Management of Acute Coronary Syndromes in Patients with Diabetes

Case Study

J.H. is a 62-year-old Hispanic woman with a 15-year history of non–insulin-dependent diabetes mellitus. She had been experiencing intermittent intercapular discomfort with right-sided shoulder pain that was precipitated by exertion and relieved by rest. Because of its location, she assumed that the pain was most likely musculoskeletal. She has no prior history of atherosclerotic disease, chest pain, claudication, transient ischemic attack, or stroke. She has a history of hypertension, dyslipidemia, and microalbuminuria, with an estimated glomerular filtration rate of 67 mL/min/1.73 m². Her current medications include atorvastatin 80 mg qd, losartan 100 mg qd, aspirin 81 mg qd, metformin 1000 mg bid, liraglutide 1.8 mg SQ qd, and carvedilol 12.5 mg bid.

Her blood pressure is consistently in the 120s/70s mm Hg, and her most recent glycated hemoglobin (A1C) is 6.7%, with low-density lipoprotein cholesterol 61 mg/dL, triglycerides 171 mg/dL, and non-high-density lipoprotein cholesterol 85 mg/dL. On the day of presentation, she suddenly developed persistent intercapular and right shoulder pain with shortness of breath and diaphoresis. Her husband transported her to the emergency room. An electrocardiogram revealed ST-segment elevations in leads V1-V4, and her troponin level was elevated. She was diagnosed with an anterior wall myocardial infarction and immediately taken to the cardiac catheterization laboratory. She was found to have an acutely ruptured atherosclerotic lesion in the proximal left anterior descending coronary artery and underwent placement of a drug-eluting stent.

Introduction

Diabetes mellitus presents a significant public health challenge worldwide. Projections suggest that the global prevalence of diabetes mellitus will reach 7.7% by 2030, affecting an estimated 439 million adults.1 Presently, 30 million people in the United States—one out of every 10 people—have diabetes mellitus, at an annual total cost of $245 billion in direct medical expenditure and lost work and wages.2 In addition, the cardiovascular morbidity and mortality associated with diabetes mellitus cannot be overstated. Compared with those without diabetes, patients with a history of diabetes—such as the female patient described in the case study—have a 4- to 6-fold increased risk for cardiovascular events, and cardiovascular disease accounts for 65% of all deaths among patients with diabetes.3

Diabetes mellitus is also associated with adverse outcomes following acute coronary syndromes (ACS),4-6 a clinical spectrum encompassing unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).1 The TRILOGY ACS (Targeted Platelet Inhibition to Clarify Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial demonstrated diabetes mellitus to be a strong predictor of spontaneous myocardial infarction (MI) following a non–ST-segment elevation ACS (NSTEMI) event managed without revascularization.5 Moreover, patients with diabetes mellitus undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) experience worse outcomes than those without diabetes.3 For instance, the 9-year rate of nonfatal MI after angioplasty is 1.6-fold higher in patients with diabetes vs those without diabetes, and diabetes is associated with an 80% increased risk of death 9 years after angioplasty (risk ratio [RR], 1.82; 95% confidence interval [CI], 1.41–2.34; P < .001).3 Patients with diabetes also report worse health-related quality of life following an ACS event, compared with those without diabetes.9

Key challenges and considerations

Chest pain or discomfort is considered the hallmark symptom of ACS.10,11 However, in clinical practice, up to 35% of all patients with MI present atypically without chest pain or discomfort.12 Diabetes mellitus is a predictor of atypical presentation, along with female gender and high Killip class.13,14 Patients who present atypically are less likely to be diagnosed with confirmed MI at the time of admission, and have a higher in-hospital mortality rate than those presenting with chest pain.14 Studies have shown, however, that despite their
Glycemic control is critical when managing patients with diabetes mellitus and ACS. Patients with diabetes presenting with hyperglycemia (≥10–11 mmol/L [180–198 mg/dL]) in the setting of an acute MI have been found to have an increased risk of in-hospital mortality (odds ratio [OR], 1.7; 95% CI, 1.2–2.4). Another analysis, involving 16,871 patients with acute MI, had similar findings: Patients with diabetes mellitus who exhibited mean hospitalization glucose levels greater than 200 mg/dL had a significantly higher risk of in-hospital mortality relative to those with mean glucose levels below 110 mg/dL (OR, 4.1; 95% CI, 1.81–9.26). Patients with a history of diabetes mellitus also have a greater long-term mortality following an acute MI. Blood glucose levels upon admission for acute MI have been demonstrated to be an independent predictor of 3-year mortality in patients with diabetes (OR per 1 mmol/L blood glucose, 1.08; 95% CI, 1.05–1.11; P < .001). Furthermore, a study of patients with diabetes mellitus admitted for NSTE-ACS found high admission blood glucose (hazard ratio [HR], 2.66; 95% CI, 1.83–3.86) and hypoglycemia (HR, 1.77; 95% CI, 1.09–2.86) during hospitalization to be independently associated with increased 2-year all-cause mortality risk. Given the relationship between poorly controlled glycaemia and death following acute MI, effective glycemic control is essential in ACS patients with diabetes. Insulin-based glycemic control should be considered in ACS patients with significant hyperglycemia (>180 mg/dL).

