Platelets play a central role in the pathobiology of atherogenesis and atherothrombosis. Therefore, therapies that are directed toward platelet inhibition are widely used in patients with established coronary heart disease (CHD) or in moderate- to high-risk individuals for primary prevention of cardiovascular (CV) events. As our armamentarium of potent antiplatelet therapies continues to expand, there is growing interest in identifying the appropriate groups of patients who will derive the greatest benefit from more potent therapies. To that end, several studies over the past few decades have highlighted that individuals with diabetes mellitus (DM) exhibit abnormalities in platelet function that place them at increased risk of adverse outcomes, as compared with their nondiabetic counterparts (see also Chapter 10).

Although the mechanisms that contribute to platelet hyperreactivity in diabetic patients continue to be elucidated, it appears that diabetic platelets are characterized by the dysregulation of several signaling pathways that occur both at the level of the platelet receptor and with subsequent downstream signaling. In addition, glycosylation may impair endothelial function and promote oxidative stress, thereby further promoting platelet reactivity and procoagulant activity. There is therefore a priori biologic plausibility to support the concept that diabetic patients may derive enhanced benefit from particular therapies directed toward blocking the platelet. However, differences in platelet biology in diabetic patients may also contribute to diminished antiplatelet drug responsiveness. This chapter reviews the use of established and novel oral antiplatelet therapies in diabetic patients for use in primary or secondary prevention of CV events.

**ASPIRIN**

To date, aspirin remains the cornerstone of antiplatelet therapy in the primary and secondary prevention of CV events. Aspirin selectively acetylates the hydroxyl group of a serine residue leading to irreversibility inhibition of the cyclooxygenase-1 (COX-1) enzyme. In turn, inhibition of the COX-1 enzyme blocks downstream production of thromboxane A2 (TXA2; Fig. 16-1), thereby preventing thromboxane-mediated platelet aggregation and vasoconstriction. Because the platelet is enucleate, it is unable to resynthesize COX-1 and the effects of aspirin persist throughout the lifetime of the platelet.

**Aspirin in Primary Prevention**

Although its role in secondary prevention is well established, the clinical efficacy of aspirin in primary prevention remains an ongoing area of investigation. Several large primary prevention trials of aspirin have been conducted in the general population, and investigators have subsequently evaluated the benefit of aspirin within their diabetic subgroups. Although limited by small numbers of diabetic patients and by post hoc design, many trials were able to demonstrate a consistent benefit of aspirin in the primary prevention of CV events for both their diabetic and nondiabetic patients. These results were supported by the Early Treatment Diabetic Retinopathy Study (ETDRS), which included a mixed population of 3711 patients with DM with or without a history of CHD who were randomized to aspirin 650 mg daily or placebo. Although aspirin did not reduce the primary endpoint of all-cause death (hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.75-1.11), a favorable trend was observed toward a reduction in fatal or nonfatal myocardial infarction (MI) at 5 years that did not achieve statistical significance (HR 0.83, 95% CI 0.66-1.04).

In contrast, a benefit for aspirin could not be definitively demonstrated in diabetic patients enrolled in the Primary Prevention Project (PPP), a randomized trial of low-dose aspirin (100 mg daily) versus placebo in 4495 patients with one or more CV risk factors. Although underpowered to detect a significant benefit within the diabetic subgroup (n = 1031), the investigators were unable to demonstrate a significant reduction in CV death, MI, or stroke in diabetic patients (HR 0.90, 95% CI 0.50-1.62) or in total CV events (HR 0.89, 95% CI 0.62-1.26). Moreover, an unfavorable trend was observed toward an increased risk of CV death (HR 1.23, 95% CI 0.69-2.19) in aspirin-treated diabetic patients. In contrast, a more consistent benefit was seen with aspirin in nondiabetic patients with regard to reduction in the risk of CV death, MI, or stroke (HR 0.59, 95% CI 0.37-0.94), total CV events (HR 0.69, 95% CI 0.53-0.90), and CV death (HR 0.32, 95% CI 0.14-0.72).
Because individual trials of aspirin therapy in primary prevention enrolled relatively few diabetic patients, De Berardis and colleagues combined data from six trials and 10,117 patients to examine the clinical efficacy of aspirin to reduce major CV events in primary prevention. The meta-analysis demonstrated a benefit of aspirin in the overall study population, yet the authors were unable to identify a statistically significant benefit in the diabetic subgroup. Although a directional trend was observed, aspirin did not significantly reduce the risk of major CV events in diabetic patients as compared with placebo (HR 0.90, 95% CI 0.81-1.00). Furthermore, aspirin did not reduce either CV mortality (HR 0.94, 95% CI 0.72-1.23) or all-cause mortality (HR 0.93, 95% CI 0.82-1.05) in diabetic patients. However, limitations of the meta-analysis included evidence of significant heterogeneity across trials for key endpoints including MI. To that end, aspirin significantly reduced the risk of MI in men (HR 0.57, 95% CI 0.34-0.94), but did not reduce the risk of MI in women (HR 1.08, 95% CI 0.71-1.65; P for interaction = 0.056). Because women had a higher prevalence of DM, sex-restricted enrollment in some of the trials may have contributed to the observed heterogeneity. Consistent findings were observed in an updated meta-analysis that included individuals with DM across nine trials of aspirin in primary prevention. Aspirin reduced the risk of CHD events by 9%, but the results were not statistically significant (relative risk 0.91, 95% CI 0.79-1.05). Similarly, the use of aspirin was associated with a nonsignificant 10% reduction in the risk of stroke (relative risk 0.90, 95% CI 0.71-1.13; Fig. 16-2). These findings therefore raised concerns that the antiplatelet effects of aspirin were insufficient to attenuate risk of CV events in diabetic patients with baseline abnormalities in platelet function.

Because subgroup analyses from randomized trials may yield spurious results, dedicated trials of aspirin for primary prevention in diabetic patients have since been completed or are still ongoing. The Japanese Primary Prevention of Atherosclerosis with Aspirin in Diabetes (JPAD) study was the first prospectively designed trial to evaluate the use of low-dose aspirin (81 or 100 mg daily) versus placebo in 2539 type 2 diabetic patients in Japan aged 30 to 85 years and without a known history of atherosclerotic disease. After a median of 4.37 years, only 154 atherosclerotic events (including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease [PAD]) occurred during follow-up and the trial was therefore unable to demonstrate clinical efficacy with aspirin in diabetic patients despite a directional trend (HR 0.80, 95% CI 0.58-1.10, P = 0.16). In addition to being underpowered, other limitations of the trial included its open label design, which introduced the possibility of bias. However, among the subgroup of patients older than 65 years, aspirin reduced the risk of atherosclerotic events by 32% (P = 0.047). The incidence of hemorrhagic stroke or gastrointestinal (GI) bleeding was low and did not differ significantly between groups.

Subsequently, the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial evaluated the efficacy of low-dose aspirin (100 mg daily) versus placebo in 1276 adults in Scotland older than 40 years with type 1 or type 2 DM and an ankle brachial pressure index below 0.99 in the absence of symptomatic CV disease. Although the trial was relatively small, the incidence of CV events (death from congestive heart failure [CHF] or stroke, nonfatal MI or stroke, or amputation because of critical limb ischemia) was almost identical between treatment arms during a median of 6.7 years follow-up (116 versus 117 events; HR 0.98, 95% CI 0.76-1.26). Aspirin did not reduce the risk of death from CHD or stroke (HR 1.23, 95% CI 0.79-1.93). GI bleeding was infrequent, and its incidence did not differ between groups.

