Diabetes mellitus (DM) is a key risk factor for recurrent atherothrombotic events in patients with acute coronary syndrome (ACS) and in those undergoing percutaneous coronary intervention (PCI). The prothrombotic milieu that characterizes patients with DM underscores the importance of oral antithrombotic therapy for secondary prevention of recurrent events in these patients. Indeed, dual antiplatelet therapy (DAPT) with aspirin and the P2Y12 inhibitor clopidogrel, which has represented the mainstay of treatment for many years, has significantly reduced the incidence of recurrent atherothrombotic events. However, recurrence rates in DM patients still remain high despite this treatment regimen, which may be partly related to inadequate platelet inhibition induced by standard DAPT with aspirin and clopidogrel. This underpins the need for more potent antithrombotic treatment regimens for secondary prevention of atherothrombotic events in DM patients following ACS or PCI. The development of antiplatelet therapies associated with more potent oral platelet P2Y12 receptor inhibition, including prasugrel and ticagrelor, as well as platelet inhibitors blocking alternative pathways, such as thrombin-mediated platelet inhibition with vorapaxar, may represent potential treatment options in DM patients. Moreover, with the introduction of the target-specific oral anticoagulants, there has been a reappraisal of the use of anticoagulation in addition to antiplatelet therapy for secondary prevention in patients with ACS. This review provides an update on the recent advances and limitations of oral antithrombotic agents used for secondary prevention in DM patients following ACS or PCI. (Circ J 2016; 80: 791–801)

Key Words: Antiplatelet therapy; Diabetes mellitus; Secondary prevention

Diabetes mellitus (DM) is a pandemic public health burden with a prevalence of 346 million patients worldwide. Importantly, DM patients have a 3-fold higher risk of coronary artery disease (CAD), 5-fold higher cardiovascular (CV) mortality and 3-fold higher all-cause mortality than non-DM patients. Moreover, DM is a key determinant of recurrent CV events in patients with acute coronary syndrome (ACS) or those undergoing percutaneous coronary intervention (PCI). These observations suggest the need for DM-specific therapeutic regimens. Multiple factors, such as hyperglycemia, oxidative stress, endothelial dysfunction, platelet dysfunction and abnormal coagulation factors, contribute to the prothrombotic milieu that characterizes DM patients and thus to the high prevalence of cardiovascular disease (CVD) manifestations in this patient population. These observations underscore the need for effective oral antithrombotic treatment regimens for secondary prevention of atherothrombotic events, particularly after ACS and/or PCI. Indeed, dual antiplatelet therapy (DAPT) with aspirin and the P2Y12 inhibitor clopidogrel, which has represented the mainstay of treatment for many years, has significantly reduced the incidence of recurrent atherothrombotic events. However, recurrence rates in DM patients still remain high despite this treatment regimen, which may be partly related to inadequate platelet inhibition induced by standard DAPT with aspirin and clopidogrel. This underpins the need for more potent antithrombotic regimens for secondary prevention of atherothrombotic events in DM patients following an ACS or PCI. This review article encompasses the most recent updates and pitfalls of oral antithrombotic therapies for secondary prevention of DM patients following ACS or PCI.
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These mediators further recruit platelets from the circulation and amplify platelet aggregation in the high shear rate conditions, which culminates in extension and stabilization of the thrombotic plug. The effects of these mediators are achieved through activation of G protein-coupled receptors on platelet surfaces. Therefore, there are several classes of oral antiplatelet agents that target these mediators (Figure 2). They include aspirin, which by blocking cyclooxygenase-1 (COX-1) enzyme activity mitigates TXA2 mediated platelet activation, as well as agents that specifically inhibit ADP- and thrombin-mediated platelet activation by blocking the P2Y12 receptor (ie, clopidogrel, prasugrel, and ticagrelor) and the protease-activated receptor-1 (PAR-1) (ie, vorapaxar), respectively (Table 1). Other antiplatelet agents, such as cilostazol, a phosphodiesterase inhibitor that modulates intraplatelet levels of cyclic adenosine 3',5'-monophosphate (cAMP), have also been used for secondary prevention in Asian countries. Moreover, the observation that the concentrations of factors activating the coagulation cascade, such as thrombin, remain elevated after ACS has also suggested a role for the long-term use of an oral anticoagulant as a secondary prevention measure.