Besides glycemic control, cardiac rehabilitation in ACS patients with diabetes mellitus should include risk modification efforts such as weight loss, lipid and blood pressure management, smoking cessation, and exercise training. Secondary prevention after stent placement following an ACS or in patients with a history of NSTE-ACS managed medically without revascularization should also include dual antiplatelet therapy, that is, the combined use of an oral P2Y12 receptor antagonist—namely, clopidogrel, prasugrel, or ticagrelor—and aspirin.

Patients with diabetes mellitus and a history of ACS should be evaluated for peripheral arterial disease (PAD). Data from the Framingham Heart Study showed that 20% of patients with intermittent claudication had diabetes. The American Diabetes Association (ADA) therefore recommends that the initial screening for PAD in patients with diabetes include an assessment of pedal pulses and a medical history assessing decline in walking speed, leg fatigue, and claudication. A referral for further vascular assessment should be considered for patients with diabetes who are 50 years or older, and for patients presenting with symptoms of claudication, or diminished or absent pedal pulses. Ankle-brachial index testing is indicated for any patient with known diabetes who exhibits signs or symptoms of PAD.

The potential impact of polypharmacy should be recognized when managing ACS patients with diabetes mellitus. In a cross-sectional US survey of 875 individuals with diabetes, half of respondents reported taking at least 7 prescription medications, and 49% were on 2 or more antihyperglycemic agents. Apart from antihyperglycemic agents, the most commonly reported medications were cardioprotective, for the treatment of hypertension (71% of respondents) and hyperlipidemia (53%). Given this evidence, it is important for physicians to consider the glycemic impact of cardioprotective agents, and vice versa.

Evidence indicates that antihyperglycemic agents, such as sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) analogues, may be cardioprotective. The EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes) trial found that patients with type 2 diabetes mellitus (T2DM) who received empagliflozin, an SGLT-2 inhibitor, had significantly lower rates of the primary composite cardiovascular outcome (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) than those on placebo (10.5% vs 12.1%; HR, 0.86; 95% CI, 0.74–0.99; P = 0.04). The empagliflozin group also had lower rates of death from cardiovascular causes (3.7% vs 5.9% in the placebo group; HR, 0.62; 95% CI, 0.49–0.77; P < .001), hospitalization for heart failure (2.7% vs 4.1%; HR, 0.65; 95% CI, 0.50–0.85; P = .002), and all-cause mortality (5.7% vs 8.3%; HR, 0.68; 95% CI, 0.57–0.82; P < .001). The ongoing DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events) trial is evaluating the effect of dapagliflozin on cardiovascular outcomes when added to background therapy in patients with T2DM and established cardiovascular disease or cardiovascular risk factors.

The cardioprotective effect of liraglutide, a GLP-1 analog, was investigated in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial. In this trial, the rate of the primary composite outcome of first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke among patients with T2DM was shown to be lower with liraglutide than placebo (13% vs 14.9%; HR, 0.87; 95% CI, 0.78–0.97; Pnoninferiority < 0.001; Psuperiority = 0.01). Similarly, the rates of death from cardiovascular causes (4.7% vs 6.0%; HR, 0.78; 95% CI, 0.66–0.93; P = 0.007) and all-cause death (8.2% vs 9.6%; HR, 0.85; 95% CI, 0.74–0.97; P = 0.02) were lower in the liraglutide group compared with the placebo group. Although the rates of nonfatal MI, nonfatal hospitalization, and hospitalization for heart failure were lower with liraglutide than placebo, these differences were not shown to be significant.

