17 *Recent Advances in Antiplatelet Drugs*

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Abstract: With rapid expansion in the use of percutaneous intervention (PCI) in the past decade, we have come a long way in the management of acute coronary syndromes. Despite the extensive technologic advancement in the field, pharmacotherapy has remained a cornerstone in the overall treatment strategy. Optimizing the ischemic complications mediated through a complex coagulation cascade, with the ever-present risk of bleeding from antiplatelet and anticoagulant therapy, has remained a challenge for drug developers and for clinicians.

Though our journey is a long one starting from aspirin, still this drug has stood the test of time and many drugs like oral GP IIb/IIIa inhibitors, have proved to be more harmful in clinical trials. However, the future looks very promising as far as the reduction in mortality and MACE is concerned, both in conservative and invasive treatment groups.

PLATELET BIOLOGY

Platelets have a critical role in maintaining the integrity of the vasculature. Following vessel trauma, platelets adhere to the exposed subendothelial components, particularly collagen. von Willebrand factor rapidly attaches to the injury site through its interaction with the GP Ib-IX-V complex. These initial platelet-vessel wall reactions trigger the sequences involved in platelet activation and aggregation. The eicosanoid pathway is stimulated, ultimately leading to the formation of thromboxane A2. Irrespective of the agonist pathway responsible for platelet activation, the process of platelet aggregation is mediated exclusively through the platelet membrane GP IIb/IIIa receptor. The fibrin interlacing consolidates the hemostatic plug.

Rupture of an atherosclerotic plaque is the usual initiating event in an acute coronary syndrome (ACS), leading to subsequent thrombus formation. Persistent thrombotic occlusion results in acute myocardial infarction (MI). Platelets play an important role in this process. Aggregating platelets form the core of the growing thrombotic mass, with upstream and/or downstream propagation of fibrin and red blood cell-rich clot. Platelet-rich thrombi are more resistant to clot lysis than red blood cell-rich thrombi and, if lysis occurs, platelet-rich thrombi promote the development of reocclusion.

CLASSIFICATION OF ANTIPLATELETS DRUGS

Oral

- Cycloxygenase inhibitor*: Aspirin, sulfinpyrazone*
- ADP receptor antagonists: Theinopyridines—*ticlopidine, clopidogrel, prasugrel*
  Non-theinopyridines—*AZD6140*
- Cyclic AMP phosphodiesterase inhibitors: *dipyridamole, cilostazol*
- GP IIb-IIIa inhibitors: Orofiban, sibrafiban, xemilofiban, lotrafiban
- Others: Ridogrel.

Intravenous

- Chimeric monoclonal antibody—Abciximab

- Cyclic heptapeptide inhibitor—Eptifibatide
- Nonpeptide inhibitor—Tirofiban, lamifiban.

CLINICAL EVIDENCE FOR USE OF ANTIPLATELET AGENTS

Chronic Stable Angina

Hundreds of clinical trials have now demonstrated the undisputed benefit of aspirin in cardiovascular diseases. By acetylating the cycloxygenase-1 enzyme, it inhibits the synthesis of thromboxane A2, resulting in irreversible inhibition of platelet function.

Daily administration of 30-50 mg of aspirin results in virtually complete suppression of thromboxane A2 synthesis by 7-10 days in healthy subjects.[1] The use of aspirin in more than 3000 patients with stable angina was associated with a 33% (on average) reduction in the risk of adverse cardiovascular events.[2,3] In the Physicians' Health Study[4]—Aspirin (325 mg), given on alternate days to asymptomatic persons, was associated with a decreased incidence of MI. In the Swedish Angina Pectoris Aspirin Trial.[5] in patients with stable angina, the addition of 75 mg of aspirin to sotalol resulted in a 34% reduction in primary outcome events of MI and sudden death and a 32% decrease in secondary vascular events. A meta-analysis of 140,000 patients in 287 randomized trials showed that the reduction in vascular events was comparable for doses of 75 to 150 mg daily and 160 to 325 mg daily; however, daily doses of less than 75 mg had less benefit.[6]

Ticlopidine decreases platelet function in patients with stable angina but, unlike aspirin, has not been shown to decrease adverse cardiovascular events.[7,8] It may, however, induce neutropenia and, albeit infrequently, thrombotic thrombocytopenic purpura (TTP).