Classification and Pharmacological Properties of Antithrombotic Agents

After the adhesion of platelets to vascular injury sites, activated platelets release secondary mediators, such as thromboxane A2 (TXA2), adenosine diphosphate (ADP) and thrombin. These mediators further recruit platelets from the circulation and amplify platelet aggregation in the high shear rate conditions, which culminates in extension and stabilization of the thrombotic plug. The effects of these mediators are achieved through activation of G protein-coupled receptors on platelet surfaces. Therefore, there are several classes of oral antiplatelet agents that target these mediators (Figure 2). They include aspirin, which by blocking cyclooxygenase-1 (COX-1) enzyme activity mitigates TXA2 mediated platelet activation, as well as agents that specifically inhibit ADP- and thrombin-mediated platelet activation by blocking the P2Y12 receptor (ie, clopidogrel, prasugrel, and ticagrelor) and the protease-activated receptor-1 (PAR-1) (ie, vorapaxar), respectively (Table 1). Other antiplatelet agents, such as cilostazol, a phosphodiesterase inhibitor that modulates intraplatelet levels of cyclic adenosine 3',5'-monophosphate (cAMP), have also been used for secondary prevention in Asian countries. Moreover, the observation that the concentrations of factors activating the coagulation cascade, such as thrombin, remain elevated after ACS has also suggested a role for the long-term use of an oral anticoagulant as a secondary prevention measure.
Antithrombotics in DM Patients With CAD

Efficacy and Safety of Oral Antithrombotic Treatment Approaches in DM

This section provides an overview of the efficacy and safety of currently recommended oral antithrombotic, both antiplatelet and anticoagulant, treatment regimens used for secondary prevention of atherothrombotic events in DM patients. A description of intravenous therapies, which are limited to the acute phase of treatment of ACS/PCI patients, goes beyond the scope of this paper and is provided elsewhere.\(^\text{13}\)

**Aspirin**

Aspirin irreversibly inhibits COX-1 activity of platelet prostaglandin-endoperoxide synthase 1 by acetylation of the serine residue, which subsequently prevents conversion of arachidonic acid into multiple downstream bioactive prostanooids including TXA\(_2\), prostaglandins and prostacyclin (Table 1).\(^\text{3,14}\) Consequently, aspirin irreversibly inhibits platelet activation and aggregation by the G protein-coupled thromboxane and prostaglandin endoperoxide receptors.\(^\text{3,14}\) Aspirin inhibits both TXA\(_2\)-induced platelet aggregation and prostacyclin induced counter-regulation, which is also important in gastric mucosal protection.\(^\text{14}\) Although TXA\(_2\) is mainly derived from COX-1 and sensitive to aspirin inhibition, prostacyclin is derived from both COX-1 and more profoundly from COX-2 under low-dose aspirin administration.\(^\text{14}\) This suggests that substantial prostacyclin synthesis may remain preserved with low-dose aspirin administration.\(^\text{14}\) Of note, with increasing doses of aspirin, COX-2 inhibition increases in a dose-dependent manner, which results in subsequent reduction of prostacyclin generation. These discrete aspirin effects on TXA\(_2\) and prostacyclin also result in a dose-dependent increase of bleeding, but with similar ischemic risk reduction.\(^\text{14}\) Therefore, low-
dose aspirin (75–162 mg) is recommended for secondary prevention of post-ACS/PCI, including in DM patients.

The benefits of aspirin are well documented in the large collaborative meta-analysis (Antithrombotic Trialists’ Collaboration), which included 43,000 person-years in 16 secondary prevention trials. In secondary prevention, aspirin was associated with significant risk reduction of major CV events (rate ratio 0.80, 95% confidence interval [CI] 0.73–0.88). The major benefits of aspirin derived from the 31% risk reduction (rate ratio 0.69, 95% CI 0.60–0.80) in nonfatal myocardial infarction (MI). Although aspirin was also effective in reducing the risk of ischemic stroke (rate ratio 0.78, 95% CI 0.61–0.99), the incidence of hemorrhagic stroke was increased by aspirin use (rate ratio 1.67, 95% CI 0.97–2.90). The benefit of aspirin in DM patients was consistent with the overall study population. However, the incidence of recurrent ischemic events remains high (~20%) despite aspirin use. The persistence of a high rate of ischemic events may be partly because of increased platelet reactivity despite aspirin therapy, which may be related to enhanced platelet turnover, increased TXA2 synthesis or early recovery of COX-1 activity in DM. These observations have led to the investigation of the use of a higher dosing regimen of aspirin or increasing its frequency of administration. However, the CURRENT-OASIS 7 (Clopidogrel and aspirin optimal dose usage to reduce recurrent events-7th organization to assess strategies in ischemic syndromes) study clarified the clinical futility of high-dose aspirin in both DM and non-DM patients. Several studies have demonstrated that twice-daily administration of aspirin resulted in greater platelet inhibition than once-daily administration and a dose-dependent suppression of serum TXB2: levels in DM patients. However, the clinical implications of a twice-daily dosing regimen remain unknown.