The cardioprotective effect of exenatide, another GLP-1 analog, was investigated in the recently completed EXCEL (Exenatide Study of Cardiovascular Event Lowering) trial, which compared the impact of exenatide and usual care with that of usual care alone on the risk of major adverse cardiovascular events in patients with T2DM. Top-line results demonstrated exenatide to be associated with fewer cardiovascular events. However, the efficacy objective of superior reduction in the composite outcome of cardiovascular-related mortality, nonfatal MI, and nonfatal stroke did not reach statistical significance.

A review of the glycemic effects of common cardiovascular medications suggests that certain beta-blockers and calcium channel blockers may be associated with favorable glycometabolic effects. For example, the use of carvedilol—a third-generation beta-blocker—in the presence of renin-angiotensin system blockade has been demonstrated to have a neutral effect on glycated hemoglobin (A1C) and to improve insulin sensitivity in patients with T2DM and hypertension. Conversely, metoprolol—a second-generation beta-blocker—has been associated with a modest increase in A1C when used in conjunction with a renin-angiotensin system blocker. Moreover, metoprolol has not been shown to improve insulin sensitivity in patients with T2DM and...
may also be associated with more frequent progression to microalbuminuria than carvedilol. Data from 4978 patients with diabetes mellitus enrolled in the REGARDS (Reasons for Geographical and Racial Differences in Stroke) study reveal calcium channel blockers in general, and verapamil particularly, to be associated with lower fasting serum glucose levels in users, compared with nonusers.

Summary: Key challenges and considerations

- Patients with a history of diabetes mellitus are more likely to present without chest pain or discomfort during an ACS.
- Poorly controlled glycemia increases the risk of mortality during hospitalization for an ACS and is associated with adverse outcomes following hospital discharge.
- Secondary prevention efforts should include risk modification (eg, exercise training, weight management, and smoking cessation) and dual antiplatelet therapy.
- All patients with a history of diabetes and ACS should be evaluated for PAD.
- Consideration should be given to the potential glycemic and cardioprotective impact of medications prescribed for patients with ACS and diabetes.

Guideline recommendations for the management of ACS in patients with diabetes

Multiple American and European organizations have issued guidelines on the management of ACS in patients with diabetes. These include jointly issued guidelines from the American Heart Association and American College of Cardiology and recommendations from the European Society of Cardiology and the ADA (TABLE 1).

It is recommended that all patients presenting with STEMI and NSTE-ACS be screened for diabetes, with glycemic measurements repeated in patients known to have diabetes. The main aim is to ensure moderate glycemic control (<180 mg/dL) is maintained while avoiding hypoglycemia. However, less stringent glycemic control (≤200 mg/dL) may be considered in the acute phase and during follow-up in patients with more advanced cardiovascular disease, older age, and longer diabetes duration.

TABLE 1. Summary of guideline recommendations for the management of acute coronary syndrome (ACS) in patients with diabetes mellitus

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>ADA Standards of Medical Care – 2017</td>
<td>• Less stringent A1C goals (eg, &lt;8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or long-standing diabetes&lt;br&gt;• High-intensity statin therapy should be combined with lifestyle therapy&lt;br&gt;• Dual antiplatelet therapy is reasonable for up to a year after ACS and may have benefits beyond this period&lt;br&gt;• In patients with a history of MI, beta-blockers should be least 2 years after the event</td>
</tr>
<tr>
<td>2012 ESC Guidelines for the Management of Acute MI in Patients Presenting with STEMI</td>
<td>• Measurement of glycemia is indicated at initial evaluation in all patients, and should be repeated in patients with known diabetes or hyperglycemia&lt;br&gt;• In the acute phase, maintain glucose concentrations ≤200 mg/dL, while avoiding fall of glucose to &lt;90 mg/dL&lt;br&gt;• Plans for optimal outpatient glucose control and secondary prevention must be determined in patients with diabetes before discharge&lt;br&gt;• Selection of antithrombotic therapies and reperfusion therapy should be the same for all patients regardless of diabetes status&lt;br&gt;• An ADP-receptor blocker is recommended in addition to aspirin for antiplatelet therapy; the benefits of potent oral P2Y12 inhibitors (prasugrel or ticagrelor) versus clopidogrel are consistent or enhanced in patients with diabetes</td>
</tr>
<tr>
<td>2013 ACCF/AHA Guideline for the Management of STEMI</td>
<td>• Management of patients with diabetes and STEMI should be the same as for patients without diabetes, with attention to moderate glycemic control&lt;br&gt;  • Blood glucose levels should be maintained below 180 mg/dL if possible, while avoiding hypoglycemia</td>
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### NSTE-ACS