In light of these conflicting data, the use of aspirin in primary prevention continues to be a topic of debate. In particular, any signal suggesting efficacy must be weighed against the potential risks of treatment. In a large population-based cohort of individuals in Italy, the use of aspirin was associated with a relative 55% increased incidence of major bleeding over a median of 5.7 years in the overall cohort, as compared with patients not taking aspirin. The risk of bleeding was increased in individuals over the age of 70, those with a higher risk of GI disease, and by concomitant use of NSAIDs. Irrespective of aspirin use, patients with DM were observed to have a 36% higher incidence of major bleeding episodes, including an increased risk of GI and intracranial bleeding, as compared with nondiabetic patients. Of interest, the use of aspirin did not appear to

**FIGURE 16-1** The platelet has multiple ligands that contribute to pathways leading to platelet activation including thrombin, adenosine diphosphate (ADP), von Willebrand factor, and thromboxane A2 (TXA2). The activated platelet then releases prothrombotic factors including ADP and TXA2, thereby further amplifying platelet activation. A platelet latticework is formed when fibrinogen cross-links activated platelets via the glycoprotein IIb/IIIa receptor. The P2Y12 subtype of the ADP receptor is the site of action for established and novel compounds, including ticlopidine, clopidogrel, prasugrel, ticagrelor, and elinogrel. (Modified from Bhatt DL: Intensifying platelet inhibition—navigating between Scylla and Charybdis, N Engl J Med 357:2078-2081, 2007.)
be associated with an increased risk of bleeding for diabetic patients. However, it remains unknown whether the absence of a bleeding signal with aspirin in diabetic patients might be explained by a diminished pharmacodynamic response to aspirin in diabetic patients with abnormal platelet biology, or attributable to other factors.

Based on the weight of the evidence to date, the American Diabetes Association (ADA) updated its recommendations in 2010 to consider low-dose aspirin therapy (75 to 162 mg/day) in primary prevention in diabetic individuals (men older than 50 years, women older than 60 years) at increased CV risk (10-year risk greater than 10%) with at least one or more major CV risk factor including family history of CV disease, hypertension, albuminuria, dyslipidemia, or current tobacco use (Table 16-1). In 2010, an expert panel that included representatives from the ADA, the American College of Cardiology Foundation (ACCF), and the American Heart Association (AHA) issued similar recommendations that included the use of aspirin (75 to 162 mg/day) in individuals (men older than 50 years, women older than 60 years) at increased CV risk (10-year risk >10%) and with established CV risk factors, who were not believed to be at increased risk of bleeding. They also noted that low-dose (75-162 mg/day) aspirin could be considered for those with

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHS</td>
<td>0.59 (0.33, 1.06)</td>
<td>5.7</td>
</tr>
<tr>
<td>ETDRS</td>
<td>0.85 (0.73, 1.00)</td>
<td>48.2</td>
</tr>
<tr>
<td>PPP</td>
<td>0.49 (0.17, 1.43)</td>
<td>1.8</td>
</tr>
<tr>
<td>WHS</td>
<td>1.34 (0.85, 2.12)</td>
<td>9.1</td>
</tr>
<tr>
<td>JPAD</td>
<td>0.87 (0.40, 1.87)</td>
<td>3.4</td>
</tr>
<tr>
<td>POPADAD</td>
<td>1.09 (0.82, 1.43)</td>
<td>21.5</td>
</tr>
<tr>
<td>TPT</td>
<td>0.90 (0.28, 2.89)</td>
<td>1.5</td>
</tr>
<tr>
<td>UKMD</td>
<td>1.00 (0.42, 2.40)</td>
<td>2.6</td>
</tr>
<tr>
<td>HOT</td>
<td>0.77 (0.44, 1.36)</td>
<td>6.2</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.91 (0.79, 1.05)</td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 16-2** A meta-analysis of randomized trials that examined the effects of aspirin on the risk on CHD events (A) and stroke (B) in diabetic patients without an overt history of CV disease. Although there was a directional trend toward a reduction in the risk of CHD events and stroke with aspirin in diabetic patients, this benefit was not statistically significant. (From Pignone M, Alberts MJ, Colwell JA, et al: Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation, Circulation 121:2694-2701, 2010.)

![Diagram of meta-analysis results](image-url)
DM at intermediate CVD risk (younger patients with one or more risk factors, or older patients with no risk factors, or patients with 10-year CVD risk of 5% to 10%). Aspirin is not recommended in diabetic patients younger than 21 years because of the risk of Reye syndrome, and the role of aspirin in diabetic patients younger than 30 years remains largely untested. The U.S. Preventive Services Task Force has recommended aspirin use in men aged 45 to 79 years and women 55 to 79 years but has not differentiated their recommendations on the presence or absence of DM. In women aged 55-79 years, encourage aspirin use when potential CVD benefit (ischemic strokes prevented) outweighs the potential harm of gastrointestinal hemorrhage (irrespective of whether the individual has DM). Do not encourage aspirin use for MI prevention in men younger than 45 years or for stroke prevention in women younger than 55 years (irrespective of whether the individual has DM). There is insufficient evidence to recommend the use of aspirin for primary prevention in individuals aged 80 years or older.

**Aspirin in Secondary Prevention**

Although the role of aspirin in primary prevention continues to be investigated, the use of aspirin in stable and unstable secondary prevention is well established. Whereas smaller studies had been suggestive, the first randomized trial that definitively demonstrated aspirin’s efficacy in patients with acute MI was the Second International Study of Infarct Survival (ISIS-2), which demonstrated a 23% reduction in the odds of vascular death with aspirin at 5 weeks when compared with placebo. Subsequent trials have since demonstrated a consistent benefit for aspirin across the spectrum of acute coronary syndrome (ACS) (see also Chapter 21).

The Antithrombotic Trialists’ Collaboration (ATC) combined data from 287 secondary prevention studies of oral antiplatelet agents, mostly aspirin, and included a total of 212,000 individuals with acute vascular disease, established vascular disease, or risk factors for vascular disease.

**Table 16-1 Summary of Recommendations Regarding the Use of Aspirin in Primary Prevention in Diabetic Individuals**

<table>
<thead>
<tr>
<th>ORGANIZATION</th>
<th>YEAR</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Diabetes Association</td>
<td>2014</td>
<td>Consider aspirin therapy (75-162 mg/day) as a primary prevention strategy in those with type 1 or type 2 DM at increased CV risk (10-year risk &gt;10%). This includes most men older than 50 years or women older than 60 years who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). (Level of evidence: C) There is not sufficient evidence to recommend aspirin for primary prevention in lower-risk individuals, such as men younger than 50 years or women younger than 60 years without other major risk factors. In patients in these age groups with multiple other risk factors, clinical judgment is required. (C)</td>
</tr>
<tr>
<td>ADA, American Heart Association (AHA), American College of Cardiology Foundation (ACCF)</td>
<td>2010</td>
<td>Low-dose (75-162 mg/day) aspirin use for prevention is reasonable for adults with DM and no previous history of vascular disease who are at increased CVD risk (10-year risk of CVD events &gt;10%) and who are not at increased risk for bleeding (based on a history of previous GI bleeding or peptic ulcer disease or concurrent use of other medications that increase bleeding risk, such as NSAIDS or warfarin).</td>
</tr>
<tr>
<td>U.S. Preventive Services Task Force</td>
<td>2009</td>
<td>In men aged 45-79 years, encourage aspirin use when potential CVD benefit (MIs prevented) outweighs the potential harm of GI hemorrhage (irrespective of whether the individual has DM).</td>
</tr>
<tr>
<td></td>
<td>2012</td>
<td>Antplatelet therapy with aspirin is not recommended for people with DM who do not have clinical evidence of atherosclerotic disease. (Level of evidence A)</td>
</tr>
</tbody>
</table>