In a randomized trial that compared clopidogrel with aspirin in patients with previous MI, stroke, or symptomatic peripheral vascular disease (i.e., at risk of ischemic events), clopidogrel appeared to be slightly more effective than aspirin in decreasing the combined risk of MI, vascular death, or ischemic stroke.[9]

In a recently published CHARISMA study,[10] 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors were randomly assigned to receive clopidogrel (75 mg per day) plus low-dose aspirin (75-162 mg per day) or placebo plus low-dose aspirin and followed them for a median of 28 months. The primary efficacy end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. There was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors. Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes.

ACC/AHA Guidelines

Class I

- Aspirin in the absence of contraindications. (Level of Evidence: A).
- Start and continue indefinitely aspirin 75 to 150 mg/d if not contraindicated. Consider clopidogrel as an agent/alternative if aspirin contraindicated.

UNSTABLE ANGINA/ NON-ST ELEVATION MI

Some of the strongest evidence available about the long-term prognostic effects of therapy in patients with coronary disease pertains to aspirin.[11] Among all clinical investigations with aspirin, trials in UA/NSTEMI have most consistently documented a striking benefit of the drug (> 50% reduction in the risk of death or MI) independent of the differences in study design, such as time of entry after the acute phase, duration of follow-up, and doses used.[14-15]

No trial has directly compared the efficacy of different doses of aspirin in patients who present with UA/NSTEMI. However, trials in secondary prevention of stroke, MI, death, and graft occlusion have not shown an added benefit for aspirin doses of greater than 80 and 160 mg per day but have shown a higher risk of bleeding. An overview of trials with different doses of aspirin in long-term treatment of patients with CAD suggests similar efficacy for daily doses ranging from 75 to 324 mg.[3] The prompt action of aspirin and its ability to reduce mortality rates in patients with suspected AMI enrolled in the ISIS-2 trial led to the recommendation that aspirin be initiated immediately in the emergency department as soon as the diagnosis of ACS is made or suspected. In patients who are already receiving aspirin, it should be continued. The protective effect of aspirin has been sustained for at least 1 to 2 years in clinical trials in UA. Long-term follow-up data in this population are lacking. Given the relatively short-term prognostic impact of UA/NSTEMI in patients with coronary disease, long-term efficacy can be extrapolated from other studies of aspirin therapy in CAD. Studies in patients with prior MI, stroke, or transient ischemic attack have shown statistically significant benefit during the first 2 years and some additional but not statistically significant benefit during the third year. In the absence of large comparison trials of different durations of anti-platelet treatment in patients with cardiovascular disease or in primary prevention, it seems prudent to continue aspirin indefinitely unless side effects are present.

Because the mechanisms of the anti-platelet effects of aspirin and ADP antagonists, ticlopidine has been used successfully for the secondary prevention of stroke and MI and for the prevention of stent closure and graft occlusion. In an open-label trial[16], 652 patients with UA were randomized to receive 250 mg of ticlopidine twice a day or standard therapy without ASA. At 6-month follow-up, ticlopidine reduced the rate of fatal and nonfatal MI by 46% (13.6% vs 7.3%, p = 0.009). The benefit of ticlopidine in the study developed after only 2 weeks of treatment, which is consistent with the delay of the drug to achieve full effect.

Most clinical experience with clopidogrel is derived from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial.[17] A total of 19,185 patients were randomized to receive 325 mg per day ASA or 75 mg per day clopidogrel. Entry criteria consisted of atherosclerotic vascular disease manifested as recent ischemic stroke, recent MI, or symptomatic peripheral arterial disease. Follow-up extended for 1 to 3 years. The RR of ischemic stroke, MI, or vascular death was reduced by 8.7% in favor of clopidogrel from 5.83 to 5.32% (p = 0.043).

The Clopidogrel in Unstable angina to Prevent recurrent ischemic Events (CURE) trial randomized 12,562 patients with UA and NSTEMI presenting within 24 hours to placebo or clopidogrel (loading dose of 300 mg followed by 75 mg daily) and followed them for 3 to 12 months. All patients received aspirin. Cardiovascular death, MI, or Stroke occurred in 11.5% of patients assigned to placebo and 9.3% assigned to clopidogrel (RR = 0.80, p less than 0.001). In addition, clopidogrel was associated with significant reductions in the rate of inhospital severe ischemia and revascularization, as well as the need for thrombolytic therapy or intravenous GP IIb/IIIa receptor antagonists. These results were observed across a wide variety of subgroups. A reduction in recurrent ischemia was noted within the first few hours after randomization.