#### 2014 AHA/ACC Guideline for the Management of Patients with NSTE-ACS
- Medical treatment in the acute phase of NSTE-ACS and decisions to perform stress testing, angiography, and revascularization should be similar in patients with and without diabetes
- Screen all patients with NSTE-ACS for diabetes; monitor blood glucose levels frequently in patients with known diabetes or admission hyperglycemia
- Glucose-lowering therapy should be considered in ACS patients with blood glucose >180 mg/dL, while avoiding hypoglycemia
  - Less stringent glucose control should be considered in the acute phase and at follow-up in patients with more advanced disease, older age, longer diabetes duration, and more comorbidities
- The same antithrombotic treatment may be administered in patients with and without diabetes
- An invasive strategy is recommended over noninvasive management
- Renal function should be monitored for 2-3 days after coronary angiography or PCI in patients with baseline renal impairment or on metformin
- For PCI, new-generation drug-eluting stents are recommended over bare-metal stents
- For patients with stabilized multivessel CAD:
  - CABG is recommended over PCI if the surgical risk is acceptable
  - PCI should be considered as an alternative to CABG when the SYNTAX score is ≤22

#### 2015 ESC Guidelines for the Management of ACS in Patients Presenting without Persistent ST-segment Elevation
- The same antithrombotic treatment may be administered in patients with and without diabetes
- An invasive strategy is recommended over noninvasive management
- Renal function should be monitored for 2-3 days after coronary angiography or PCI in patients with baseline renal impairment or on metformin
- For PCI, new-generation drug-eluting stents are recommended over bare-metal stents
- For patients with stabilized multivessel CAD:
  - CABG is recommended over PCI if the surgical risk is acceptable
  - PCI should be considered as an alternative to CABG when the SYNTAX score is ≤22

#### PCI

#### 2011 ACCF/AHA/SCAI Guideline for PCI
- An early invasive strategy is preferable to an initial conservative approach
- CABG may be used in preference to PCI to improve survival in patients with multivessel CAD and diabetes, particularly if a left internal mammary artery graft can be anastomosed to the left anterior descending artery
- Drug-eluting stents are recommended over bare-metal stents
- Following PCI, diabetes management (eg, lifestyle modification, pharmacotherapy) should be coordinated with the patient’s primary care physician and/or endocrinologist

### Abbreviations:
- A1C, glycated hemoglobin; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACS, acute coronary syndrome; ADA, American Diabetes Association; ADP, adenosine diphosphate; AHA, American Heart Association; CABG, coronary artery bypass grafting; CAD, coronary artery disease; ESC, European Society of Cardiology; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Interventions; STEMI, ST-segment elevation myocardial infarction; SYNTAX, synergy between PCI with TAXUS and cardiac surgery.

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Guidelines generally recommend that treatment decisions be similar for all ACS patients, regardless of diabetes status. Moreover, guidelines recommend an early invasive strategy (coronary angiography and revascularization within 72 hours of symptom onset) for patients with diabetes and ACS. Despite this recommendation, it has been demonstrated that invasive strategies are underused in this population. A Danish cohort study of 24,952 patients reported that ACS patients with diabetes mellitus were significantly less likely to undergo coronary angiography (64% vs 74%; \( P < 0.0001 \)) and subsequent revascularization (47% vs 57%; \( P < 0.0001 \)) than patients without diabetes. When invasive intervention is indicated, CABG is recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel coronary artery disease (CAD). Data from BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes)—a study of 2368 patients with T2DM and CAD—showed that prompt revascularization significantly reduced the rate of major cardiovascular events, compared with medical therapy, for patients selected for CABG (22.4% vs 30.5%; \( P < 0.01 \); \( P_{\text{interaction}} = 0.002 \)), but not those selected for PCI. For PCI, drug-eluting stents are recommended over bare-metal stents based on at least comparable safety, superior prevention of restenosis, and reduced need for repeat revascularization.