### Table 1. Pharmacological Properties of Oral Antithrombotic Agents Approved for Secondary Prevention in Patients With DM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemistry</th>
<th>Dose</th>
<th>Target</th>
<th>Mechanism of action</th>
<th>Half-life</th>
<th>Time to peak target receptor inhibition</th>
<th>Off-set</th>
<th>Metabolism</th>
<th>Level of inhibition at steady state</th>
<th>Drug interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clopidogrel</strong></td>
<td>Thienopyridine, prodrug</td>
<td>LD: 300–600 mg, MD: 75 mg qd</td>
<td>P2Y12 receptor</td>
<td>Irreversible covalent bond to the receptor</td>
<td>8 h</td>
<td>8 h</td>
<td>5 days</td>
<td>Multiple CYP isoenzymes</td>
<td>40–50% with wide variability</td>
<td>CYP3A4 or CYP2C19 inducers or inhibitors</td>
</tr>
<tr>
<td><strong>Prasugrel</strong></td>
<td>Thienopyridine, prodrug</td>
<td>LD: 60 mg, MD: 10 mg qd (MD: 5 mg for special populations*)</td>
<td>P2Y12 receptor</td>
<td>Irreversible covalent bond to the receptor</td>
<td>7 h</td>
<td>2–4 h</td>
<td>7 days</td>
<td>CYP (3A4, 2B6 &gt;2C9, CYP2C19)</td>
<td>65–80%</td>
<td>None</td>
</tr>
<tr>
<td><strong>Ticagrelor</strong></td>
<td>Direct acting</td>
<td>LD: 180 mg, MD: 90 mg twice daily</td>
<td>P2Y12 receptor</td>
<td>Reversible conformational change of the receptor</td>
<td>7 h</td>
<td>2–4 h</td>
<td>3–5 days</td>
<td>CYP 3A4 and 3A5</td>
<td>65–80%</td>
<td>CYP3A4 or 3A5 inducers or inhibitors</td>
</tr>
<tr>
<td><strong>Vorapaxar</strong></td>
<td>Phosphonoacetyl-L-aspartate, active drug</td>
<td>MD: 2.5 mg qd</td>
<td>PAR-1 receptor</td>
<td>Competitive inhibition of the receptor</td>
<td>–20 h</td>
<td>1 h with 40 mg LD, within 7 days with 2.5 mg MD</td>
<td>–4 weeks</td>
<td>CYP3A4</td>
<td>≥80%</td>
<td>CYP3A4 inducers or inhibitors</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>Oxazolidinone, active drug</td>
<td>2.5 mg b.i.d.</td>
<td>FXa</td>
<td>Selective direct factor Xa inhibitor</td>
<td>5–13 h</td>
<td>2–4 h</td>
<td>12 h</td>
<td>CYP3A4, CYP2J2, CYP-independent, renal P-gp</td>
<td>22%</td>
<td>CYP3A4 and P-gp inducers or inhibitors</td>
</tr>
</tbody>
</table>

*Dose reduction recommended by both US Federal Drug Agency and European Medicines Agency in patients weighing <60 kg and only by European Medicines Agency in patients ≥75 years of age. CPTP, cyclopentyl-triazolo-pyrimidine; CYP, hepatic cytochrome P450; DM, diabetes mellitus; FXa, activated coagulation factor X; LD, loading dose; MD, maintenance dose; PAR, protease-activated receptor; P-gp, P-glycoprotein.

### P2Y12 Inhibitors

**Clopidogrel** Clopidogrel irreversibly blocks the ADP binding site on the P2Y12 receptor after undergoing complex biological activation processes (Table 1). Clopidogrel is in fact a prodrug that is up to 85% hydrolyzed into an inactive acid metabolite by human carboxylesterase-1 after intestinal absorption. The remaining 15% of the prodrug requires a 2-step oxidation processes using multiple hepatic cytochrome P450 CYP isoenzymes to generate an active metabolite. The CYP2C19 isoenzyme is involved in both metabolic steps. Therefore, genetic polymorphisms associated with reduced function of this enzyme or drugs interfering with enzyme activity, such as certain proton pump inhibitors, may impair clopidogrel’s effects. Because ADP-induced P2Y12 receptor activation plays a pivotal role in pathological thrombosis, a clopidogrel-based antiplatelet regimen has represented the mainstay of secondary prevention in patients with ACS or PCI, built on the results of numerous large-scale investigations, as described next. In addition, because of its more favorable safety profile compared with ticlopidine, it soon became the P2Y12 receptor inhibitor of choice.

In the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) study consisting of 19,185 patients with recent MI, recent ischemic stroke or established peripheral artery disease (PAD), clopidogrel (75 mg daily) was associated with a significant 8.7% relative risk reduction of the composite endpoint (ischemic stroke, MI, or vascular death) compared with aspirin (325 mg daily) (Table 2). In that study, DM patients showed higher ischemic recurrence rates than non-DM patients in both the clopidogrel and aspirin groups (15.6% vs. 11.8% in clopidogrel group; 17.7% vs. 12.7% in aspirin group). In the subgroup analysis including 3,866 DM patients, clopidogrel showed a 21% risk reduction of the primary end point as aspirin (Table 2). Importantly,
Clopidogrel was also associated with significant 37% relative risk reduction of any bleeding events compared with aspirin (Table 2). The observation of persistently elevated event rates in a high-risk setting subsequently led to investigations into the effect of combining aspirin with clopidogrel on clinical outcomes. The efficacy of DAPT with clopidogrel and aspirin was well documented in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study consisting of 12,562 patients with non-ST segment elevation acute coronary syndrome (CAD), coronary artery disease; CV, cardiovascular; CVD, cerebrovascular disease; HR, hazard ratio; NA, not applicable; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; Pint, P for interaction vs. non-DM; RRR, relative risk reduction. Other abbreviations as in Table 1.