CVD = Cardiovascular disease; NSAIDs = nonsteroidal anti-inflammatory drugs.
Overall, in patients with established CV disease, antiplatelet therapy reduced the odds of recurrent CV events by 22% and of nonfatal stroke by 25%. Although individuals with DM had a higher absolute event rate than nondiabetic patients, the relative benefit of antiplatelet therapy toward reducing vascular events was consistent across patient groups. For every 1000 diabetic patients treated with aspirin, it was estimated that 42 vascular events could be prevented with use of antiplatelet therapy.21

Of note, it was observed in the ATC analysis that lower doses of aspirin (75 to 150 mg/day) appeared to be as efficacious as high doses of aspirin (>150 mg/day). Furthermore, the use of lower doses of aspirin was associated with a reduced risk of bleeding complications as compared with higher doses. The evidence to support the use of lower doses of aspirin was also supported by an observational analysis from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARIOT) trial that demonstrated that aspirin doses exceeding 100 mg daily were not associated with increased efficacy as compared with lower doses in patients with stable CV disease or CV risk factors.22 Moreover, there was an unfavorable trend toward a higher risk of CV death, MI, or stroke (adjusted HR 1.16, 95% CI 0.93-1.14) and increased risk of severe or life-threatening bleeding (adjusted HR 1.30, 95% CI 0.83-2.04) when aspirin doses above 100 mg daily were combined with clopidogrel. More recently, the question of optimal aspirin dosage was directly addressed in a randomized clinical trial of low-dose (325 mg loading dose, 75 to 100 mg daily) versus higher-dose aspirin (325 mg loading dose, 300 to 325 mg daily) in patients with ACS.23 The use of higher-dose aspirin did not reduce the risk of CV death, MI, or stroke (HR 0.97, 95% CI 0.86-1.09) as compared with lower-dose aspirin after 30 days, but increased the risk of minor bleeding by 13% (HR 1.13, 95% CI 1.00-1.27, P = 0.04).23

The ADA currently recommends the use of low-dose aspirin (75 to 162 mg/day) for secondary prevention of CV events (including stroke) in all diabetic patients without contraindication. Based on the strength of the data, the use of low-dose aspirin is now supported by the ACC/AHA guidelines in patients after non-ST-elevation ACS or percutaneous coronary intervention (PCI) (see also Chapter 21).24,25

### TABLE 16-2 Ongoing Trials of Aspirin for Primary Prevention in Individuals with Type 1 or Type 2 DM

<table>
<thead>
<tr>
<th>TRIAL NAME</th>
<th>DESIGN</th>
<th>POPULATION</th>
<th>INTERVENTION</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D; ISRCTN48110081)</td>
<td>Open label, randomized, parallel group</td>
<td>Approximately 5170 patients; type 1 or type 2 DM without clinical evidence of vascular disease and with an indication for statin therapy</td>
<td>Aspirin (100 mg/day) plus simvastatin versus simvastatin alone</td>
<td>CV death, MI, stroke, or CV hospitalization</td>
</tr>
<tr>
<td>A Study of Cardiovascular Events in Diabetes trial (ASCEND; clinicaltrials.gov NCT00135226)</td>
<td>Double-blind, 2 x 2 factorial randomized design</td>
<td>Approximately 15,480 patients; type 1 or type 2 DM, older than 40 years, and without known history of vascular disease</td>
<td>Aspirin (100 mg/day) versus placebo (2 x 2: 1 g/day omega-3 ethyl esters versus placebo)</td>
<td>Vascular death, MI, or stroke (excluding cerebral hemorrhage)</td>
</tr>
</tbody>
</table>

### Ticlodipine

Ticlodipine was the first thienopyridine to be approved for clinical use, in 1991. It is a first-generation thienopyridine that irreversibly blocks the ADP P2Y12 receptor and thereby prevents platelet activation and aggregation mediated by ADP signaling pathways.27 When combined with aspirin, ticlodipine has been shown to reduce the risk of CV events in patients undergoing coronary stenting as compared with aspirin monotherapy or aspirin with warfarin.27 However, an unfavorable safety profile (including risk of neutropenia) and slow onset of action led the way for clopidogrel to emerge shortly thereafter as the preferred thienopyridine in appropriate settings.

### Clopidogrel

When compared with ticlodipine, clopidogrel has been shown to have similar efficacy in addition to improved safety and tolerability27 and faster pharmacodynamic effects after a loading dose.26 In a meta-analysis that combined data from 13,995 patients in randomized trials and registries of ticlodipine versus clopidogrel, the use of clopidogrel was associated with a significant reduction in mortality and recurrent ischemic events when compared with ticlodipine and had fewer side effects.21 The efficacy of clopidogrel monotherapy (75 mg/day) versus aspirin (325 mg/day) in secondary prevention was evaluated in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial.30 The CAPRIE trial compared clopidogrel (75 mg/day) versus aspirin (325 mg/day) in 19,185 patients with established atherosclerotic disease, including recent MI, recent stroke, or symptomatic PAD. Overall, clopidogrel monotherapy significantly reduced the risk of vascular death, MI, or ischemic stroke by 8.7% compared with aspirin alone (P = 0.043) and reduced the risk of GI bleeding (P = 0.05).26 Patients with DM in the trial (n = 3866) were observed to have approximately a threefold higher event rate compared with their nondiabetic counterparts.21 Overall, the relative risk reduction (RRR) of clopidogrel versus aspirin for reducing
vascular events was statistically similar in diabetic and non-diabetic patients (12.5% versus 6.1%, respectively, \( P \) for interaction = 0.36). However, because of the higher absolute event rate in diabetic patients and the trend toward a greater RRR, clopidogrel conferred a greater absolute benefit in diabetic patients. To that end, the number of events (vascular death, MI, stroke, rehospitalization with ischemia, bleeding) prevented per 1000 patients per year was 21 in diabetic patients versus 9 in nondiabetic patients treated with clopidogrel as compared with aspirin. The absolute benefit of clopidogrel further improved to 38 events prevented per 1000 patients per year in insulin-treated patients with diabetes treated with clopidogrel as compared with aspirin (Fig. 16-3). Following the publication of the CAPRIE findings, the ADA issued recommendations that clopidogrel be used as monotherapy in very high-risk diabetic patients and as an alternative to aspirin in intolerant patients.32 Although individuals with DM have higher platelet reactivity, randomized trials have been unable to demonstrate a greater relative benefit for clopidogrel in diabetic versus nondiabetic patients. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial enrolled 12,562 patients with non-ST-elevation ACS and randomized them to clopidogrel versus placebo on a background of aspirin for up to 1 year.33 After a mean of 9 months, clopidogrel reduced the risk of vascular death, MI, or stroke by 20% compared with placebo (HR 0.80, 95% CI 0.72-0.90). This clinical benefit was associated with a 38% increase in the risk of major bleeding (3.7% versus 2.7%, \( P < 0.001 \)) but no increase in the risk of fatal bleeding.34 The benefit of clopidogrel appeared early but was maintained beyond 30 days (HR 0.82, 95% CI 0.70-0.95). Consistent with prior studies, diabetic patients in the trial (\( n = 2840 \)) were observed to have almost a two-fold higher rate of CV events (14.2% versus 7.9%) as compared with their nondiabetic counterparts, thereby translating into a greater absolute benefit from clopidogrel. However, the relative benefit of clopidogrel was grossly similar in diabetic and nondiabetic patients with an approximate 17% RRR in the primary endpoint in diabetic patients, as compared with 20% in the overall population.33