### Efficacy and safety of oral antplatelet agents in patients with diabetes
Patients with diabetes mellitus exhibit platelet dysfunction and increased production of several prothrombotic factors, which place them at greater risk for adverse cardiovascular events, compared with patients without diabetes. Dual antiplatelet therapy is the mainstay of medical management of ACS for secondary prevention of ischemic events. While aspirin may be continued indefinitely, P2Y12 inhibition is currently recommended for 1 year following an ACS event. However, for ACS patients who receive PCI or noninvasive management (ie, medical therapy alone or fibrinolytic therapy), dual antiplatelet therapy may be continued for longer than a year if they tolerate treatment without bleeding complication and are not at high bleeding risk. Furthermore, in patients with NSTE-ACS or STEMI managed with dual antiplatelet therapy following PCI, and in patients with NSTE-ACS treated with medical therapy alone (ie, without revascularization or fibrinolytic therapy), it is reasonable to use ticagrelor in preference to clopidogrel for P2Y12 inhibition.

The oral P2Y12 receptor antagonists—clopidogrel, prasugrel, and ticagrelor—inhibit adenosine diphosphate (ADP)–mediated platelet aggregation. Despite this similarity in function, ticagrelor is chemically, pharmacologically, and pharmacokinetically different from clopidogrel and prasugrel. Unlike clopidogrel and prasugrel, which belong to the thienopyridine class of P2Y12 inhibitors, ticagrelor is a cyclopentyl–triazolol–pyrimidine. Also, in contrast to the thienopyridines, ticagrelor binds reversibly to the platelet P2Y12 receptor and does not require hepatic activation.

FIGURE 1. Mechanism of action of oral P2Y12 antiplatelet agents

Abbreviations: AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; CYP, cytochrome P450; PDE-III, phosphodiesterase III; PGR, prostaglandin receptor; PKA, protein kinases; VASP, vasodilator-stimulated phosphoprotein; VASP-P, phosphorylation of vasodilator-stimulated phosphoprotein.


TABLE 2. Clinical and pharmacologic overview of oral P2Y12 platelet inhibitors
Historically, clopidogrel has been the most widely used P2Y₁₂ inhibitor.⁴⁹ However, multiple studies have demonstrated that patients with diabetes exhibit an impaired response to clopidogrel.⁵⁰-⁵² For example, when the effect of clopidogrel was studied in 64 patients with stable CAD, results showed that patients with T2DM exhibited significantly less inhibition of platelet function than patients without diabetes.⁵⁰ Likewise, in a population with coronary stenting and ACS, patients with T2DM exhibited a lower response to a 600-mg clopidogrel loading dose, compared with patients without diabetes.⁵⁴ In the OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus) study, which involved patients with T2DM on dual antiplatelet therapy with clopidogrel, a suboptimal response was observed in 60% of patients randomized to a high-dose 150-mg maintenance regimen.⁵³ This impaired response may stem from attenuation of clopidogrel's pharmacokinetic profile in this patient population. Pharmacodynamic assessments reveal that patients with diabetes mellitus have approximately 40% less exposure to clopidogrel's active metabolite than patients without diabetes.⁵⁴ Landmark data from TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel – Thrombolysis in Myocardial Infarction 38) demonstrated prasugrel to be more efficacious than clopidogrel in treating patients with diabetes mellitus.⁵⁵ In this trial of 13,608 patients (with diabetes: n=3146; without diabetes: n=10,462), there was a reduction in the primary endpoint (cardiovascular death, nonfatal MI, or nonfatal stroke) with prasugrel versus clopidogrel among patients without diabetes (9.2% vs 10.6%; HR, .86; 95% CI, .76–.98; P=0.02) and with diabetes (12.2% vs 17%; HR, .70; 95% CI, .58–.85; P<.001; Pinteraction=0.09) (FIGURE 2A). The incidence of MI was reduced with prasugrel by 18% in patients without diabetes (7.2% vs 8.7%; HR, .82; 95% CI, .72–.95; P=0.006) and by 40% among those with diabetes (8.2% vs 13.2%; HR, .60; 95% CI, .48–.76; P<.001; Pinteraction=0.02) (FIGURE 2B). Prasugrel use resulted in a greater reduction in stent thrombosis than clopidogrel for patients with diabetes (2.0% vs 3.6%; HR, .52; 95% CI, .33–.84; P=0.007) and without diabetes (0.9% vs 2.0%; HR, .45; 95% CI, .31–.75; P<.001; Pinteraction=0.63) (FIGURE 2C). Among patients without diabetes, prasugrel therapy was associated with a 43% increase in non–CABG-related major hemorrhage (P=0.02); however, there was no significant difference in major hemorrhage for patients with diabetes. In all, no interaction between treatment and diabetes status was observed for major bleeding (FIGURE 2D). Ultimately, the net clinical benefit (death, nonfatal MI, nonfatal stroke, and nonfatal major bleeding) observed with prasugrel was greater for patients with diabetes (14.6% vs 19.2%; HR, .74; 95% CI, .62–.89; P=0.001) than those without diabetes (11.5% vs 12.3%; HR, .92; 95% CI, .82–1.03; P=.16; Pinteraction=0.05) (FIGURE 2E).

