

Discharge Management of Patients With Diabetes and ACS

Optimizing long-term outcomes.

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Due to multiple advances in the invasive and medical management of patients with acute coronary syndromes (ACS), outcomes have improved significantly during the last 2 decades.¹ However, patients with diabetes continue to experience a higher risk of recurrent adverse cardiac events after ACS, including short- and long-term mortality, compared with patients who do not have diabetes.^{2,3} It is estimated that nearly seven in 10 patients presenting with an acute myocardial infarction have some degree of dysglycemia, with 38% having diabetes and an additional 31% with prediabetes (Figure 1).⁴ These numbers are likely to increase in the future given the rising prevalence of diabetes and prediabetes in the United States and globally. Therefore, it is critically important to better understand both the reasons behind the high rates of adverse events and the potential opportunities to improve quality of care and outcomes in this important patient group.

As cardiologists, we tend to focus our recommendations on the acute cardiac issues at hand, often with limited consideration of the patient's other chronic diseases. However, in the setting of diabetes, the two disease processes (diabetes and cardiovascular disease) can interact in a number of ways. The presence of diabetes may affect the effectiveness of the cardiac medications (ie, on-target effects). In addition, the cardiac medications may have an impact on the glycemic control of the patient with diabetes (ie, off-target effects). Both of these factors may alter the choice of medications recommended at the time of discharge for the patient with diabetes and ACS.

ON-TARGET EFFECTS

Antianginal Therapies

Due to a number of anatomic and physiologic factors, including more diffuse atherosclerosis⁵ and microvascular impairment,⁶ patients with diabetes report more residual

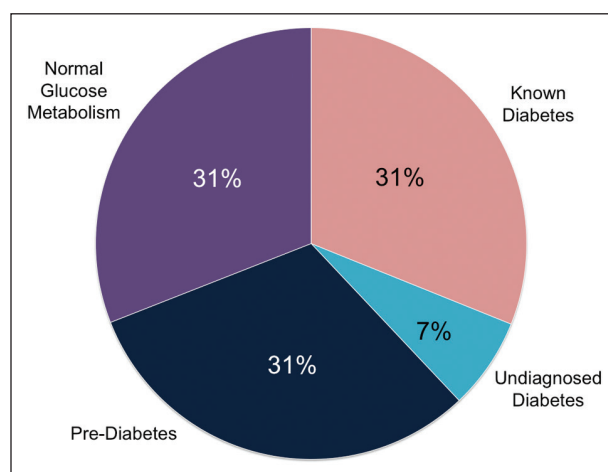


Figure 1. Prevalence of dysglycemia among patients in the United States presenting with acute myocardial infarction.

angina^{7,8} after an ACS event than those without diabetes, and this higher burden of angina persists for at least a year after discharge (Figure 2). Whether this greater burden of angina can be affected by discharge management is less clear. Strategies to reduce the progression of coronary atherosclerosis, including intensive statins and smoking cessation, are clearly indicated in patients with diabetes and ACS and have been shown to be used suboptimally in patients with diabetes.⁹ However, it should be noted that these strategies are also indicated in all ACS patients and have not been shown to be differentially more effective in patients with concomitant diabetes.¹⁰

One potential discharge strategy that has not been explicitly tested but could be considered is preemptive antianginal medications. Typically, during an ACS hospitalization, we perform revascularization, discharge the patient on standard ACS medications, and then wait until follow-up to add or titrate antianginal medications if angina persists. However,

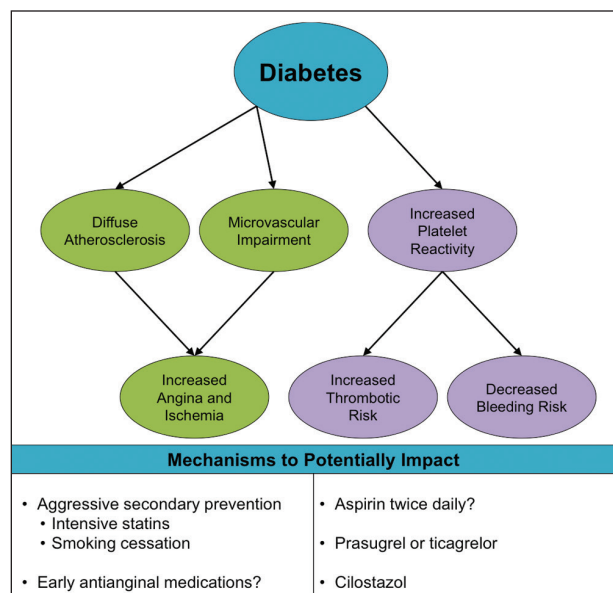


Figure 2. Effects of diabetes on the presentation and management of patients with ACS.