More recently, the clinical efficacy of clopidogrel was evaluated in a nonrandomized analysis of a large nationwide Danish registry of patients who had survived 30 days after an MI.34 After multivariable adjustment and propensity-score matching, clopidogrel was associated with a smaller reduction in all-cause mortality (adjusted HR 0.89, 95% CI 0.79-1.00 versus 0.75, 95% CI 0.70-0.80, \( P \) interaction = 0.001) and CV mortality (adjusted HR 0.93, 0.81-1.06 versus 0.77, 95% CI 0.72-0.83, \( P \) interaction = 0.01) in patients with DM, as compared with those who did not have diabetes. Clopidogrel was associated with only a marginal difference in the risk of death or reinfarction in either patient group (0.91, 0.87-0.96 versus 1.00, 0.91-1.10, \( P \) interaction = 0.08).34 However, this differential association for clopidogrel between diabetic and nondiabetic patients was not observed in patients undergoing PCI, and no differential association was observed between patient groups with regard to the efficacy of aspirin.35 Limitations of this analysis included the fact that use of clopidogrel was not randomized and therefore there is the risk of confounding despite adjustments having been made for known confounders. Supporting this hypothesis, clopidogrel appeared to have a greater magnitude of association toward reduced risk of death as compared with the risk of reinfarction, a finding not supported by existing trials.36

Notwithstanding the limitations of a nonrandomized analysis, there are mechanistic data to support the hypothesis that clopidogrel may have diminished efficacy in diabetic patients. Pharmacodynamic studies have demonstrated that almost two thirds of diabetic patients have an inadequate response to clopidogrel.36 Moreover, platelet aggregation on dual antiplatelet therapy is even further heightened in insulin-treated diabetic patients, as compared with those who do not require insulin therapy (Fig. 16-4).37 The latter finding is perhaps explained by the fact that insulin inhibits platelet aggregation by suppressing the P2Y12 pathway. Because diabetic patients have a loss of responsiveness to insulin, there is subsequent upregulation of the P2Y12 pathway, leading to heightened platelet reactivity and diminished response to antiplatelet agents.

Multiple trials have examined the benefit of clopidogrel and the optimal timing of loading dose administration in patients undergoing PCI. Because clopidogrel is a prodrug, approximately 6 hours are required to attain steady state.

![FIGURE 16-3](https://example.com/fig16-3.png) The number of events (vascular death, MI, stroke, rehospitalization for ischemia or bleeding) prevented per 1000 patients per year treated with clopidogrel instead of aspirin in nondiabetic patients, all diabetic patients, and diabetic patients treated with insulin in the CAPRIE trial. (Modified from Bhatt DL, Marso SP, Hirsch AT, et al: Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus, Am J Cardiol 90:625-628, 2002.)

![FIGURE 16-4](https://example.com/fig16-4.png) Platelet aggregation after stimulation with 6 μM and 20 μM adenosine diphosphate (ADP) in nondiabetic patients, non–insulin-treated diabetic patients, and insulin-dependent diabetic patients. On stable doses of dual antiplatelet therapy. (Modified from Angiolillo DJ, Bernardi E, Ramirez C, et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment, J Am Coll Cardiol 48:298-304, 2006.)
concentrations after a 300-mg loading dose. The PCI-CURE substudy examined outcomes for those patients enrolled in the CURE trial who underwent PCI (see also Chapter 21). The CURE trial enrolled 12,562 patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) and randomized them to clopidogrel (300-mg loading dose, 75 mg daily) versus placebo on a background of aspirin. Those patients who were pretreated with clopidogrel before PCI and who continued clopidogrel for up to 1 year had a 31% lower risk of CV death or MI compared with patients who were not pretreated and who were treated for only 4 weeks after PCI. Although numerically smaller in magnitude, this benefit was comparable in diabetic patients in whom clopidogrel reduced the risk of CV death or MI by 23% compared with placebo after PCI.

Similar early and long-term benefits with clopidogrel were demonstrated in the Clopidogrel for the Reduction of Events during Observation (CREDO) trial, in which patients were randomized to a loading dose of clopidogrel 3 to 24 hours before PCI and then to continued maintenance therapy with clopidogrel beyond the first month after the procedure, compared with patients who were not administered a loading dose and were treated with clopidogrel for only 28 days after PCI. Overall, patients randomized to early and sustained clopidogrel treatment had a 26.9% reduction in the risk of death, MI, or stroke. It is important to note that there appeared to be continued benefit for long-term treatment with clopidogrel throughout the treatment period of 1 year. As was seen in the diabetic subgroup of the PCI-CURE substudy, the relative benefit of clopidogrel in diabetic patients was comparable, but numerically smaller, than that seen in nondiabetic patients (11.2% RRR, 95% CI 46.2% to –46.8 versus 32.8% RRR, 95% CI 51.6%–6.8%).

Higher loading (600 mg) and maintenance doses (150 mg daily for 6 days) of clopidogrel were compared with standard doses of clopidogrel in patients after ACS in the Clopidogrel Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial (see also Chapter 21). Although double-dosing did not reduce the risk of 30-day CV events in the overall study population (HR 0.94, 95% CI 0.83–1.06), the higher-dose regimen was associated with a reduced risk of CV death, MI, or stroke (HR 0.86, 95% CI 0.74–0.99) in the cohort of patients who underwent PCI. However, the higher dose of clopidogrel also increased the risk of major bleeding by 42% (HR 1.42, 95% CI 1.09–1.83). There was no evidence of heterogeneity by DM status for the primary efficacy endpoint (P for interaction = 0.32).

The use of dual antiplatelet therapy in stable secondary prevention and high-risk primary prevention was evaluated in the CHARISMA trial. Overall, clopidogrel did not reduce the risk of CV events when compared with placebo, and there was no evidence of interaction by DM status. In a post hoc analysis, the subgroup of patients with prior MI, ischemic stroke, or symptomatic PAD showed a 17% RRR with dual antiplatelet therapy. In contrast, there was no clear benefit and an increased risk of bleeding in high-risk patients in the absence of established vascular disease (Fig. 16–5). Of note, the primary prevention cohort was enriched with diabetic patients based on the entry criteria. Therefore the results of the CHARISMA trial do not support the use of dual antiplatelet therapy in diabetic patients for primary prevention, but ongoing trials may demonstrate a benefit for more prolonged dual antiplatelet therapy in patients with established vascular disease.

Another area of ongoing investigation is the optimal duration of dual antiplatelet therapy after PCI (see also Chapter 17). Several studies have demonstrated that there is an increased risk of adverse outcomes after discontinuation of clopidogrel. In a study of 749 patients with DM who underwent stenting, the use of more prolonged dual antiplatelet therapy was associated with a reduced risk of death or MI in patients after bare metal stent placement (P = 0.01) and a reduced risk of death in patients with a drug-eluting stent (DES) (P = 0.03). However, many of the analyses to date have been observational in design, and therefore it is plausible that the results might be explained by confounding. In particular, clopidogrel is often discontinued in the setting of bleeding or surgery, which may independently place a patient at increased risk of CV events.