FIGURE 2. Kaplan–Meier curves stratified by diabetes status and treatment group for (A) primary endpoint (cardiovascular death, nonfatal myocardial infarction [MI] or nonfatal stroke), (B) fatal or nonfatal MI, (C) definite or probable stent thrombosis, (D) Thrombolysis in Myocardial Infarction [TIMI] major bleeding not related to CABG, and (E) net benefit endpoint.
(death, nonfatal MI, nonfatal cerebrovascular accident, nonfatal TIMI major bleeding not related to CABG) in the TRITON-TIMI 38 trial.\textsuperscript{55}
A substudy of the 18,624 patients enrolled in the PLATO (Platelet Inhibition and Patient Outcomes) trial investigated the outcome of patients treated with ticagrelor (180 mg loading dose; 90 mg twice daily maintenance dose) and clopidogrel (300 mg loading dose; 75 mg daily maintenance dose). Among patients without diabetes (n=13,951), ticagrelor was associated with a significant reduction in the primary end point (cardiovascular death, MI, or stroke; HR, .83; 95% CI, .74–.93), all-cause mortality (HR, .77; 95% CI, .65–.91), and stent thrombosis (HR, .68; 95%; CI, .48–.97). For patients with diabetes (n=4662), the reduction in the primary end point (HR, .88; 95% CI, .76–1.03; P = .49), all-cause mortality (HR, .82; 95% CI, .66–1.01; P = .56), and stent thrombosis (HR, .65; 95% CI, .36–1.17; P = .89) with ticagrelor versus clopidogrel was consistent with the overall trial results but did not reach statistical significance. Major bleeding events occurred with similar frequency for patients with diabetes (HR, .95, 95% CI, .81–1.12) and those without diabetes (HR, 1.08; 95% CI, .97–1.2; P = .21). Of note, in patients with A1C levels ≥6%, ticagrelor significantly reduced the primary end point (HR, .80; 95% CI, .70–.91) and all-cause mortality (HR, .78; 95% CI, .65–.93), and numerically reduced stent thrombosis (HR, 0.62; 95% CI, .39–1), with a bleeding rate comparable to that of clopidogrel (HR, .98; 95% CI, .86–1.12). Altogether, the study underscored ticagrelor’s efficacy in reducing ischemic events in ACS patients irrespective of diabetes status or glycemic control (FIGURE 3).

FIGURE 3. Cumulative incidence of (A) the primary end point, (B) total mortality, and (C) major bleeding stratified by diabetes status and treatment group in a substudy from the PLATO trial

Abbreviations: DM, patients with diabetes mellitus; no DM, patients without diabetes mellitus.

A post hoc analysis from the Ad Hoc PCI trial, an open-label, phase 4 pharmacodynamic study, revealed that ticagrelor may be faster and more potent than clopidogrel in achieving platelet inhibition. This study randomized troponin-negative NSTE-ACS patients undergoing ad hoc PCI to receive either ticagrelor (180 mg loading dose; n=51) or clopidogrel (600 mg loading dose; n=49). Platelet reactivity was measured periodically: pre-loading dose, at 0.5, 2, and 8 hours post-loading dose, and at the end of PCI. Two hours post-loading dose, mean platelet reactivity levels in patients with diabetes were lower with ticagrelor (130.1) than clopidogrel (287.6; 95% CI difference −157.5 [−225.3, −89.8]; P<.001). Similar effects were observed in patients without diabetes (75.3 vs 243; 95% CI difference −167.7 [−207.1, −128.8]; P<.001). High on-treatment platelet reactivity rates were lower with ticagrelor irrespective of diabetes status. Two hours after loading dose,
high on-treatment platelet reactivity was present in 21.1% of patients with diabetes in the ticagrelor arm and 93.3% in the clopidogrel arm ($P<.001$). Among patients without diabetes, 7.7% of patients in the ticagrelor group exhibited high on-treatment platelet reactivity 8 hours following loading dose, compared with 7.0% in the clopidogrel group ($P<.001$). Eight hours after loading dose, high on-treatment platelet reactivity was observed in 5.9% of patients with diabetes in the ticagrelor arm and 81.3% in the clopidogrel group ($P<.001$). For patients without diabetes, 0% of patients in the ticagrelor group exhibited high on-treatment platelet reactivity 8 hours following loading dose as opposed to 37.9% in the clopidogrel group ($P<.001$).57