**Table 2. Outcomes in Patients With DM in Major Secondary Prevention With Oral Antithrombotic Therapy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients (DM/Overall)</th>
<th>Setting</th>
<th>Treatment arm</th>
<th>Primary efficacy endpoint</th>
<th>Outcomes in DM</th>
<th>Bleeding risks in DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRIE²⁴,²⁵</td>
<td>3,866/19,185</td>
<td>Recent MI, stroke, established PAD</td>
<td>Aspirin+clopidogrel vs. placebo</td>
<td>Vascular death, MI or ischemic stroke</td>
<td>15.6% vs. 17.7%, RRR=21% (NA), P=0.042*</td>
<td>1.8% vs. 2.8%, RRR=37% (3.8–58.7), P=0.031</td>
</tr>
<tr>
<td>CURE³⁶</td>
<td>2,840/12,562</td>
<td>NSTE-ACS</td>
<td>Aspirin+clopidogrel vs. aspirin</td>
<td>CV death, nonfatal MI or stroke</td>
<td>14.2% vs. 16.7%, RRR=0.84 (0.70–1.02), P&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>CHARISMA²⁷</td>
<td>6,556/15,603</td>
<td>Multiple risk factors, documented CAD, CVD, or symptomatic PAD</td>
<td>Aspirin+clopidogrel vs. aspirin+placebo</td>
<td>CV death, MI, or stroke</td>
<td>Not provided but no interaction with the overall results</td>
<td>3.0% vs. 4.1%, not provided with statistical analysis</td>
</tr>
<tr>
<td>TRITON-TIMI 38²²,²³</td>
<td>3,146/13,608</td>
<td>ACS patients undergoing PCI</td>
<td>Aspirin+prasugrel vs. aspirin+clopidogrel</td>
<td>CV death, nonfatal MI or nonfatal stroke</td>
<td>12.2% vs. 17.0%, HR=0.70 (0.58–0.85), P&lt;0.001</td>
<td>2.6% vs. 2.5%, HR=1.06 (0.66–1.69), P=0.29</td>
</tr>
<tr>
<td>PLATO⁴¹,⁴²</td>
<td>4,662/18,624</td>
<td>ACS</td>
<td>Aspirin+ticagrelor vs. aspirin+clopidogrel</td>
<td>Vascular death, MI or stroke</td>
<td>14.1% vs. 16.2%, HR=0.88 (0.76–1.03), P=0.49</td>
<td>14.1% vs. 14.8%, HR=0.81 (0.81–1.12), P=0.21</td>
</tr>
<tr>
<td>TRA 2P-TIMI 50⁴⁹,⁵⁰</td>
<td>6,724/26,449</td>
<td>History of MI, ischemic stroke, or PAD</td>
<td>Standard APT+ vorapaxar vs. standard APT+ placebo</td>
<td>CV death, MI or stroke</td>
<td>14.6% vs. 16.3%, HR=0.89 (0.78–1.02), P=0.02</td>
<td>4.4% vs. 2.6%, HR=1.60 (1.07–2.40), P=0.02</td>
</tr>
<tr>
<td>ATLAS ACS-TIMI 51⁵⁷</td>
<td>4,964/15,526</td>
<td>ACS</td>
<td>Standard APT+ rivaroxaban (2.5 or 5mg) vs. standard APT+placebo</td>
<td>CV death, MI or stroke</td>
<td>7.1% vs. 7.5%, HR=0.96 (0.77–1.20), P=0.14**</td>
<td>1.2% vs. 0.2%, HR=5.09 (1.82–14.24), P=0.58**</td>
</tr>
</tbody>
</table>

* Composite of vascular death, MI, stroke, or rehospitalization for ischemia or bleeding; **comparison between combined rivaroxaban vs. placebo. ACS, acute coronary syndrome; APT, antiplatelet therapy; NSTE-ACS, non-ST segment elevation acute coronary syndrome; CAD, coronary artery disease; CV, cardiovascular; CVD, cerebrovascular disease; HR, hazard ratio; NA, not applicable; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; Pint, P for interaction vs. non-DM; RRR, relative risk reduction. Other abbreviations as in Table 1.