Clopidogrel is the preferred thienopyridine because of its more rapid onset of action, especially after a loading dose[18,19] and better safety profile than ticlopidine.[20] Initiation of only 75 mg/d achieves the target level of platelet inhibition after 3 to 5 days, whereas the loading dose of 300 mg achieves effective platelet inhibition within 4 to 6 hours. Use of a 600 mg loading dose has been shown to achieve steady-state level of platelet inhibition after just 2 hours.

GP IIb-IIIa Inhibitors

Experimental and clinical studies have suggested that occupancy of greater than or equal to 80% of the receptor population and inhibition of platelet aggregation to ADP (5 to 20 micromoles per L) by greater than or equal to 80% results in potent anti-thrombotic effects.[21] The various GP

IIb/IIIa antagonists, however, possess significantly different pharmacokinetic and pharmacodynamic properties.[22]

Oral GP IIb/IIIa receptor blockers were tested in one PCI trial and three UA/NSTEMI trials; the four trials failed to document a benefit and two showed an excess mortality rate.[23-25]

In meta-analysis not including GUSTO IV ACS, largely evaluating "small molecule" GP IIb/IIIa inhibitors, a 20% reduction in death or MI was observed at 30 days. However, when GUSTO IV ACS was included, the benefit was only a 9% reduction in death or MI at 30 days.[26]

GUSTO IV–ACS[27] enrolled patients in whom early (less than 48-hours) revascularization was not intended. At 30 days, death or MI occurred in 8.0% of patients taking placebo, 8.2% of patients taking 24-hours ***abciximab***, and 9.1% of patients taking 48-hours abciximab, differences that were not statistically significant. At 48 hours, death occurred in 0.3%, 0.7%, and 0.9% of patients in these groups, respectively (placebo vs abciximab 48 hr, p = 0.008). Although the explanation for these results is not clear, they indicate that abciximab at the dosing regimen used in GUSTO IV–ACS is *not* indicated in the management of patients with UA or NSTEMI in whom an early invasive management strategy is not planned.

The PRISM trial[28] directly compared tirofiban with heparin in 3,232 patients. The primary composite outcome (death, MI, or refractory ischemia at the end of a 48-hour infusion period) was reduced from 5.6% with UFH to 3.8% with tirofiban (p = 0.01). At 30 days, the frequency of the composite outcome was similar in the 2 groups (17.1% for UFH vs 15.9% for tirofiban, p = 0.34), but a trend toward reduction in the rate of death or MI was present with tirofiban (7.1% vs 5.8%, p = 0.11), and a significant reduction in mortality rates was observed (3.6% vs 2.3%, p = 0.02). The benefit of tirofiban was mainly present in patients with an elevated Trop 'I' or Trop 'T' concentration at baseline.[29]

In the PRISM-PLUS trial[30], which enrolled 1,915 patients, the combination of tirofiban and UFH compared with UFH alone reduced the primary composite end point of death, MI, or refractory ischemia at 7 days from 17.9% to 12.9% (p = 0.004). This composite outcome was also significantly reduced by 22% at 30 days (p = 0.03) and by 19% at 6 months (p = 0.02). The end point of death or nonfatal MI was reduced by 43% at 7 days (p = 0.006), 30% at 30 days (p = 0.03), and 22% at 6 months (p = 0.06). The combination of tirofiban and UFH showed a significant reduction in the thrombus load at the site of the culprit lesion and improved coronary flow as assessed according to the TIMI criteria.[31]

Eptifibatide was studied in the Pursuit trial (n = 10,948)[32]. The study drug was added to standard management until hospital discharge or for 72 hours. The infusion could be continued for an additional 24 hour if an intervention was performed near the end of the 72-hour infusion period. The primary outcome rate of death or nonfatal MI at 30 days was reduced from 15.7% to 14.2% with eptifibatide (p = 0.042). Within the first 96-hour, a substantial treatment effect was seen (9.1% vs 7.6%, p = 0.01). The benefits were maintained at 6-month follow-up.

Tirofiban and Eptifibatide, in combination with heparin, has been approved for the treatment of patients with ACS, including patients who are managed medically as well as those undergoing PCI.