Additionally, the comparative efficacy of ticagrelor and prasugrel has been investigated in patients with diabetes undergoing PCI.58,59 In a prospective, open-label, randomized trial of 100 patients with diabetes mellitus and ACS, a 180-mg loading dose of ticagrelor lowered platelet reactivity significantly more than a 60-mg prasugrel loading dose (17.3 ± 14.2% vs 27.7 ± 23.3%; $P=0.009$).59 Although the high on-treatment platelet reactivity rate tended to be lower in the ticagrelor group, this difference did not reach statistical significance (6% vs 16%; $P=.2$).59 Likewise, an observational study involving 777 patients with diabetes mellitus compared platelet function 1 month after PCI in patients receiving either prasugrel (10 mg once daily; n=315) or ticagrelor (90 mg twice daily; n=462) maintenance therapy.56 Treatment with ticagrelor decreased platelet reactivity by 58% relative to prasugrel.58 Among patients in the ticagrelor group, platelet reactivity did not differ with diabetes or insulin-treatment status (patients without diabetes: 26 [first quartile to third quartile: 9–48]; diabetes, not requiring insulin: 31.5 [16.3–53.8]; diabetes, requiring insulin: 35 [10–47]; $P=1$).58 However, for the prasugrel group, platelet reactivity levels were higher among patients with diabetes requiring insulin (122 [69–161]), compared with patients without diabetes (70 [36.3–113]) and patients with diabetes not requiring insulin (69 [44.5–115.3]; $P=0.01$).58 In the prasugrel group, high on-treatment platelet reactivity rates were 3.3% in patients without diabetes, 7.1% in patients with diabetes not requiring insulin, and 10.5% in patients with diabetes requiring insulin ($P=0.01$).58 In contrast, no ticagrelor-treated patient presented with high on-treatment platelet reactivity. Overall, ticagrelor provided stronger and more consistent platelet inhibition than prasugrel.58

The results of these studies evaluating antiplatelet therapy are encouraging, suggesting that patients with diabetes attain a benefit from medical management of ACS similar to those without diabetes. The efficacy of ticagrelor in patients with diabetes and CAD is being further investigated in the ongoing THEMIS (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) trial, a multinational study of approximately 19,000 patients with T2DM. This trial seeks to evaluate the effect of a twice-daily regimen of ticagrelor on the incidence of cardiovascular death, MI, or stroke in patients with T2DM.

Conclusions

Given the heightened risk for adverse cardiovascular outcomes in patients with diabetes mellitus, it is important that primary care clinicians be comfortable with the routine management of ACS in this patient population. Notably, patients with diabetes are more likely to present atypically during an ACS, which may affect cardiac rehabilitation. Clinicians should also be cognizant of the high rate of polypharmacy in patients with diabetes and the potential glycemic and cardioprotective impact of medications they prescribe for these patients. For patients with diabetes presenting with an acute ACS, guidelines recommend an early invasive strategy as opposed to an initial conservative approach. Apart from ensuring effective glycemic control, guidelines largely recommend that patients with and without diabetes be treated similarly. Accordingly, dual antiplatelet therapy is the standard of care for ACS patients, irrespective of diabetes status. Although clopidogrel may be the most widely used of the P2Y12 inhibitors recommended for dual antiplatelet therapy, there is evidence of an impaired response in patients with diabetes. Newer oral P2Y12 inhibitors such as ticagrelor and prasugrel have demonstrated greater efficacy than clopidogrel in improving the cardiovascular outcomes of patients with ACS and diabetes.

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