To date, only a small number of studies have addressed the optimal duration of dual antiplatelet therapy with a randomized design. The Prolonging Dual Antiplatelet Treatment after Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) trial randomized 2013 patients who had undergone PCI to dual antiplatelet therapy for a period of 6 versus 24 months. The incidence of CV death, MI, or stroke was observed to be similar in both treatment arms (10.1% versus 10.0%, P = 0.92), whereas the incidence of bleeding (Bleeding Academic Research Consortium [BARC] type 2, 3, and 5) was higher for patients who continued dual antiplatelet therapy for 24 months (7.4% versus 3.5%, P < 0.001). Similar findings were seen in two trial populations that were composed of 2701 patients in Korea who were randomized to aspirin alone versus continued dual antiplatelet therapy 12 months after PCI. Although the study was underpowered because of a low event rate, more prolonged dual antiplatelet therapy failed to demonstrate any signal toward clinical efficacy. In a second study underpowered to assess noninferiority, a similar lack of efficacy was demonstrated for dual-antiplatelet therapy beyond

![FIG 16-5](image-url)
The efficacy and safety of prolonged dual antiplatelet therapy beyond 12 months are currently undergoing evaluation in the larger Dual Antiplatelet Therapy (DAPT) Study (clinicaltrials.gov NCT00977938). The DAPT trial is enrolling patients after PCI and then randomizing those patients who are event free after 12 months to an additional 18 months of treatment with a thienopyridine versus placebo.

**Clopidogrel Response Variability**

There exists significant interindividual variability in pharmacodynamic response to clopidogrel. In turn, diabetic patients with an inadequate response to clopidogrel vary considerably depending on the applied definitions, type of assay, dose of clopidogrel, and patient population. In patients undergoing elective PCI, it has been described that approximately 31% of individuals will have less than 10% inhibition of platelet aggregation (IPA) at 24 hours as measured by light transmission aggregometry after a 300-mg loading dose of clopidogrel. It is important to note there is evidence that the prevalence of clopidogrel hyporesponders is higher in patients with DM and is highest in patients requiring insulin therapy (see Fig. 16-4). In the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) trial, individuals with DM had higher baseline platelet reactivity, and almost two thirds of diabetic patients were demonstrated to have an inadequate response to clopidogrel. Higher baseline platelet reactivity and diminished response to clopidogrel may therefore in part explain the persistent risk of CV events that is observed in diabetic patients.

It remains unknown whether specific genetic, cellular, and clinical causes may contribute to the higher prevalence of clopidogrel hyporesponders in diabetic patients. Regardless of DM status, several studies have demonstrated that clopidogrel-treated patients with at least one copy of a reduced-function CYP2C19 allele have an increased risk of CV events after undergoing PCI; however, genotype appears to explain only a small fraction of observed interpatient variability. In diabetic patients, in the setting of excess insulin, there is evidence to suggest that platelets develop insulin resistance leading to upregulation of the P2Y12 receptor and heightened platelet reactivity. Additional cellular factors that may contribute to the observed attenuation in response in diabetic patients include alterations in calcium metabolism, increased ADP exposure, and accelerated platelet turnover.

Because patients with DM may have upregulation of the P2Y12 receptor, there has been interest in using a higher dose of clopidogrel to help overcome pharmacodynamic resistance. In the OPTIMUS trial, the use of 150 mg of clopidogrel daily resulted in greater IPA than the 75-mg dose in diabetic patients with poor pharmacodynamic response to clopidogrel. However, despite the use of the 150-mg maintenance dose, a substantial fraction of diabetic patients continued to have high post-treatment platelet reactivity. Similar findings were observed in Gauging Responsiveness with a VerifyNow P2Y12 Assay—Impact on Thrombosis and Safety (GRAVITAS) (see also Chapter 17), a trial of 2214 patients with high on-treatment platelet reactivity with clopidogrel after placement of a DES; the patients were randomized to high-dose (600-mg loading dose then 150 mg daily) or standard-dose (75 mg daily) clopidogrel. The prevalence of high on-treatment platelet reactivity was observed to be higher among diabetic patients, and as a consequence almost half the patients who were determined to have high on-treatment platelet reactivity had diabetes. Although higher doses of clopidogrel reduced the in vitro prevalence of pharmacodynamic clopidogrel hyporesponders, clopidogrel 150 mg daily failed to reduce the risk of CV events as compared with standard dosing in these high-risk patients. Therefore there are no prospective data that support routine platelet function testing at the present time.

**Prasugrel**

Prasugrel is a third-generation thienopyridine that irreversibly binds to the P2Y12 receptor to inhibit platelet activation and aggregation. Although the active metabolites of both clopidogrel and prasugrel have similar affinity for the P2Y12 receptor in vitro, prasugrel achieves more rapid and more potent IPA than clopidogrel. It is hypothesized that this is because of its more efficient pathway of drug metabolism and activation. Clopidogrel requires two separate CYP-dependent oxidative steps to form its active metabolite, and most of the prodrug is metabolized by esterases that shunt the drug toward a dead-end inactive pathway. In contrast, esterases assist with activation of the prasugrel prodrug, and prasugrel is oxidized to its active metabolite in a single CYP-dependent step. After a 60-mg loading dose, prasugrel has been shown to significantly inhibit platelets within 30 minutes of ingestion. In contrast, a 300-mg loading dose of clopidogrel requires approximately 6 hours to achieve steady-state, and a 600-mg loading dose takes approximately 2 hours to demonstrate clinically relevant antiplatelet effects. In addition to its enhanced potency, prasugrel demonstrates diminished interpatient variability as compared with clopidogrel.

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 enrolled 13,608 patients with ACS and undergoing PCI to prasugrel (60-mg loading dose, 10 mg daily) or clopidogrel (300-mg loading dose, 75 mg daily) on a background of aspirin (see also Chapter 21). After a median of 14.5 months, prasugrel significantly reduced the risk of CV death, MI, or stroke by 19% as compared with clopidogrel (HR 0.81, 95% CI 0.73-0.90). Furthermore, prasugrel significantly reduced the risk of MI (9.7% versus 7.4%, P < 0.001), urgent target-vessel revascularization (3.7% versus 2.5%, P < 0.001), and stent thrombosis (2.4% versus 1.1%, P < 0.001). The benefit of prasugrel appeared early, and landmark analyses demonstrated that the benefit appeared to persist over time. Although the incidence of bleeding was low, prasugrel significantly increased the risk of non–coronary artery bypass graft (CABG) surgery–related TIMI major bleeding by 32%, including a significant increase in the risk of life-threatening and fatal bleeding. Subsequent post hoc analyses demonstrated the patients with a history of stroke or TIA do not appear to benefit from prasugrel and may incur harm from more potent antiplatelet therapy. In addition, a net clinical benefit was not observed in patients aged older than 75 years or weighing less than 60 kilograms.