ACC/AHA GUIDELINES

Class I

1. Antiplatelet therapy should be initiated promptly. ASA should be administered as soon as possible after presentation and continued indefinitely (Level of evidence: A).
2. Clopidogrel should be administered to hospitalized patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance (Level of evidence: A).

3. In hospitalized patients in whom an early non-interventional approach is planned, clopidogrel should be added to ASA as soon as possible on admission and administered for at least 1 month (Level of evidence: A) and for up to 9 months (Level of evidence: B).
4. In patients for whom a PCI is planned, clopidogrel should be started and continued for at least 1 month (Level of evidence: A), and up to 9 months in patients who are not at high risk for bleeding (Level of evidence: B).
5. In patients taking clopidogrel in whom elective CABG is planned, the drug should be withheld for 5 to 7 days (Level of evidence: B).
6. A platelet GP IIb/IIIa—antagonist should be administered, in addition to ASA and heparin, to patients in whom catheterization and PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI (Level of evidence: A).

Class IIa

1. Eptifibatide or tirofiban should be administered, in addition to ASA and LMWH or UFH, to patients *with* continuing ischemia, an elevated troponin or with other high-risk features in whom an invasive management strategy is *not* planned (Level of evidence: A).
2. A platelet GP IIb/IIIa antagonist should be administered to patients already receiving heparin, ASA, *and clopidogrel* in whom catheterization and PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI (Level of evidence: B).

Class IIb

Eptifibatide or tirofiban, in addition to ASA and LMWH or UFH, to patients *without* continuing ischemia who have no other high-risk factors and in whom PCI is *not* planned (Level of evidence: A).

Class III

1. Abciximab administration in patients in whom PCI is not planned (Level of evidence: A).

ST Elevation MI

The Second International Study of Infarct Survival (ISIS-2) has shown conclusively the efficacy of aspirin alone for treatment of evolving acute MI, with an absolute risk difference in 35-day mortality of 2.4% (relative risk reduction [RRR] 23%).[33] When aspirin was combined with streptokinase, the absolute risk difference in mortality was 5.2% (RRR 42%). A meta-analysis demonstrated that aspirin reduced coronary reocclusion and recurrent ischemic events after fibrinolytic therapy with either streptokinase or alteplase.[34] Accordingly, aspirin now forms part of the early management of all patients with suspected STEMI and should be given promptly, certainly within the first 24 hours, at a dose between 162 and 325 mg and continued indefinitely at a daily dose of 75 to 162 mg.[35] Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations.[36]

Clopidogrel combined with aspirin is recommended for patients with STEMI who undergo coronary stent implantation.[37-41] However, in patients in whom aspirin is contraindicated because of aspirin sensitivity, clopidogrel is probably useful as a substitute for aspirin to reduce the risk of occlusion.[42]

All patients recovering from STEMI should, in the absence of contraindications, continue taking aspirin for an indefinite period.[43]

To improve rates of achieving TIMI-3 flow by pharmacological reperfusion therapy, ***GP IIb/IIIa antagonists*** have been combined with fibrinolytic agents to achieve both platelet disaggregation and fibrinolysis.[44] TIMI-14, SPEED and Intro AMI[45,46,47] have demonstrated higher TIMI 3 flow rates at 60 to 90 minutes. When combination therapy is used, the dose of

fibrinolytic agent is reduced by 50%. A large-scale mortality study, GUSTO-V[48], tested half-dose reteplase and full-dose abciximab compared with full-dose reteplase in 16,588 patients in the first 6 hours of STEMI. Thirty-day mortality rates were similar in the 2 groups (5.9% versus 5.6%). However, nonfatal reinfarction rates were reduced in the combination therapy group (2.3% versus 3.5%, p less than 0.0001), as were other complications of MI. Despite the reduction in reinfarction by combination therapy, the 1-year mortality rates were the same (8.38%) in both groups.[49]

ASSENT-3[50] randomized 6095 patients with STEMI to full-dose tenecteplase with UFH versus full-dose tenecteplase with enoxaparin or half-dose tenecteplase plus abciximab plus weight-adjusted, reduced-dose UFH. Similar to the GUSTO V trial, combination of abciximab and half-dose tenecteplase did not reduce mortality compared with full-dose tenecteplase but did result in significantly reduced in-hospital infarction and refractory ischemia. The tenecteplase plus enoxaparin arm showed superiority compared with UFH. The need for urgent PCI was reduced in the GP IIb/IIIa antagonist and fibrinolytic combination therapy arms in both trials.

