding over the one-year study period. During one year of follow-up, any bleeding (major or minor) occurred in 8.1 and 8.9 percent, major bleeding in 3.9 and 5.6 percent, and minor bleeding in 4.2 and 3.3 percent of placebo and clopidogrel treated patients, respectively.[167] These differences were not significant. Major GI bleeding occurred in significantly more patients on clopidogrel compared to placebo (1.4 versus 0.3 percent, p=0.011).

In the MATCH trial, in patients who were already on clopidogrel 75 mg daily, the addition of aspirin 75 mg daily was compared to placebo to see if the combination had a greater benefit in preventing vascular events and to assess the potential for increased bleeding risk over 18 months.[168] The study was a randomized, double-blind, placebo-controlled trial in 7,599 high risk patients having had a recent ischemic stroke or TIA and at least one additional risk factor. The primary endpoint was a composite of ischemic stroke, MI, vascular death, or rehospitalization for acute ischemic attack [TIA, angina, worsening peripheral arterial disease (PAD)]. The primary endpoint was seen in 15.7 percent of the aspirin/clopidogrel group and 16.7 percent in the clopidogrel alone group (relative risk reduction of 6.4 percent [95% CI, -0.46 to 16.3], absolute risk reduction one percent [-0.6 to 2.71]). Combination therapy with clopidogrel and aspirin did not reduce the risk of major vascular events compared with clopidogrel monotherapy. The combination of aspirin and clopidogrel was associated with a higher rate of life-threatening bleeding episodes (2.6 percent) compared to clopidogrel monotherapy (1.3 percent). Major bleeding episodes were more common with the combination; however, mortality was unaffected.

CLARITY-TIMI-28 study: Clopidogrel was evaluated for safety and efficacy in the treatment of acute MI with ST-segment elevation in addition to standard treatment of fibrinolytics, aspirin, and weight-dosed heparin.[169] Patients were scheduled to undergo angiography 48 to 192 hours after the start of the study medication. Patients between ages 18 and 75 years (n=3,491) who presented within 12 hours of ST-elevation were randomized to clopidogrel 300 mg loading dose then 75 mg daily or placebo. Angiography identified occluded infarct-related arteries (TIMI flow grade 0 or 1) in 21.7 percent of patients in the placebo group and 15 percent of patients in the clopidogrel group (6.7 percent difference; 95% CI, 24 to 47 percent; p<0.001). After 30 days, clopidogrel had a relative risk reduction of 20 percent for the composite of cardiovascular death, recurrent MI, or recurrent ischemia requiring revascularization (14.1 percent placebo versus 11.6 percent clopidogrel, p=0.03). Death from cardiovascular causes was similar between the groups and extremely low for the ST-segment acute MI population (2.6 and 2.2 percent for clopidogrel and placebo groups, respectively). Incidences of major bleeding (1.3 and 1.1 percent for clopidogrel and placebo groups, respectively) and intracranial hemorrhage were similar in both groups.

The PCI-CLARITY trial evaluated if pre-treatment with clopidogrel in the setting of PCI in patients with recent ST-segment elevation MI would affect the rate of major adverse cardiovascular events.[170] Patients (n=1,863) were those who underwent PCI after the required angiography as a part of the CLARITY trial discussed above. In the double-blind, placebo-controlled trial, patients received aspirin and were randomized to receive clopidogrel 300 mg once then 75 mg daily or placebo in addition to the fibrinolytics and weight-based heparin for two to eight days until angiography. In patients undergoing PCI with stenting, open-labeled clopidogrel including the loading dose were administered after the angiography but prior to PCI. The primary outcome was the composite of cardiovascular death, MI, or stroke from date of PCI to 30 days after randomization. Pre-treatment with clopidogrel was associated with a significant reduction in the composite outcome (3.6 versus 6.2 percent, adjusted OR, 0.54; 95% CI, 0.35 – 0.85; p=0.008). From randomization to 30 days, the clopidogrel group had a significant reduction in cardiovascular death, MI, or stroke (7.5 versus 12 percent; adjusted OR 0.59; [95% CI, 0.43-0.81]; p=0.001). Bleeding was not significantly different between the groups. Authors concluded that aspirin plus clopidogrel in addition to fibrinolytics and heparin reduce the composite outcome and should be administered prior to and after PCI.