Of interest, the balance between efficacy and safety for prasugrel compared with clopidogrel appeared most favorable in diabetic patients enrolled in the TRITON-TIMI 38 trial with DM. Of the 3146 patients with DM, prasugrel...
significantly reduced the risk of CV death, MI, or stroke by 30% (HR 0.70, 95% CI 0.58–0.85, P < 0.001, P interaction = 0.09) and this benefit was further increased to 37% in insulin-treated patients (HR 0.63, 95% CI 0.44–0.89, Fig. 16-6). Prasugrel reduced the risk of MI by 40% in diabetic patients (HR 0.60, 95% CI 0.48–0.76), as opposed to 18% in nondiabetic patients (HR 0.82, 95% CI 0.72–0.95, P interaction = 0.02). Also, prasugrel reduced the risk of stent thrombosis in the overall diabetic cohort (3.6% versus 2.0%, HR 0.52, 95% CI 0.33–0.84), and this benefit was further enhanced in diabetic patients requiring insulin (5.7% versus 1.8%, HR 0.31, 95% CI 0.12–0.77). Although diabetic patients had a higher absolute rate of bleeding, prasugrel did not appear to substantially increase the risk of major bleeding as compared with clopidogrel in this high-risk patient group (2.6% versus 2.5%, HR 1.06, 95% CI 0.66–1.69). Because of the higher event rate and greater benefit of prasugrel in insulin-treated patients, the absolute risk reduction in CV events with prasugrel was 8% indicating that only 13 insulin-treated diabetic patients would need to be treated to prevent one ischemic event, contrasted with a number-needed-to-treat of 26 for DM patients not on insulin. The observations from the diabetic subgroup of the TRITON-TIMI 38 trial therefore support the hypothesis that the achieved degree of platelet reactivity is an important predictor of outcome. Because individuals with DM have higher baseline platelet reactivity and diminished pharmacodynamic response to clopidogrel, it is plausible that diabetic patients derive enhanced benefit from this more potent antiplatelet therapy that is able to attain lower levels of on-treatment platelet reactivity.

The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial was a two-phase study of 201 patients undergoing PCI that compared the pharmacodynamic response to prasugrel (60-mg loading dose, 10 mg daily) with higher-dose clopidogrel (600-mg loading dose, 150 mg daily). Prasugrel achieved greater IPA as compared with higher-dose clopidogrel in both the loading dose and maintenance dose phases. The rate of patients who were hyporesponsive to clopidogrel (IPA ≤20% in response to 20 μM ADP) was higher in diabetic patients than nondiabetic patients at all timepoints. In contrast, no hyporesponders were observed for patients on prasugrel at 6 hours regardless of diabetes status. Consistent findings were observed in the OPTIMUS-3 trial, which exclusively enrolled patients with DM. In OPTIMUS-3, individuals with DM and coronary artery disease (CAD) were randomized to prasugrel (60-mg loading dose, 10 mg daily) or clopidogrel (600-mg loading dose, 150 mg daily) over two 1-week treatment periods separated by a 2-week washout. Prasugrel achieved greater platelet inhibition than high-dose clopidogrel at 4 hours after a loading dose. This difference was maintained throughout the loading dose and maintenance phase (from 1 hour through 7 days, P < 0.001). Prasugrel reduced the number of diabetic patients with an inadequate response to thienopyridine therapy as compared with high-dose clopidogrel.

After the publication of the TRITON-TIMI 38 trial findings, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial compared the long-term efficacy of prasugrel (10 mg daily) versus clopidogrel (75 mg daily) in 7243 patients with ACS who were managed medically without coronary revascularization (see also Chapter 21). A lower dose of prasugrel (5 mg daily) was used in patients who weighed less than 60 kg or were older than 75 years. The primary analysis was restricted to patients younger than 75 years. In this patient group, prasugrel did not significantly reduce the risk of CV death, MI, or stroke as compared with clopidogrel (HR 0.91, 95% CI 0.79–1.05). The findings were consistent in the subset of 2811 patients with DM (HR 0.90, 95% CI 0.73–1.09, P interaction = 0.71). The prespecified analysis of first or recurrent ischemic events (all components of the primary endpoint) suggested a lower risk for prasugrel among patients under the age of 75 years (HR 0.85; 95% CI 0.72 to 1.00; P = 0.04). Rates of severe and intracranial bleeding were similar in the two groups in all age groups. Therefore the findings of the TRILOGY ACS trial do not support the use of prasugrel in patients who are managed without coronary revascularization.

The 2012 Focused Update to the ACCF/AHA Guidelines for the Management of Patients with non–ST-elevation ACS offers a class I recommendation for the use of clopidogrel, prasugrel, or ticagrelor (see later) on a background of aspirin in patients with unstable angina (UA) or non–ST-segment myocardial infarction (NSTEMI) who are undergoing PCI, with no distinction in the recommendations with regard to drug of choice based on DM status (see also Chapter 21). If prasugrel is used, it should be given promptly and no later than 1 hour after PCI once the coronary anatomy is defined and the decision is made to proceed with PCI (see also Chapters 17 and 22). Based on the findings from TRITON-TIMI 38, prasugrel should not be administered to patients with a history of stroke or transient ischemic attack (TIA). In patients over the age of 75 years, the use of prasugrel is generally not recommended but may be considered in high-risk patients such as those with DM. A lower dose of 5 mg daily can be considered in patients over the age of 75 or who weigh less than 60 kg. Prasugrel should be continued for at least 12 months in ACS patients who undergo PCI. Earlier discontinuation of
a P2Y12 receptor inhibitor can be considered in patients in whom the anticipated morbidity from bleeding exceeds its benefits.

**Ticagrelor**

Ticagrelor is the first reversibly binding oral P2Y12 receptor antagonist. It is a nonthienopyridine and does not require metabolism to form its active metabolite. It has been shown to bind the P2Y12 receptor with a noncompetitive binding mechanism toward ADP. Similar to prasugrel, ticagrelor demonstrates rapid onset of action and decreased interpatient variability as compared with clopidogrel. Because of an elimination half-life of 7 hours and its reversible binding characteristics, it is administered twice daily. However, its antiplatelet effects have been shown to extend to approximately 120 hours. Although it is more potent than clopidogrel, its ability to inhibit platelet aggregation is roughly equivalent to that of clopidogrel at 24 hours after drug discontinuation because of its faster offset kinetics. Ticagrelor may therefore be less likely than clopidogrel to increase the risk of bleeding in patients who require surgery 48 to 120 hours after the last dose.

The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial evaluated the safety and efficacy of ticagrelor in 18,624 patients across the spectrum of ACS (see also Chapter 21). Patients were randomized to clopidogrel (300- to 600-mg loading dose, 75 mg daily) or ticagrelor (180-mg loading dose, 90 mg daily). At 12 months, ticagrelor reduced the risk of vascular death, MI, or stroke by 16% (HR 0.84, 95% CI 0.77-0.92), as compared with clopidogrel. In addition, ticagrelor reduced the risk of death from vascular causes (4.0% versus 5.1%, P=0.001) and all-cause mortality (4.5%, versus 5.9% with clopidogrel, P<0.001), but increased the risk of non-CABG-related Thrombolysis in Myocardial Infarction (TIMI) major bleeding by 25% (P=0.03). Of the P2Y12 inhibitors that have been evaluated to date, ticagrelor is the only drug to have demonstrated a mortality benefit across the spectrum of ACS. However, ticagrelor did not increase the risk of fatal bleeding (P=0.66) or CABG-related major bleeding (P=0.32).

The relative benefit of ticagrelor appeared to be comparable in diabetic and nondiabetic patients in PLATO, although the absolute benefits were greater in insulin-treated diabetic patients. Ticagrelor reduced the risk of vascular death, MI, or stroke by 12% in diabetic patients (HR 0.88, 95% CI 0.76-1.03) versus 17% in nondiabetic patients (HR 0.83, 95% CI 0.74-0.92, P interaction =0.49, Fig. 16-7). Similarly, in diabetic patients, ticagrelor reduced the risk of all-cause mortality (HR 0.82, 95% CI 0.66-1.01) and stent thrombosis (HR 0.65, 95% CI 0.36-1.17) to an extent that was consistent with the overall cohort. Ticagrelor tended to increase non-CABG-related PLATO major bleeding in both diabetic and nondiabetic patients (HR 1.13, 95% CI 0.86-1.49; HR 1.22, 95% CI 1.01-1.46, respectively, P interaction =.69). There was no heterogeneity in the efficacy or safety of ticagrelor with regard to patients who were or were not treated with insulin.