The clinical efficacy of DAPT with clopidogrel and aspirin was well documented in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with clopidogrel) trial. The mechanisms contributing to inadequate antiplatelet effects of clopidogrel are multifactorial, but most significantly attributed to impaired generation of active metabolite (Figure 3). Prasugrel Prasugrel is a 3rd-generation thienopyridine that, similarly to clopidogrel, also needs activation to exert its multifactorial, but most significantly attributed to impaired generation of active metabolite (Figure 3). Prasugrel is a 3rd-generation thienopyridine that, similarly to clopidogrel, also needs activation to exert its antiplatelet effect. The OPTIMUS-3 study showed that standard-dose prasugrel (60 mg of loading dose [LD] plus 10 mg of MD) achieved greater platelet inhibition compared with double-dose clopidogrel (600 mg of LD plus 150 mg of MD) in DM patients. However, DM patients have reduced generation of active metabolites and platelet inhibition than non-DM patients even when treated with prasugrel. Prasugrel is an attractive antiplatelet agent for DM patients because it is characterized by greater platelet inhibition and less variability than clopidogrel. The OPTIMUS-3 study showed that standard-dose prasugrel (60 mg of loading dose [LD] plus 10 mg of MD) achieved greater platelet inhibition compared with double-dose clopidogrel (600 mg of LD plus 150 mg of MD) in DM patients. However, DM patients have reduced generation of active metabolites and platelet inhibition than non-DM patients even when treated with prasugrel. Prasugrel is an attractive antiplatelet agent for DM patients because it is characterized by greater platelet inhibition and less variability than clopidogrel. The OPTIMUS-3 study showed that standard-dose prasugrel (60 mg of loading dose [LD] plus 10 mg of MD) achieved greater platelet inhibition compared with double-dose clopidogrel (600 mg of LD plus 150 mg of MD) in DM patients. However, DM patients have reduced generation of active metabolites and platelet inhibition than non-DM patients even when treated with prasugrel.
Prasugrel-Thrombolysis in Myocardial Infarction (TIMI) study that included 13,608 ACS patients undergoing PCI. During the 15-month study period, prasugrel was associated with a 19% relative risk reduction of ischemic events and a 52% relative risk reduction of stent thrombosis, but with a 32% risk increase of TIMI major bleeding than clopidogrel. However, the subgroup analysis showed a neutral effect of prasugrel in patients ≥75 year of age or weighing <60 kg because of the higher risk of bleeding complications compared with clopidogrel. Importantly, patients with a previous history of stroke or transient ischemic attack (TIA) had more ischemic and bleeding events when treated with prasugrel. In a prespecified subgroup analysis, DM patients (n=3,146) tended to have a greater reduction in ischemic events than non-DM patients (12.2% vs. 17.0%; hazard ratio (HR), 0.70; P<0.001 in DM patients, and 9.2% vs. 10.6%; HR, 0.86; P=0.02 in non-DM patients, P for interaction=0.09) (Table 2). Of note, prasugrel was not associated with an increase in TIMI major bleeding in DM patients (Table 2). Net clinical benefit with prasugrel was greater in DM patients (14.6% vs. 19.2%; HR, 0.74; P=0.001) than in non-DM patients (11.5% vs. 12.3%; HR, 0.92; P=0.16, P for interaction=0.05). Importantly, DM
patients ≥75 year of age also achieved a significant 36% risk reduction in the primary endpoint with prasugrel use.33

In the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) study, prasugrel did not reduce the rate of the primary endpoint (a composite of CV death, nonfatal MI and nonfatal stroke) among medically managed patients (n=7,243) with NSTE-ACS at a median follow-up of 17 months.34 Although the incidence of the primary end point through 12 months was similar between prasugrel and clopidogrel groups, there was a trend towards a reduced risk in the prasugrel group after 12 months (P=0.07 for interaction).34 In addition, prasugrel reduced ischemic events in patients with angiographically confirmed-CAD (10.7% vs. 14.9%, HR 0.77, 95% CI 0.61–0.98; P=0.032) but not in patients who did not undergo coronary angiography (16.3% vs. 16.7%, HR 1.01, 95% CI, 0.84–1.20; P=0.94; P for interaction=0.08).35 Rates of severe and intracranial bleeding were similar between groups. DM patients showed a higher event rate irrespective of treatment group (17.8% in prasugrel group vs. 20.4% in clopidogrel group) than non-DM patients (11.5% in prasugrel group vs. 13.2% in clopidogrel group).36 The neutral clinical effect of prasugrel was consistent in patients with and without DM (P for interaction=0.7).34

Based on these findings, prasugrel (60 mg LD and 10 mg MD) is indicated for use in ACS patients after PCI, but is not recommended for those undergoing non-invasive treatment or being medically managed.36,37 Prasugrel is contraindicated in patients with a prior history of stroke or TIA, with high risk of bleeding or hypersensitivity. In elderly patients (≥75 years old), prasugrel can be cautiously used only in high-risk patients (≥75 year of age, DM requiring medication, myocardial infarction ≥65 years of age, DM requiring medication, and/ or history of MI 1–3 years before enrollment plus at least 1 additional risk factor (≥65 years of age, DM requiring medication, a second prior spontaneous MI, multivessel CAD, or chronic renal dysfunction).38 Patients were randomized to either one of 2 doses of ticagrelor (90 mg b.i.d. or 60 mg b.i.d.) or placebo in addition to aspirin. Similar reduction of the primary efficacy endpoint (CV death, MI, and stroke) was observed in patients treated with either dose of ticagrelor at 3 years (7.85% in 90 mg b.i.d. vs. 7.77% in 60 mg b.i.d. vs. 9.04% in placebo; P=0.004 for 90 mg b.i.d. vs. placebo and P=0.008 for 60 mg b.i.d. vs. placebo).39 However, both doses of ticagrelor were associated with significantly increased major bleeding compared with placebo, albeit a numerically lower rate was shown with the 60 mg dose than with the 90 mg dose (2.60% in 90 mg b.i.d. vs. 2.30% in 60 mg b.i.d. vs. 1.06% in placebo; P<0.001 both for 90 mg b.i.d. vs. placebo and 60 mg b.i.d. vs. placebo). Importantly, ticagrelor did not increase the incidence of fatal or intracranial bleeding. A dose-dependent increase in dyspnea resulted in a higher treatment discontinuation rate in ticagrelor users (6.5% in 90 mg b.i.d. vs. 4.55% in 60 mg b.i.d. vs. 0.79% in placebo; P<0.001 for each ticagrelor dose vs. placebo).39 DM subjects (n=6,806, 32%) showed a higher rate of the primary efficacy endpoint (10.1% in 90 mg b.i.d. vs. 10.0% in 60 mg b.i.d. vs. 11.60% in placebo) compared with non-DM patients (6.77% in 90 mg b.i.d. vs. 6.68% in 60 mg b.i.d. vs. 7.83% in placebo). There was no heterogeneity in the efficacy of ticagrelor (either dose) according to DM status (P for interaction=0.97 and 0.96 in 90 mg b.i.d. and 60 mg b.i.d., respectively).39