the strongest predictor of whether a patient will have residual angina after an ACS hospitalization is his or her burden of angina in the month prior to the ACS event.¹¹ As such, patients with diabetes who have a high burden of angina prior to their ACS could potentially benefit from antianginal medications at the time of discharge. While this needs to be formally tested, a similar strategy was essentially evaluated in the MERLIN-TIMI 36 clinical trial, in which empiric ranolazine after ACS resulted in less angina and better quality of life among patients with a history of prior angina.¹²

Antiplatelet Agents

Both the hyperglycemia and insulin resistance that accompany diabetes affect platelet reactivity through increased platelet aggregation and impaired response to antithrombotic molecules. Patients with diabetes also have increased platelet turnover, which leads to decreased response to antithrombotic medications.¹³ All of these factors contribute to a greater risk of thrombosis and less bleeding after ACS in patients with diabetes.^{14,15} The question, again, is whether (and how) this can be affected with a change in discharge management. Three mechanisms to reduce platelet reactivity and potentially improve outcomes in patients with diabetes merit consideration. Importantly, however, these three strategies each reduce platelet reactivity and have only been tested individually, and should therefore be used with considerable caution in combination.

First, the aspirin resistance that is common in patients with diabetes¹³ is likely driven by the increased platelet turnover.¹⁶ Although increasing the dose of aspirin has not

been effective at improving overall platelet reactivity, previous pharmacodynamic studies have demonstrated that this resistance can be overcome by increasing the dosing to twice daily.¹⁷ However, the potential benefit of using twice-daily aspirin after ACS, in terms of reducing recurrent ischemic events after ACS, is not yet known and will need to be formally evaluated in large outcomes studies. Second, a more intensive thienopyridine, such as prasugrel or ticagrelor, can improve outcomes in patients with diabetes and ACS. In the TRITON-TIMI 38 trial, prasugrel reduced ischemic events by a greater degree in patients with diabetes compared to those without diabetes. Furthermore, while patients without diabetes had more bleeding with prasugrel versus clopidogrel therapy, there was no difference in bleeding rates between the two treatments among patients with diabetes.¹⁴ In the PLATO trial, there was no differential effect of ticagrelor on ischemic or bleeding events in patients with diabetes (ie, similar relative risk reduction in ischemic events with ticagrelor in patients with and without diabetes).¹⁸ However, in a pharmacodynamic study of patients with diabetes and ACS, loading with ticagrelor resulted in lower platelet reactivity than loading with prasugrel.¹⁹ As such, either prasugrel or ticagrelor may result in better outcomes after ACS in patients with diabetes compared with clopidogrel. Finally, a third strategy is to add cilostazol to dual-antiplatelet therapy. While its use in the United States is generally limited to peripheral artery disease, cilostazol is commonly used as a third antiplatelet agent for ACS patients in Asia. It has been shown to reduce platelet reactivity on top of dual-antiplatelet therapy²⁰ and, in a moderately sized clinical trial, to reduce the incidence of major adverse cardiac events after an ACS—an effect that was particularly pronounced in patients with diabetes.²¹ Furthermore, cilostazol reduces the risk of restenosis after coronary stenting,²² an event for which patients with diabetes are also at high risk. While these results are promising, larger studies are needed to investigate the effects of cilostazol on top of dual-antiplatelet therapy, specifically in patients with diabetes and ACS.

OFF-TARGET EFFECTS

When selecting medications at discharge for a patient with ACS and diabetes, it is also important to consider how cardiac medications may have an impact on glycometabolic status. While certain clinical factors may contribute to the appropriate selection of medications that adversely affect glycemic control, diabetes-friendly medications should be selected in the absence of such factors (Table 1).

Favorable Glycometabolic Effects

Cardiovascular medications with potentially favorable glycometabolic effects include angiotensin-converting enzyme

TABLE 1. GLYCOMETABOLIC EFFECTS OF TREATMENTS FOR CARDIOVASCULAR DISEASE

Favorable Glycometabolic Effects	Mixed Glycometabolic Effects
• Angiotensin-converting-enzyme inhibitor and angiotensin II receptor blockers • Cilostazol • <i>Limited data/might be beneficial</i> • Ranolazine	• Calcium channel blockers • <i>Cilnidipine might be better</i> • Beta blockers • <i>Vasodilating better than traditional</i>
Neutral Glycometabolic Effects	Unfavorable Glycometabolic Effects
• Thienopyridines • Clonidine • Hydralazine • Nitrates	• Statins • Thiazide diuretics

inhibitors/angiotensin II receptor blockers (renal protection), cilostazol (possible reduction in albuminuria),^{23,24} and ranolazine (possible reduction in HbA1c level).²⁵⁻²⁷ Ranolazine is an antianginal medication that reduces myocardial ischemia at the cellular level (ie, no vasodilation) and has been shown to reduce angina to an even greater degree in patients with poorly controlled diabetes.²⁸ Furthermore, through a reduction in glucagon secretion,²⁹ ranolazine appears to reduce hemoglobin A1c by ~0.5% to 0.7% (clinicaltrials.gov: NCT01163721, NCT01494987, NCT01472185, NCT01555164), an effect that is even more pronounced among patients with poor baseline glycemic control.²⁵⁻²⁷