CHARISMA: Clopidogrel and aspirin were compared to aspirin alone in the prevention of the composite endpoint of MI, stroke, or cardiovascular death in a population of patients at high risk for cardiovascular diseases.[171] In the prospective, double-blind, randomized trial, a total of 15,603 patients with a history of cardiovascular disease or multiple risk factors were randomized to clopidogrel 75 mg daily plus aspirin 75 to 162 mg daily or placebo plus aspirin 75 to 162 mg daily. After a median of 28 months, 6.8 percent of the clopidogrel-aspirin group and 7.3 percent of the placebo-aspirin group reached the primary endpoint (relative risk, 0.93; 95% CI, 0.83 to 1.05; p=0.22). The clopidogrel-aspirin group had significantly fewer patients reach the secondary efficacy endpoint of the composite of MI, stroke, cardiovascular-related death, and hospitalizations due to unstable angina, TIA, and revascularization procedures (clopidogrel-aspirin: 11.1 percent, placebo-aspirin: 12.3 percent; relative risk 0.90 (95% CI, 0.82 to 0.98), p<0.02). A subgroup analysis found that patients with only risk factors (approximately 20 percent of total population) had a higher risk of death from all causes (5.4 versus 3.8 percent, p=0.04) and cardiovascular death (3.9 versus 2.2 percent, p=0.01) with both drugs than with aspirin alone. Those with established cardiovascular disease (nearly 80 percent of total population) had a lower risk in the primary end point with clopidogrel (6.9 versus 7.9 percent with placebo; RR=0.88; 95% CI, 0.77 to 0.998; p=0.046). The rate of severe bleeding was similar in both treatment groups with 1.7 percent and 1.3 percent for clopidogrel-aspirin and placebo-aspirin groups, respectively (relative risk, 1.25; 95% CI, 0.97 to 1.61 percent; p=0.09). Moderate bleeding occurred more often in patients on the combination therapy indicating potentially more harm in the setting of no difference overall for efficacy in patients with stable CAD or high-risk for cardiovascular events (2.1 versus 1.3 percent; relative risk 1.62 (95% CI, 1.27 to 2.10); p<0.001). Treatment discontinuation was reported in 20.4 and 18.2 percent of the clopidogrel-aspirin versus placebo-aspirin groups, respectively (p<0.001).

The COMMIT trial was a randomized, double-blinded trial in which the combination of clopidogrel and aspirin was compared to aspirin alone in 45,852 patients with suspected acute MI in 1,250 sites in China.[172] Patients were randomized within 24 hours of suspected acute MI to clopidogrel 75 mg daily or placebo in addition to aspirin 162 mg daily until discharge or up to four weeks in the hospital. ST-segment elevation or bundle branch block was noted in 93 percent of patients, and ST-segment depression was noted in the remaining seven percent. Fibrinolysis was administered in half of the patients. Metoprolol use was also being evaluated in the same population. The two primary endpoints were 1) the composite of death, reinfarction,

or stroke or 2) death from any cause. Clopidogrel-aspirin combination significantly reduced the risk of the composite outcome compared to aspirin alone [clopidogrel: 9.2 percent, (n=2,125) versus aspirin alone: 10.1 percent, (n=2,311); p=0.002]. All-cause mortality by hospital discharge was significantly lower in the clopidogrel group (7.5 versus 8.1 percent, p=0.03). Any type of major bleed (fatal, transfused, and cerebral bleeds) occurred in 0.58 and 0.54 percent of the clopidogrel-aspirin and placebo-aspirin groups, respectively (p=NS).