The ongoing THEMIS (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study;
NCT01991795) study is including type 2 DM patients with documented CAD but without MI. The study randomizes 19,000 patients to either ticagrelor (90 or 60 mg b.i.d.) or placebo for up to 48 months. This study will highlight the role of a potent antiplatelet agent for secondary prevention in DM patients without ACS.

Based on these observations, ticagrelor (180 mg LD and 90 mg b.i.d. MD) is recommended for the management of ACS patients irrespective of planned treatment strategies (invasive or non-invasive). After 1 year from ACS, ticagrelor is recommended for secondary prevention at a lower dosing regimen (60mg b.i.d.). High-dose aspirin (>100 mg) should be avoided because of a possible reduction in the effectiveness of ticagrelor. Ticagrelor is also contraindicated in patients with a history of intracranial bleeding, active pathological bleeding, severe hepatic dysfunction or hypersensitivity to the drug.

**PAR-1 Inhibitor**

Vorapaxar is the only PAR-1 inhibitor approved by drug regulating agencies. Vorapaxar is a potent and competitive inhibitor of PAR-1, which blocks thrombin-mediated platelet activation without affecting fibrinogen cleavage in the coagulation cascade (Table 1). Importantly, the synergistic inhibition of thrombin-induced platelet activation is achieved by much lower dose combinations of thrombin and P2Y12 receptor inhibitors than any single doses of the inhibitors required for the same effect. Vorapaxor was studied in 2 large-scale phase 3 clinical trials as described next.

In the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) study, including 12,944 NSTE-ACS patients, vorapaxor did not reduce the primary efficacy outcome (CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) at 2 years as compared with placebo. The study utilized 40 mg LD and 2.5 mg daily MD of vorapaxor as a study drug on top of standard treatment regimens, including DAPT with aspirin and clopidogrel. Vorapaxor significantly increased major bleeding events and intracranial hemorrhage. The risk of intracranial hemorrhage was more pronounced in patients with history of prior stroke.

In another phase 3 trial, the TRA 2P-TIMI 50 (Trial to Assess the Effects of Vorapaxor in Preventing Heart Attack and Stroke in Patients With Atherosclerosis) study, including 26,449 patients with a history of atherosclerosis, which was defined as MI or ischemic stroke within the previous 2 weeks to 12 months or PAD, vorapaxor (2.5 mg daily MD without LD) added on top of aspirin and/or a thienopyridine (as part of standard of care) was associated with significant 13% relative risk reduction of the primary endpoint (a composite of CV death, MI, stroke), as compared with placebo after a median of 30 months’ follow-up. However, vorapaxor was also associated with 66% increase of moderate to severe bleeding and 2-fold increase of intracranial hemorrhage after a median follow-up of 30 months. Importantly, vorapaxor was associated with an excess of intracranial bleeding in patients with a history of stroke. In a prespecified subgroup analysis of the TRA 2P-TIMI 50 study including 16,896 patients with a history of MI, 3,623 (21%) of entire population had DM. The occurrence of the primary endpoint (CV death, MI, or stroke) was more frequent in DM patients than in non-DM patients (14.3% vs. 7.6%; HR, 1.47; P=0.001). Vorapaxor was effective in reducing the primary endpoint in both DM- and non-DM patients (Table 2). However, vorapaxor increased the incidences of moderate or severe bleeding in both DM patients (4.4% vs. 2.6%; HR, 1.60; 95% CI 1.07–2.40; P=0.02), and non-DM patients (2.9% vs. 1.9%; HR, 1.56; 95% CI, 1.22–2.00; P=0.001) (P for interaction=0.93). Nevertheless, vorapaxor improved the net clinical benefit, which was a combined outcome of CV death, MI, stroke, recurrent ischemia leading to revascularization, and moderate or severe bleeding, in DM patients (16.4% vs. 19.6%; HR 0.79; 95% CI, 0.67–0.93; P=0.005), whereas the net clinical benefit of vorapaxor was not significant in non-DM patients (10.4% vs. 10.9%; HR, 0.95; 95% CI, 0.85–1.06; P=0.32). Another cohort of interest is represented by patients with PAD, which is known to frequently affect DM patients. In fact, in the subgroup of PAD patients (n=3,787), 36% had DM. In this subanalysis, although vorapaxor failed to reduce the primary efficacy endpoint compared with placebo (11.3% vs. 11.9%; HR, 0.94; 95% CI, 0.78–1.14; P=0.53), it reduced the rates of hospitalization for acute limb ischemia (2.3% vs. 3.9%; HR, 0.58; 95% CI, 0.39–0.86; P=0.006) and peripheral artery revascularization (18.4% vs. 22.2%; HR, 0.84; 95% CI, 0.73–0.97; P=0.017).