Mixed Glycometabolic Effects

Calcium channel blockers have traditionally been considered to have neutral metabolic effects. However, a newer medication in this class, cilnidipine, has both N- and L-type inhibitory activity (compared with amlodipine, which has only L-type) and has been shown in a small study to have favorable effects on insulin resistance, triglycerides, and albuminuria.³⁰ If this is confirmed in a larger study, cilnidipine may be beneficial as an antihypertensive and antianginal medication in patients with diabetes.

The metabolic issues associated with beta blockers are both more established and more relevant to the ACS patient population, in which they are indicated for mortality reduction.³¹ Nonvasodilating beta blockers, such as atenolol and metoprolol, reduce heart rate and myocardial contractility, inducing compensatory peripheral vasoconstriction, which leads to increased insulin resistance and a more atherogenic lipid profile.³²⁻³⁴ In contrast, vasodilating beta blockers, such as carvedilol and labetalol, have shown neutral or beneficial effects on metabolic parameters.³³⁻³⁵

In head-to-head trials, patients with diabetes who were treated with vasodilating (vs nonvasodilating) beta blockers had small but significant decreases in hemoglobin A1c levels, improved insulin sensitivity, lower cholesterol levels, less weight gain, and less progression to microalbuminuria.^{33,36-38} Furthermore, in a real-world population, we found that more than 85% of patients with diabetes were prescribed nonvasodilating beta blockers at discharge for acute myocardial infarction—a practice that was associated with a trend toward increases in HbA1c and intensification of diabetes medications over time.³⁹ Although factors such as arrhythmias or orthostasis may make a nonvasodilating beta blocker more desirable in a patient with ACS and diabetes, a beta blocker that exhibits more beneficial glycometabolic effects would ideally be chosen in a patient with diabetes if none of these factors is present.

Unfavorable Glycometabolic Effects

Multiple studies and meta-analyses have repeatedly demonstrated that statins are associated with a modest, but significant increase in the risk of developing incident diabetes.⁴⁰ Importantly, however, this risk has also been shown to be far overshadowed by the cardiovascular protective effect of statin therapy.^{41,42} Therefore, while there may be some apprehension about the impact of statins on glycemic control, intensive statins should be prescribed to all patients with diabetes and ACS, per guidelines.³¹ At this point, the glycemic effects of statins are believed to be a class effect. A small study of patients with metabolic syndrome has shown promising glycometabolic effects with pitavastatin.⁴³ While this study is encouraging, it had several important limitations, and whether pitavastatin has differential glycemic effects compared with other statins will need to be definitively determined in a larger study before making any specific recommendations about particular statins in patients with ACS and diabetes. At this point, given the greater atherosclerotic disease progression in patients with diabetes, using the most intensive statin that can be tolerated by the patient would be the most appropriate strategy after an ACS event.

Thiazide diuretics, used as antihypertensive medications, also have well-established adverse glycometabolic effects, which are believed to be due to both a reduction in insulin sensitivity and secretion.⁴⁴ In both the ALLHAT and SHEP trials, the chlorthalidone group had higher fasting glucose levels and a greater incidence of new-onset diabetes.^{45,46} However, the clinical relevance of these glycometabolic effects is still questionable. In the short-term follow-up of the trials, these increases in glucose were not associated with increased risk of morbidity or mortality,^{46,47} although new-onset diabetes was associated with an increase in the incidence of coronary heart disease.⁴⁷ Furthermore, in

the overall populations, chlorthalidone reduced adverse cardiovascular events.^{45,46} However, in a separate cohort study with follow-up up to 16 years, thiazide-associated new-onset diabetes was associated with a nearly threefold increased risk of adverse cardiovascular events,⁴⁸ which likely indicates that incident diabetes does have clinical importance in the long term, as would be expected.

CONCLUSION

Because patients with diabetes and prediabetes comprise the majority of patients with ACS—a proportion that is only increasing over time—it is becoming ever more important to understand how best to treat a patient with both conditions. Not only does diabetes affect the efficacy of the cardiovascular treatments that we provide (and therefore should affect our treatment choices), but the cardiovascular medications we choose also have an impact on glycemic control. We should strive not to treat patients in silos—with cardiologists only focusing on the heart with limited attention to other conditions—as a more comprehensive approach will maximize the opportunities to improve the quality of care and outcomes and the general health of this high-risk patient group. ■

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