The Randomized Argentine Clopidogrel Stent (RACS) trial was a prospective, randomized, non-blinded study of 1,004 patients undergoing PCI who were randomized after successful bare metal stent placement to 30 versus 180 days of clopidogrel.[173] All patients also received aspirin. The primary endpoint was a composite of death, MI, and stroke at 180 days. At hospital discharge and 30 days (when both arms received the same treatment), there were no significant differences in frequency of death, MI, or stroke. In comparison from 30 days to 180 days, the patients in the 180 days of clopidogrel reached the primary endpoint (death, MI, and stroke) less frequently (4.99 versus 1.74 percent, 65 percent relative risk reduction, p=0.010). No significant differences in frequency of total bleeding were reported.

Data from consecutive acute STEMI survivors and either concomitant therapy with aspirin or aspirin plus clopidogrel at discharge, which were prospectively enrolled in the Acute COronary Syndromes (ACOS) registry, were analyzed.[174] The 5,886 patients were divided into three groups based on the initial reperfusion therapy (no reperfusion therapy n=1,445; fibrinolysis n=1,734; or primary PCI n=2,707). Mortality was significantly lower in the clopidogrel plus aspirin group versus the aspirin group in the total group as well as the reperfusion therapy [total group odds ratio (OR) 0.48, 95% CI, 0.48 to 0.61; no reperfusion therapy OR 0.96, 95% CI, 0.65 to 1.45; fibrinolysis OR 0.53, 95% CI, 0.32 to 0.87; primary PCI OR 0.38, 95% CI, 0.23 to 0.62].

clopidogrel (Plavix) versus ticlopidine (Ticlid) in coronary stenting

Clopidogrel and ticlopidine have been shown to reduce major adverse cardiac events at 30-days following successful coronary stent implantation.[175,176,177,178,179,180] Differences in the studies include patient populations, dose regimens, timing of initial therapy, duration of therapy, outcome parameters, and follow-up study period. Many of the studies are small and located in single centers. While both drugs have been shown to provide a reduction in major adverse cardiac events following successful coronary stent implantation, it is difficult to determine if one agent is superior as many studies are not powered to detect possible differences in efficacy.[181,182,183] In earlier studies, antiplatelet therapy with clopidogrel or ticlopidine with or without aspirin was given after PCI or stent placement whereas currently, clopidogrel and aspirin are given prior to PCI in much higher loading doses than previously studied.[184,185,186,187,188]

clopidogrel (Plavix) versus aspirin/dipyridamole ER (Aggrenox)

The PRoFESS study was a randomized, double-blind, 2-by-2 factorial design, multicenter secondary stroke prevention trial.[189] A total of 20,332 patients, who had a noncardioembolic ischemic stroke within the previous 120 days, were randomized to aspirin 25 mg/dipyridamole ER 200 mg twice daily or to clopidogrel 75 mg daily and followed for a mean of 2.5 years. The comparison for the primary outcome of recurrent stroke did not meet the predefined criterion for noninferiority (margin of 1.075 or a 75 percent noninferiority difference) and the number of recurrent strokes was similar between groups: recurrent stroke occurred in 9.0 percent and 8.8 percent receiving of patients on aspirin/dipyridamole ER and clopidogrel, respectively, (HR, 1.01; 95% CI, 0.92 to 1.11). The secondary outcome of composite stroke, MI, or vascular death,

was identical between groups: 13.1 percent in each group (HR for aspirin/dipyridamole ER, 0.99; 95% CI, 0.92 to 1.07). Major hemorrhagic events were increased in aspirin/dipyridamole ER compared to clopidogrel 4.1 percent versus 3.6 percent (HR, 1.15; 95% CI, 1.00 to 1.32), including intracranial hemorrhage (HR, 1.42; 95% CI, 1.11 to 1.83). Despite the increase in hemorrhage, the net risk of recurrent stroke or major hemorrhagic events was similar in the both groups: aspirin/dipyridamole ER 11.7 percent compared with clopidogrel 11.4 percent (HR, 1.03; 95% CI, 0.95 to 1.11).

dipyridamole (Persantine)

Very little new clinical data are available for dipyridamole monotherapy. Older data with dipyridamole provides evidence that in patients with prosthetic heart valves, the addition of dipyridamole to warfarin therapy reduces the incidence of systemic emboli.[190] It should be noted that the extended-release dipyridamole formulation not the immediate-release dipyridamole was used in the ESPS-2 and ESPIRIT trials.[191,192]

ticlopidine (Ticlid)