Based on these findings, vorapaxor 2.5 mg once daily combined with other antiplatelet agents (aspirin, clopidogrel or both) is indicated in patients with a history of MI or with PAD. It is contraindicated in patients with a history of stroke, TIA, intracranial hemorrhage or in those with active bleeding. Strong CYP3A inhibitors or inducers should also be avoided.

**Cilostazol**

Cilostazol, a phosphodiesterase 3 inhibitor, increases intraplatelet cAMP levels and VASP phosphorylation. Cilostazol also inhibits adenosine reuptake, which in turn leads to an additional increase in the intracellular cAMP level. Cilostazol inhibits both the initial activation and amplification of platelets by collagen, arachidonic acid, ADP, and epinephrine. Although cilostazol per se has only modest antiplatelet effects, combined use with aspirin or clopidogrel showed synergistic inhibition of platelet aggregation. In contrast, it has not been associated with increased bleeding risks possibly because of not having any effect on the thrombin-mediated hemostatic process. Adjunctive cilostazol therapy in patients on standard DAPT was particularly effective for DM patients. In the OPTIMUS-2 study, adding cilostazol 100 mg twice daily to standard DAPT significantly enhanced P2Y12 inhibition. Compared with double-dose clopidogrel, triple antiplatelet therapy including cilostazol also achieved greater platelet inhibition in DM patients. Importantly, studies conducted in Asia have shown that cilostazol reduces the rate of ischemic events, including target lesion revascularization and stent thrombosis, without increasing bleeding events in DM patients. However, drug regulating committees in the USA and Europe do not recommend cilostazol as an antiplatelet therapy for secondary prevention because of the lack of large randomized clinical trials.

**Anticoagulants**

Platelets and the coagulation system closely interact in pathological thrombosis in ACS, and persistent activation of the coagulation system is associated with the occurrence of long-term ischemic events. A classical anticoagulant, an oral vitamin K antagonist (VKA), is not suitable for secondary prevention of CAD because of the high risk of bleeding. However, recently developed TSOACs have shown a comparable efficacy and more favorable safety profile than VKAs.

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**Table 1**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Vorapaxor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>2.6%</td>
<td>3.9%</td>
<td>1.56 (1.22–2.00)</td>
</tr>
<tr>
<td>MI</td>
<td>11.4%</td>
<td>13.6%</td>
<td>1.19 (0.94–1.50)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.1%</td>
<td>2.8%</td>
<td>2.54 (1.19–5.40)</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>7.4%</td>
<td>11.3%</td>
<td>1.55 (1.23–1.96)</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Event</th>
<th>DM Patients</th>
<th>Non-DM Patients</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>16.4%</td>
<td>19.6%</td>
<td>0.81 (0.67–1.00)</td>
</tr>
<tr>
<td>MI</td>
<td>10.4%</td>
<td>10.9%</td>
<td>0.95 (0.80–1.14)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.1%</td>
<td>1.2%</td>
<td>1.09 (0.72–1.66)</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>7.4%</td>
<td>8.9%</td>
<td>1.19 (0.90–1.57)</td>
</tr>
</tbody>
</table>
Despite the theoretic rationality, only rivaroxaban among the varieties of TSOACs was effective in secondary prevention of thrombotic events in ACS. Apixaban has been tested in the phase III ACS study APPRAISE-2 (Apixaban for Prevention of Acute Ischemic and Safety Events-2). However, apixaban (5 mg b.i.d. MD) failed to reduce ischemic events and just increased the bleeding risks. Another factor Xa inhibitor, darexaban, and a direct thrombin inhibitor, dabigatran, also did not achieve reductions in the primary endpoints in the phase II ACS studies.