ACC/AHA GUIDELINES

Class I

1. Aspirin 162 to 325 mg should be given on day 1 of STEMI and in the absence of contraindications should be continued indefinitely on a daily basis thereafter at a dose of 75 to 162 mg (Level of evidence: A).
2. A thienopyridine (preferably clopidogrel) should be administered to patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance (Level of evidence: C).
3. For patients taking clopidogrel for whom CABG is planned, the drug should be withheld for at least 5 days if possible, and preferably for 7, unless the urgency for revascularization outweighs the risks of bleeding. (Level of evidence: B).

Percutaneous Coronary Interventions (PCI)

Aspirin reduces the frequency of ischemic complications after PCI. Although the minimum effective aspirin dosage in the setting of PCI has not been established, for those patients not already taking chronic aspirin therapy (75 to 162 mg per day), an empiric dose of aspirin (300 to 325 mg) given at least 2-hour and preferably 24-hour before the PCI procedure is generally recommended.[51-54]

Among theinopyridines, ***clopidogrel*** may be more efficacious in addition to having a more favourable safety profile.[55] In the *PCI-CURE* trial, 2658 patients undergoing PCI who received the loading dose of 300 mg a median of 10 days before the procedure, the primary end point of cardiovascular death, MI, or urgent revascularization was significantly reduced in the clopidogrel treatment group (4.5% versus 6.4%), with no differences in major bleeding.[56]

In the *CREDO* trial,[57] 2116 patients undergoing PCI received either a 300-mg loading dose of clopidogrel or placebo 3 to 24-hour before PCI. All patients thereafter received clopidogrel 75 mg daily through day 28. For the following 12 months, patients in the loading dose group received clopidogrel and those in the control group received placebo. At one year, long-term clopidogrel therapy was associated with a 27% RRR in the combined risk of death, MI, or stroke for an absolute reduction of 3% (*P* equals 0.02). Clopidogrel pretreatment did not significantly reduce MACE at 28 days. However, in a prespecified subgroup analysis, the patients who received clopidogrel at least 6-hour before PCI had a RRR of 39% (*P* equals 0.051) for the combined end point compared with no reduction with treatment less than 6-hour before PCI. These data suggest that after PCI, long-term clopidogrel therapy (1 year) significantly reduced the risk of adverse ischemic events. A 300 mg loading dose of clopidogrel given at least 3-hour before the

procedure did not reduce events at 28 days, but longer intervals between the loading dose and PCI appeared to be associated with a highly favorable trend toward reduced events.

More recently, 300 mg versus 600 mg loading doses of clopidogrel were directly compared prospectively in the ARMYDA-2 trial.[58] Patients who had stable and unstable angina scheduled for PCI were randomized to one of these loading doses 4 to 8 hours before their procedure. The primary end point of death, MI or urgent revascularization occurred significantly less often in the group receiving a 600 mg (4% versus 12%), although this difference was solely accounted for by a reduction in periprocedural MI.

The concept of a higher loading dose was advanced further by the recently reported ALBION trial evaluating 103 patients who had ACS and received a 300 mg, 600 mg, or 900 mg loading dose of clopidogrel on presentation. Compared with the 300 mg loading dose, 600 mg dose of clopidogrel demonstrated a more rapid onset of action and higher level of inhibition while maintaining a similar safety profile: 900 mg appeared to provide slightly higher antiplatelet inhibition than 600 mg loading dose.[59]

The ISAR-CHOICE study demonstrated additional platelet inhibition with a 600 mg loading dose, although 900 mg did not provide any further antiplatelet effect compared with the 600 mg loading dose.[60]

In PCI Clarity, patients treated with fibrinolysis for STEMI who underwent PCI, 2 to 8 days after receiving a 300 mg loading dose of clopidogrel, had reduced incidence of CV death or ischemic complications when compared to those receiving 300 mg clopidogrel immediately prior to PCI.[61]

In another trial (ISAR-REACT), a higher loading dose of clopidogrel (600 mg) was used before elective, low-risk stent procedures with favorable results compared with routine abciximab administration.[62]

The *clear platelets* study concluded that a strategy of eptifibatide administration was associated with superior platelet inhibition and lower cardiac biomarker release than high-dose (600 mg) or standard-dose (300 mg) clopidogrel at the time of PCI.[63]

On the basis of randomized clinical trial protocols, aspirin 325 mg daily and clopidogrel 75 mg daily should be given for at least 1 month after BMS implantation, 3 months after SES implantation, and 6 months after PES implantation, and ideally up to 12 months in patients who are not at high risk of bleeding, after which daily chronic aspirin should be continued indefinitely at a dose of 75 to 162 mg.