The CATS 24-month study concluded that ticlopidine 250 mg twice daily reduced the relative risk of stroke, MI, or vascular death by 30 percent (95% CI, 7.5-48.3, p=0.006) compared with placebo in stroke patients.[193] An intention-to-treat analysis gave a smaller estimate of relative risk reduction for stroke, myocardial infarction, or vascular death (23.3 percent, p=0.020).

ticlopidine (Ticlid) and aspirin

A randomized, double-blind trial enrolling 1,809 Black patients with a recent history of noncardioembolic ischemic stroke compared the efficacy and safety of aspirin and ticlopidine to prevent recurrent strokes, MI, and vascular death.[194] Patients were given either aspirin 650 mg daily or ticlopidine 250 mg twice daily and were followed for two years. The study was stopped early due to the low probability of ticlopidine being superior to aspirin. The primary outcome was recurrent stroke, MI, or vascular death that occurred in 14.7 percent of ticlopidine patients and 12.3 percent of aspirin patients (hazard ratio, 1.22; 95% CI, 0.94-1.57). Neutropenia was reported in 3.4 percent of ticlopidine patients compared to 2.2 percent of aspirin patients (p=0.12). One possible case of thrombotic thrombocytopenia purpura was in the ticlopidine treated group.

Meta-Analysis

Dipyridamole has no clear evidence of substantial benefit on vascular death compared to controls based on a systematic review evaluating the role of dipyridamole for preventing stroke and other vascular events in patients with vascular disease.[195] A total of 29 trials with 23,019 participants were included. Compared to the control group, dipyridamole had no effect on vascular death (relative risk 0.99, 95% CI, 0.87 to 1.12). The dose of dipyridamole did not influence the outcome nor did the type of vascular disease at presentation. For the risk of vascular events, dipyridamole did significantly reduce the risk only for patients presenting with cerebral ischemia (relative risk 0.88, 95% CI 0.81 to 0.95). There was no evidence that dipyridamole monotherapy was more efficacious than aspirin.

The combination of aspirin with dipyridamole ER (Aggrenox) has shown to be beneficial in the ESPS-2 trial in patients with cerebral ischemia.[196] A meta-analysis pooling data from five trials with a total of 11,659 patients with a history of TIA or ischemic stroke found that

aspirin/dipyridamole reduced the composite of nonfatal stroke, nonfatal MI, and vascular death as compared with aspirin alone (OR, 0.84; 95% CI, 0.72 to 0.97), dipyridamole alone (OR, 0.76; 95% CI, 0.64 to 0.90), or control (OR, 0.66; 95% CI, 0.57 to 0.75).[197] It should be noted that 57 percent of the data were from the ESPS-2 trial.

A meta-analysis of three randomized trials, PCI-CURE, CREDO, and PCI-CLARITY, was performed to evaluate the efficacy and safety of clopidogrel (Plavix) pre-treatment before PCI intervention with and without glycoprotein IIb/IIIa inhibitor (GPI) use.[198] A total of 6,325 patients were included; 32.4 percent of them received a GPI. There was a consistent benefit of clopidogrel pretreatment in reducing the incidence of cardiovascular death, MI, or stroke after PCI both in patients who did not receive a GPI (OR 0.72, 95% CI 0.53 to 0.98, p=0.03) and in those who did (OR 0.69, 95% CI 0.47 to 1.00, p=0.05). Clopidogrel pretreatment was not associated with a significant increase in bleeding.

A meta-analysis of six randomized trials with 7,648 patients showed a significant reduction in the overall stroke risk ratio with aspirin plus dipyridamole compared with aspirin alone (relative risk 0.77, 95% CI, 0.67 to 0.89) and composite outcome of stroke, myocardial infarction, or vascular death with relative risk 0.85 (0.76 to 0.94).[199] Studies using immediate-release dipyridamole showed a nonstatistically significant trend in favor of the combination for stroke alone with relative risk 0.83 (0.59 to 1.15) and for the composite outcome with relative risk 0.95 (0.75 to 1.19). Studies using predominantly extended-release dipyridamole showed a statistically significant difference in favor of the combination for stroke alone with relative risk 0.76 (0.65 to 0.89) and for the composite outcome with relative risk 0.82 (0.73 to 0.92). Approximately 80 percent of the patients in this meta-analysis were from the ESPS-2 and ESPIRIT trials.