If diabetic patients indeed derive enhanced benefit from more potent antiplatelet therapy after ACS, it is unclear why these findings were not observed in the PLATO trial. In patients who are hyporesponsive to clopidogrel, switching to ticagrelor has been shown to inhibit platelet aggregation to the same extent as it does when clopidogrel-responsive patients are treated with ticagrelor. In this same study, almost all patients treated with ticagrelor (25% of whom had diabetes) achieved platelet reactivity levels below the threshold that has been shown to be associated with an increased risk of ischemic events regardless of their clopidogrel response status.

There are limited head-to-head data to compare the pharmacodynamic or clinical efficacy of prasugrel with that of ticagrelor. In a study of 44 patients with ACS (23% of whom had DM) and high on-treatment platelet reactivity on clopidogrel, patients were randomized in a double-blind crossover design to either ticagrelor 90 mg twice daily or prasugrel 10 mg daily without a loading dose for 15 days before crossing over to the alternate therapy. At the end of the two treatment periods, ticagrelor achieved a greater degree of platelet inhibition than prasugrel (P<0.001). Both drugs were effective at reducing platelet reactivity below the predefined threshold for poor response. It remains unknown whether the two drugs would demonstrate similar clinical efficacy if compared in a large-scale head-to-head clinical trial or if similar pharmacodynamic effects would have been observed if a loading dose of the drugs had been administered.

Unlike with prasugrel, the benefit of ticagrelor has not been directly assessed in a dedicated trial population of patients managed without PCI. However, in the PLATO trial, ticagrelor reduced the risk of vascular death, MI, or stroke in patients who were intended to be managed noninvasively (HR 0.85, 95% CI 0.73-1.00, P=0.04), of whom 29% eventually underwent PCI. Ticagrelor is the first of the two novel P2Y12 antagonists to be evaluated in a population of patients with stable CAD. The ongoing Prevention with Ticagrelor of Secondary Thrombotic Events in High-Risk Patients with Prior Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction (PEGASUS-TIMI) 54 trial (clinicaltrials.gov NCT01225562) has enrolled intermediate- to high-risk individuals with a history of MI in the past 1 to 3 years to one of two doses of ticagrelor (60 mg or 90 mg twice daily) or placebo on a background of low-dose aspirin.

<table>
<thead>
<tr>
<th>FIGURE 16-7</th>
<th>Clinical events and comparative efficacy (HR, 95% CI) of ticagrelor versus clopidogrel for patients without DM, diabetic patients not treated with insulin, and patients with diabetes treated with insulin in the PLATO trial. The absolute benefit of ticagrelor appeared largest in diabetic patients treated with insulin, although the relative benefits were similar in all three groups. (Modified from James S, Angiolillo DJ, Cornel JH, et al: Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial, Eur Heart J 31:3006-3016, 2010.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CV death, MI, or stroke (%)</strong></td>
<td><strong>Ticagrelor</strong></td>
</tr>
<tr>
<td>No DM</td>
<td>HR 0.83</td>
</tr>
<tr>
<td>n = 13,951</td>
<td>10.2</td>
</tr>
<tr>
<td>DM no insulin</td>
<td>HR 0.93</td>
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<tr>
<td>n = 3,625</td>
<td>14.2</td>
</tr>
<tr>
<td>DM with insulin</td>
<td>HR 0.78</td>
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<tr>
<td>n = 1,036</td>
<td>22.8</td>
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directly address the clinical efficacy of ticagrelor in patients with stable CAD and will also help to assess the optimal duration of dual antiplatelet therapy in patients after MI. As well, The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) trial is evaluating the efficacy and safety of ticagrelor (90 mg twice daily) in patients with type 2 diabetes mellitus and either a documented history of obstructive coronary artery disease or prior coronary revascularization (clinicaltrials.gov NCT01991795).

**OTHER ANTIPLATELET MEDICATIONS**

**Cilostazol**
Cilostazol is a phosphodiesterase III inhibitor that raises cyclic adenosine monophosphate (cAMP) levels in platelets and vascular smooth muscle cells, leading to inhibition of platelet activation and arteriolar vasodilation.71 When cilostazol was added to a background of dual antiplatelet therapy, nonrandomized studies demonstrated that this agent appeared to reduce the risk of stent thrombosis72,73 and ischemic events,72,73 without a significant increase in bleeding. Thus far, randomized trials of triple antiplatelet therapy in patients after PCI have yielded conflicting results, although most trials have been underpowered for clinical outcomes (see also Chapter 17).74 In the Efficacy of Cilostazol on Ischemic Complications after Drug-Eluting Stent Implantation (CILON-T) trial, the addition of cilostazol failed to reduce the risk of death, nonfatal MI, ischemic stroke, or target lesion revascularization in patients after DES implantation (8.5% versus 9.2%, P = 0.74), despite achieving a reduction in platelet reactivity.74 In contrast, in a second trial of patients after ACS undergoing PCI, cilostazol reduced the risk of death, nonfatal MI, stroke, or target vessel revascularization (10.3% versus 15.1%, P = 0.011) when added to aspirin and clopidogrel.75 In the latter study, the benefit of cilostazol appeared to be enhanced in patients with high-risk clinical or angiographic features, including DM (n = 263, 9.9% versus 18.9%, HR 0.47, 95% CI 0.23-0.96).75

These findings are supported by pharmacodynamic data that have shown that cilostazol enhances inhibition of P2Y12 signaling in diabetic patients.76 Cilostazol combined with standard-dose clopidogrel reduces platelet reactivity to a greater extent than clopidogrel 150 mg daily in patients with type 2 DM.77 The greater pharmacodynamic effect of cilostazol in diabetic patients was observed regardless of whether or not patients carried genetic polymorphisms that have been shown to influence response to clopidogrel.77 These findings may in part explain the ability of cilostazol to reduce the risk of ischemic events in high-risk patients. To that end, the antiplatelet effects of cilostazol appear to be enhanced in diabetic patients78 and patients with high on-treatment platelet reactivity.79,80

In addition to its antiplatelet effects, cilostazol is hypothesized to exert pleiotropic effects including inhibition of neointimal hyperplasia. Supporting this concept, a systematic review that combined data from 23 randomized trials of cilostazol suggested that it may reduce the risk of in-stent restenosis (RR 0.60, 95% CI 0.49-0.73) and need for repeat revascularization (RR 0.69, 95% CI 0.55-0.86) without a significant increase in bleeding (RR 0.71, 95% CI 0.43-1.16) in patients after PCI.81 In a dedicated trial of diabetic patients receiving a DES, the addition of cilostazol to aspirin and clopidogrel reduced angiographic restenosis and extent of late luminal loss, thereby leading to a lower rate of target lesion revascularization at 9 months as compared with dual antiplatelet therapy alone.82 Although the study was underpowered for clinical events, major adverse cardiac events tended to be lower in the triple than in the dual antiplatelet therapy group (3.0% versus 7.0%, P = 0.066).83 However, the use of cilostazol is limited by a high frequency of side effects including headache, GI disturbance, and palpitations. Larger, more definitive studies of cilostazol are therefore needed before it can be routinely used as an adjunct to dual antiplatelet therapy after coronary stenting.