ISAR-REACT trial showed that in low-risk patients having elective PCI, there was no benefit to the use of ***abciximab*** in patients receiving high dose pretreatment with clopidogrel. The sample size was such that it may have been underpowered to show a benefit in low-risk populations.[62] Evaluation of high dose pretreatment in high risk patients and the implications is ongoing in the ISAR-REACT-2 study.

In the EPIC trial, patients receiving abciximab had a 30% reduction in the primary composite end point at 30 days, which maintained at 6 months and at 3 years and were greatest in those who had evolving MI.[64]

The EPILOG trial showed a significant reduction of composite end point in both high and low risk individuals with abciximab, which was maintained at 6 months and at 1 year.[65]

Validation of abciximab in the setting of intracoronary stenting came from the EPISTENT trial, wherein abciximab treated patients demonstrated a significantly lower incidence of death, MI or urgent revascularization at 30 days, which maintained at 6 months and at 1 year.[66]

Pooled analysis of these three large randomized trials confirmed the benefits of abciximab on 30-day death or MI are irrespective of sex or the PCI device used with an absolute risk reduction of mortality of 1.4% at 3 years. A long-term mortality benefit of abciximab in patients with diabetes undergoing PCI was demonstrated in a pooled analysis of 3 trials (EPIC, EPILOG, and EPISTENT; 4.5% vs 2.5%, P equals 0.03).[67]

The ISAR-SWEET trial which included diabetics, abciximab showed reduced angiographic restenosis and TVR but no difference in the incidence of death or MI at 1 year.[68]

Many trials have shown benefit of abciximab in patients of STEMI undergoing primary PCI. In the ADMIRAL study, the primary composite end point of death, MI or revascularisation was significantly lower at 30 day and at 6 months, which was maintained at 3 years.[69] Similar beneficial findings were observed in ISAR-2, RAPPORT and ACE trials. The CADILLAC trial resulted in much lesser benefit with abciximab.[70] However, a meta analysis demonstrated a significant reduction in mortality at 30 days (2.4% versus 3.4%) and between 6 and 12 months (4.4% versus 6.2%), without an increase in significant bleeding[71], a benefit seen only in patients undergoing primary PCI but not in those receiving fibrinolysis.

The clinical utility of eptifibatide, was evaluated in the IMPACT-II trial[72], the 30-day composite primary end point of death, MI, unplanned surgical or repeat percutaneous revascularization, or coronary stent implantation for abrupt closure occurred in 11.4% of placebo-treated patients compared with 9.2% in the 135/0.5 mcg eptifibatide group (*P* equals 0.063) and 9.9% in the 135/0.75 mcg eptifibatide group (*P* equals 0.22). In the PURSUIT trial[73], compared with placebo, patients receiving 180/2.0 mcg eptifibatide had a lower frequency of 30-day death or MI (15.7% vs 14.2%; *P* equals 0.042).

The ESPRIT trial[74] evaluated the efficacy and safety of eptifibatide treatment as adjunctive therapy during nonemergency coronary stent implantation. A double-bolus regimen of eptifibatide (180 mcg per kg bolus followed by a 2.0 mcg per kg per min infusion, with a second 180 mcg per kg bolus given 10 min after the first bolus) was compared with placebo treatment. There was a consistent treatment benefit across all components of the end point and across all subgroups of patients. At 30 days, the key secondary composite end point of death, MI, and urgent target-vessel revascularization was also improved 35% from 10.4% to 6.8% (*P* equals 0.0034).

The clinical effect of tirofiban during coronary angioplasty was evaluated in the RESTORE trial[75], which included patients with UA or acute MI. The rate of primary 30-day end point was reduced from 12.2% in the placebo group to 10.3% in the tirofiban group (*P* equals 0.160). Patients treated with tirofiban had a 38% relative reduction in the composite end point at 48-hour (*P* less than 0.005) and a 27% relative reduction at 7 days (*P* equals 0.022). The incidence of major bleeding was similar in the 2 groups with the TIMI criteria although major bleeding tended to be higher in tirofiban-treated patients.