**Rivaroxaban** The ATLAS ACS-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 51) study evaluated the clinical efficacy of rivaroxaban (5 mg and 2.5 mg b.i.d.) on top of aspirin alone or in combination with a thienopyridine in ACS patients. After a median follow-up of 13.1 months, both doses of rivaroxaban significantly reduced the primary endpoint (a composite of CV death, MI or stroke) (15% by 2.5 mg b.i.d. and 16% by 2.5 mg b.i.d.) at the expense of a dose-dependent increase in non-CABG-related TIMI major bleeding and a more than 3-fold increase of intracranial hemorrhage. The rate of non-CABG-related TIMI major bleeding tended to be lower in the 2.5-mg dose of rivaroxaban group in comparison with the higher 5-mg dose (1.8% vs. 2.4%, P=0.12). Importantly, the lower dose of rivaroxaban showed CV and all-cause mortality benefits (2.7% vs. 4.1%; HR, 0.66; 95% CI, 0.51–0.86; P=0.005 for CV death, and 2.9% vs. 4.5%; HR, 0.68; 95% CI, 0.53–0.87; P=0.004 for all-cause death). However, the benefits of rivaroxaban in DM patients was not higher than in non-DM patients (HR, 0.96; 95% CI, 0.77–1.20 in DM subgroup vs. HR, 0.78; 95% CI, 0.67–0.92 in non-DM subgroup; P for interaction=0.14) (Table 2). Rivaroxaban was associated with a 5-fold higher risk of non-CABG-related TIMI major bleeding in DM patients and 3.7-fold in non-DM patients (Table 2).

The EMA has approved low-dose rivaroxaban (2.5 mg b.i.d.) in ACS patients in adjunct with other antiplatelet agents (aspirin alone or conventional DAPT), but this agent has not been approved by the FDA for the ACS indication.

### Unmet Needs and Future Studies

If on the one hand current advancements in the field have focused on defining the optimal combination of antithrombotic therapies for high-risk patients with CAD, including patients with DM, on the other there has been a lot of debate on the optimal duration of a specific antithrombotic treatment regimen. This debate emerges from concerns with regard to bleeding complications with prolongation, particularly after 1 year, of intensified antithrombotic treatment regimens such as DAPT. In fact, current guidelines recommend that DAPT should be continued up to 12 months in patients with ACS/PCI. However, the observation that stent-related and -unrelated recurrences persist after 1 year has questioned the effect of prolonging DAPT beyond 1 year. The recently published DAPT study highlighted a clinical benefit of prolonged DAPT after coronary stent implantation. The study allocated 9,961 patients free from ischemic and bleeding events at 1 year after stenting to either prolonged DAPT with a thienopyridine (75 mg daily MD of clopidogrel or 10 mg daily MD of prasugrel) or low-dose aspirin alone. During the 18 months of study period, prolonged DAPT significantly reduced the composite outcome of all-cause mortality, MI, or stroke (4.3% vs. 5.9%; HR, 0.71; 95% CI, 0.59–0.85; P<0.001) and in-stent thrombosis (0.4% vs. 1.4%; HR, 0.29; 95% CI, 0.17–0.48; P<0.001). Importantly, approximately 55% of the benefit of prolonged DAPT was obtained from the significant reduction of stent-unrelated MI. However, prolonged DAPT was associated with an increase in moderate or severe bleeding events (2.5% vs. 1.6%; HR, 1.61; 95% CI, 1.21–2.16; P<0.001). The clinical benefits of prolonged DAPT were controversial in DM patients. In a subgroup analysis including 3,037 (30.4%) DM patients, prolonged DAPT tended to reduce the rate of stent thrombosis (0.6% vs. 1.1%; HR, 0.53; 95% CI, 0.23–1.20; P for interaction=0.08), but was not effective in reducing the composite outcome (6.7% vs. 6.9%; HR, 0.95; 95% CI, 0.75–1.25; P for interaction=0.01). However, in a post hoc analysis to develop a risk prediction model (DAPT score), DM was an important predictor of stent thrombosis or MI (Table 3). Accordingly to this analysis, the patients with high DAPT score (≥2) achieved a greater benefit of prolonged DAPT than those with low DAPT score (<2) (risk differences=–3.02% vs. –0.66%; number needed to treat=34 vs. 153; P<0.001). Importantly, patients with high DAPT scores also demonstrated a lower risk of GUSTO moderate or severe bleeding than those with low DAPT scores (risk differences=0.37% vs. 1.55%; number needed to harm=272 vs. 63; P=0.02). These results led to a gradient of net clinical benefit from prolonged DAPT according to DAPT score (risk difference=–2.70% vs. 0.92%; number needed to treat=37 vs. 109; P<0.001). Importantly, DM is a marker of ischemic risk in the DAPT scoring system (Table 3).

Indeed, although the use of more potent platelet-inhibiting drugs or prolongation of intensified therapy reduces ischemic events, the increase in bleeding complications has represented a major drawback. This underscores the need for strategies to reduce the risk of bleeding complications, while preserving efficacy in reducing ischemic events. An emerging area of clinical research has been that of dropping aspirin therapy and considering prolonged treatment with a P2Y12 receptor inhibitor. A series of ongoing trials are currently testing this hypothesis and will provide important insights on potential treatment alternatives for high-risk patients including those with DM.

### Conclusions

Patients with DM are at high risk for recurrent atherothrombotic events, underscoring the importance of antithrombotic...


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Antithrombotics in DM Patients With CAD