Summary

Platelet aggregation inhibitors are used to prevent and treat a variety of thrombotic events including MI, stroke and TIA, and peripheral arterial disease. Various guidelines have specific recommendations for platelet aggregation inhibitor use.

For the prevention of secondary ischemic stroke, although aspirin, the combination of aspirin/dipyridamole (Aggrenox), and clopidogrel (Plavix) all remain acceptable treatment options, aspirin/dipyridamole (Aggrenox) is now given consideration over aspirin monotherapy. Clopidogrel (Plavix) is also recommended over aspirin monotherapy and is a reasonable option in aspirin-intolerant patients. The combination of clopidogrel (Plavix) to aspirin increases the risk of hemorrhage, therefore combination therapy is not routinely recommended for ischemic stroke or TIA patients in the absence of a specific indication for use (e.g. ACS or coronary stent).

For the treatment of acute ischemic stroke, early aspirin therapy (initial dose 150 mg to 325 mg) is recommended in patients who are not receiving thrombolysis.

In the setting of UA/NSTEMI, aspirin should be given indefinitely. Clopidogrel (Plavix) is a reasonable option in aspirin-intolerant patients. In addition to aspirin, clopidogrel (Plavix) should be given ideally for up to 12 months.

STEMI patients should receive dual antiplatelet therapy with clopidogrel (Plavix) long-term and aspirin indefinitely, regardless of whether or not they undergo reperfusion with fibrinolytic therapy.

The combination of clopidogrel (Plavix) 75 mg daily and indefinite aspirin 75 mg to 100 mg daily is recommended for patients experiencing ST-segment elevation (STE) and NSTE ACS. In the STE ACS population, clopidogrel (Plavix) is recommended for duration of two to four weeks with the suggestion of continuing therapy up to 12 months post hospital discharge. In the NSTE ACS patient population, clopidogrel (Plavix) is recommended for 12 months. Clopidogrel (Plavix) as monotherapy is recommended for patients with contraindications to aspirin.

The combination of aspirin and clopidogrel (Plavix) for at least 12 months is recommended in patients with both bare metal stent and drug-eluting stent placement. In patients with drug-eluting stents who do not have bleeding or tolerability issues, the indefinite combination of aspirin and clopidogrel (Plavix) should be considered. Premature discontinuation of the antiplatelet regimen greatly increases restenosis, MI, and death.

In patients with peripheral arterial disease (PAD), aspirin is recommended over clopidogrel (Plavix) to decrease the incidence of MI, stroke, and vascular death.

Serious hematologic adverse effects limit the utility of ticlopidine.

There appears to be variability in response to clopidogrel (Plavix) due to pre-existing variability in platelet response to adenosine diphosphate (ADP), genetic variability, or drug interactions. There are conflicting data regarding reduced antiplatelet activity when clopidogrel and PPIs are taken concomitantly. The 2008 ACCF/ACG/AHA expert consensus recommends the use of PPIs in patients who are receiving NSAIDs, aspirin, dual antiplatelet therapy at risk for GI injury. However in 2009, the FDA issued an Early Communication about an Ongoing Safety Review for clopidogrel and its effectiveness when used in combination with PPIs due to potential increased risk of CV events. The FDA recommends that healthcare providers continue to prescribe clopidogrel while re-evaluating the need for prescription or OTC PPIs in patients taking clopidogrel. In May 2009, the Society for Cardiovascular Angiography and Interventions (SCAI) warned health care providers who are treating post-stent patients on dual antiplatelet therapy to consider alternative therapy with histamine-2 (H2) blockers or antacids instead of a PPI, when appropriate.

Large prospective randomized trials are needed to evaluate the interaction, to determine the degree to which individual PPIs may differ in their potential for interacting with clopidogrel, and estimate its severity on clinical outcomes.

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