A larger clinical benefit with tirofiban was seen in patients with UA undergoing coronary angioplasty in the PRISM-PLUS study[76], wherein coronary angioplasty was performed in 30.5% of patients between 49 to 96-hour after randomization. The composite end point of death, MI, or refractory ischemia was reduced significantly in the heparin plus tirofiban group compared with the heparin alone group (10.0% vs 15.7%; *P*< 0.01).

The ADVANCE trial[77] showed a significant benefit of high dose tirofiban, limited to those who had ACS and those who had diabetes. At present, the use of tirofiban remains limited to those patients who have ACS and already receiving the drug.

Another intravenous agent, lamifiban was studied in PARAGON A and B trials, which included patients with ACS. Although these studies suggested potential benefit, there is no plan to continue development of this agent.

Oral GP IIb/IIIa inhibitors have no clinical utility currently. A meta analysis of four large studies, including more than 33,000 patients not only demonstrated a clear lack of efficacy but also suggested increased mortality in addition to increased rates of major bleeding with their use.[78]

ACC/AHA Guidelines

Class I

1. Patients already taking daily chronic aspirin therapy should take 75 to 325 mg of aspirin before the PCI procedure is performed. *(Level of evidence: A.)*
2. Patients not already taking daily chronic aspirin therapy should be given 300 to 325 mg of aspirin at least 2 hours and preferably 24 hours before the PCI procedure is performed. *(Level of evidence: C).*
3. After the PCI procedure, in patients with neither aspirin resistance, allergy, nor increased risk of bleeding, aspirin 325 mg daily should be given for at least 1 month after bare-metal stent implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which daily chronic aspirin use should be continued indefinitely at a dose of 75 to 162 mg. *(Level of evidence: B).*
4. A loading dose of clopidogrel should be administered before PCI is performed. *(Level of evidence: A).* An oral loading dose of 300 mg, administered at least 6 hours before the procedure, has the best established evidence of efficacy. *(Level of evidence: B).*
5. In patients who have undergone PCI, clopidogrel 75 mg daily should be given for at least 1 month after bare-metal stent implantation (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks), 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, and ideally up to 12 months in patients who are not at high risk of bleeding. *(Level of evidence: B).*

Class IIa

1. If clopidogrel is given at the time of procedure, supplementation with GP IIb/IIIa receptor antagonists can be beneficial to facilitate earlier platelet inhibition than with clopidogrel alone. *(Level of evidence: B).*
2. For patients with an absolute contraindication to aspirin, it is reasonable to give a 300 mg loading dose of clopidogrel, administered at least 6 hours before PCI, and/or GP IIb/IIIa antagonists, administered at the time of PCI. *(Level of evidence: C).*
3. When a loading dose of clopidogrel is administered, a regimen of greater than 300 mg is reasonable to achieve higher levels of antiplatelet activity more rapidly, but the efficacy and safety compared with a 300 mg loading dose are less established. *(Level of evidence: C).*
4. It is reasonable that patients undergoing brachytherapy be given daily clopidogrel 75 mg indefinitely and daily aspirin 75 to 325 mg indefinitely unless there is significant risk for bleeding *(Level of evidence: C).*

Class IIb

In patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcating left main, or last patent coronary vessel), platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg per day if less than 50% inhibition of platelet aggregation is demonstrated. *(Level of evidence: C).*

Glycoprotein IIb/IIIa Inhibitors

Class I

In patients with UA/NSTEMI undergoing PCI without clopidogrel administration, a GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban) should be administered. *(Level of evidence: A).*

Class IIa

1. In patients with UA/NSTEMI undergoing PCI with clopidogrel administration, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban). *(Level of evidence: B).*

2. In patients with STEMI undergoing PCI, it is reasonable to administer abciximab as early as possible. *(Level of evidence: B),*
3. In patients undergoing elective PCI with stent placement, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban). *(Level of evidence: B).*

Class IIb

In patients with STEMI undergoing PCI, treatment with eptifibatide or tirofiban may be considered *(Level of evidence: C).*