**Dipyridamole**
Dipyridamole exhibits a number of properties that contribute to platelet inhibition and vasodilation. Dipyridamole inhibits thromboxane synthase leading to reduced TXA2 production and thereby reduced platelet activation.83 It inhibits adenosine deaminase and cellular reuptake of adenosine into platelets, erythrocytes, and endothelial cells causing extracellular adenosine levels to rise.83 Dipyridamole is also a phosphodiesterase inhibitor leading to higher cAMP and cyclic guanosine monophosphate (cGMP) levels within platelets and endothelial cells and thereby blocking response to ADP via the P2Y12 receptor and enhancing nitric oxide signaling.84,85

Although there are limited data to support the use of dipyridamole in patients with CHD, its use has been extensively studied in patients with cerebrovascular disease in combination with aspirin. In the European Stroke Prevention Study (ESP), the combination of aspirin (330 mg) and dipyridamole (75 mg) three times daily reduced the risk of all-cause mortality or stroke by 33.5% compared with placebo in patients with a recent stroke or TIA.86 Moreover, the benefit appeared to be further enhanced in diabetic versus nondiabetic patients (48% versus 32%, respectively).87 Furthermore, it appears that the effects of dipyridamole and aspirin are additive.87 In patients with recent stroke or TIA, the combination of dipyridamole (400 mg daily) and aspirin (50 mg daily) reduced the risk of stroke by 37% compared with placebo, whereas dipyridamole alone reduced the risk of stroke by 16% and aspirin alone by 18%.88 In the open-label European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), the combination of aspirin plus dipyridamole (200 mg twice daily) reduced the risk of CV death, MI, stroke, or major bleeding by 20% (HR 0.80, 95% CI 0.66-0.98), as compared with aspirin alone (30 to 325 mg daily) in patients with a history of an acute cerebrovascular event.89 An increased frequency of headache contributed to a higher rate of discontinuation in the dipyridamole group.90 Currently there is no role for dipyridamole for the purpose of reduction of coronary risk.

**PROTEASE-ACTIVATED RECEPTOR 1 ANTAGONISTS**

**Vorapaxar**
Thrombin stimulates platelet activation via protease-activated receptor 1 (PAR-1), the major thrombin receptor on the platelet cell surface. Although extensive research has been directed toward the ADP-dependent P2Y12 receptor, thrombin is the most potent platelet agonist.89 Because aspirin and clopidogrel do not interfere with
PAR-1–dependent platelet activation, patients on standard dual antiplatelet therapy remain at risk of recurrent CV events via alternate pathways of platelet activation.

Vorapaxar is a competitive and selective antagonist of PAR-1 that acts by binding at or near the tethered ligand binding site. Because PAR-1 receptor antagonists selectively interfere with thrombin-mediated platelet activation without disrupting the coagulation cascade or ADP-dependent platelet activation, it was hypothesized that PAR-1 receptor antagonists might reduce the risk of ischemic events without significantly increasing the risk of bleeding. This hypothesis was supported by phase II studies that suggested trends toward efficacy with increasing doses of vorapaxar and without a significant increase in major bleeding.

Vorapaxar was subsequently evaluated in two large-scale clinical trials of patients with stable atherosclerotic disease or ACS, the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Atherosclerosis (TRA2*–TIMI 50) and the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Acute Coronary Syndrome (TRA-CER), respectively. In January 2011, the joint Data and Safety Monitoring Board for the two trials reported an excess in intracranial hemorrhage in patients with a history of stroke. As a consequence, the study drug was discontinued in the TRA2*–TIMI 50 trial for patients with a history of stroke, but the trial continued to completion in patients with a history of MI or PAD. The TRA-CER trial was stopped prematurely after reaching its prespecified number of primary endpoints.

In the 26,449 patients with stable atherosclerotic disease enrolled in the TRA2*–TIMI 50 trial, vorapaxar (2.5 mg daily) significantly reduced the risk of CV death, M, or stroke by 13% and the risk of CV death, MI, stroke, or urgent coronary revascularization by 12% (HR 0.88, 95% CI 0.824–0.95) as compared with placebo during a median follow-up of 2.5 years. Although vorapaxar reduced the risk of recurrent CV events, vorapaxar increased the risk of moderate or severe bleeding by 66% (HR 1.66, 95% CI 1.43–1.93), including a significant increase in the risk of intracranial hemorrhage. The rate of fatal bleeding was not significantly increased for patients on vorapaxar (0.6% versus 0.4%, P = 0.076).

Despite an observed trend toward efficacy, vorapaxar was not superior to placebo for the management of patients with ACS in the TRA-CER trial. Vorapaxar (40-mg loading dose, 2.5 mg daily) did not significantly reduce the risk of the primary endpoint of CV death, MI, recurrent ischemia with hospitalization, or urgent coronary revascularization (HR 0.92, 95% CI 0.85–1.017) in patients after ACS. Vorapaxar did reduce the key secondary endpoint of CV death, MI, or stroke by 11% compared with placebo (HR 0.89, 95% CI 0.81–0.98), including a 12% reduction in MI (HR 0.88, 95% CI 0.79–0.98). Consistent with the findings from the TRA2*–TIMI 50 trial, vorapaxar increased the risk of GUSTO moderate or severe bleeding (HR 1.35, 95% CI 1.16–1.58) and intracranial hemorrhage (HR 3.39, 95% CI 1.78–6.45) in patients after ACS.

Atopaxar

Atofapax (E5555) is a second orally active, reversible, small molecule inhibitor that selectively inhibits PAR-1 activation by binding at or near the tethered ligand binding site. Although vorapaxar and atopaxar share similarities, vorapaxar exhibits a much longer half-life (165 to 311 hours) and achieves 50% recovery of platelet function at 4 weeks after treatment discontinuation. In contrast, atopaxar has an approximate plasma half-life of 22 to 26 hours.

The phase II Lessons from Antagonizing the Cellular Effects of Thrombin (LANCELOT) program evaluated the safety tolerability of atopaxar in patients after ACS or with stable CAD. In patients after ACS, atopaxar significantly reduced Holter-detected ischemia without a clear increase in major bleeding compared with placebo. Similar findings were observed in patients with CAD, including a nonsignificant trend toward reduced ischemic events. In a focused platelet function substudy, atopaxar achieved rapid and sustained platelet inhibition via the PAR-1 receptor. Although the drug was generally well tolerated, liver transaminase elevation and relative QTc prolongation were observed with the highest doses of atopaxar. To date, atopaxar has not been evaluated in phase III testing.

FUTURE DIRECTIONS

As the prevalence of DM continues to grow, there will be an urgent need to develop therapies that may help to attenuate CV risk in this high-risk population. In addition to the antiplatelet drugs reviewed in this chapter, several novel antiplatelet drugs remain in development. Cangrelor is a direct-acting and reversible intravenous P2Y12 receptor inhibitor whose use has been studied in the setting of PCI and as a bridge to surgery for patients off oral P2Y12 inhibition. Picotamide inhibits TXA2 synthase and TXA2 receptors and has been proposed as an alternative to aspirin. Because the drug blocks TXA2 through pathways independent of COX-1, it may offer enhanced benefit to diabetic patients who respond inadequately to aspirin. As more potent or alternate antiplatelet therapies undergo clinical evaluation, continued emphasis will need to be placed on achieving the optimal balance between efficacy and safety.

References


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