Adverse Drug Reactions

Contraindications to ***aspirin*** include intolerance and allergy (primarily manifested as asthma), active bleeding, hemophilia, active retinal bleeding, severe untreated hypertension, an active peptic ulcer, or another serious source of gastrointestinal or genitourinary bleeding. Gastrointestinal side effects such as dyspepsia and nausea are infrequent with the low doses. Acute gout due to impaired urate excretion is rarely precipitated. Primary prevention trials have reported a small excess in intracranial bleeding, which is offset in secondary prevention trials by the prevention of ischemic stroke. It has been proposed that there is a negative interaction between ACEIs and aspirin with a reduction in the vasodilatory effects of ACEIs, presumably because aspirin inhibits ACEI-induced prostaglandin synthesis. This interaction does not appear to interfere with the clinical benefits of therapy with either agent.[79]

Recent investigations have demonstrated so called "aspirin resistance" (up to 50%) among the population which may result in up to a three-fold increase in patients who have established CVD. Potential mechanisms may include pharmacodynamic interaction with other drugs, extraplatelet sources of TXA2, or COX polymorphisms that lead to interindividual variability in response.

The adverse effects of ticlopidine limit its usefulness: gastrointestinal problems (diarrhea, abdominal pain, nausea, vomiting), neutropenia in approximately 2.4% of patients, severe neutropenia in 0.8% of patients, and, rarely, thrombotic thrombocytopenia purpura (TTP). Neutropenia usually resolves within 1 to 3 weeks of discontinuation of therapy but very rarely may be fatal. TTP, which also is a very uncommon life-threatening complication, requires immediate plasma exchange. Monitoring of ticlopidine therapy requires a complete blood count that includes a differential count every 2 weeks for the first 3 months of therapy.

There is no excess neutropenia with clopidogrel, which contrasts with ticlopidine. The results provide evidence that clopidogrel is at least as effective as aspirin and may be modestly more effective. In a recent report, 11 severe cases of TTP were described as occurring within 14 days after the initiation of clopidogrel; plasma exchange was required in 10 of the patients, and 1 patient died. These cases occurred among more than 3 million patients treated with clopidogrel. Since clopidogrel, when added to aspirin, increases the risk of bleeding during major surgery, in patients who are scheduled for elective CABG, clopidogrel should be withheld for at least 5 days, and preferably for 7 days before surgery.

Laboratory measurements demonstrate upto 30% of patients may have an inadequate antiplatelet response to standard dosing of clopidogrel, a finding that correlates with cytochrome P450 3A4 metabolic activity, although this has not been correlated with clinical events per se.

Bleeding complications with currently approved iv ***GP IIb/IIIa inhibitors*** have primarily involved vascular access puncture sites in patients undergoing PCI. No increase in ICH has been observed. The need for platelet transfusion is extremely rare, particularly with the short acting agents such as eptifibatide and tirofiban. Severe thrombocytopenia (< 20000/microl) occurs in 0.1 to 0.5% of patients treated with the IV agents, and the incidence appears to be slightly higher with abciximab.

Newer Antiplatelet Agents

Cilostazol: It is a quinolone derivative that inhibits platelet phosphodiesterase-3 and has vasodilatory effects. It has been approved by the FDA for the treatment of intermittent claudication.[80]

Recently, there are studies of triple antiplatelet therapy (aspirin, clopidogrel/ticlopidine and cilostazol) after coronary stenting which seems to be more effective in preventing thrombotic complications without an increased risk of side effects.[81]

Prasugrel: It is a novel oral theinopyridine that has more predictable and potent antiplatelet effects. The JUMBO-TIMI 26 trial, a phase II dose-finding study, suggested an equivalent bleeding risk with a trend toward more efficacy at 30 days compared to clopidogrel. TRITON-TIMI 38, a large-scale randomized trial for efficacy of prasugrel versus clopidogrel in patients who have ACS undergoing PCI, is ongoing.

AZD6140: It is a new oral direct P2Y12 receptor antagonist. The DISPERSE-2 phase II trial evaluated this agent in patients who had ACS and found a similar rate of bleeding and similar ischemic events to clopidogrel, although there was a higher rate of dyspnea.

Cangrelor: Analog of the endogenous direct platelet ADP receptor inhibitor ATP, is an IV drug demonstrating more immediate antiplatelet effects.

Thromboxane synthase inhibitors (e.g., dazoxiben) and TXA2 receptor antagonists (e.g., vapiprost), as well as dual thromoxane synyhase/TXA2 receptor inhibitors (e.g., ridogrel), have been developed but generally have not been found to be superior to aspirin in limited clinical trials.

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