ORIGINAL ARTICLE

How to Best Manage Glycemia and Non-Glycemia During the Time of Acute Myocardial Infarction

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Abstract

Acute myocardial infarction (AMI) is common in patients with diabetes. Reasons for this are multifactorial, but all relate to a variety of maladaptive responses to acute hyperglycemia. Persistent hyperglycemia is associated with worse left ventricular function and higher mortality during AMI, but intervention data are far from clear. Although there is a theoretical basis for the use of glucose-insulin-potassium infusion during AMI, lack of outcome efficacy (and inability to reach glycemic targets) in recent randomized trials has resulted in little enthusiasm for this strategy. Based on the increasing understanding of the dangers of hypoglycemia, while at the same time appreciating the role of hyperglycemia in AMI patients, goal glucose levels of 140–180 mg/dL using an intravenous insulin infusion while not eating seem reasonable for most patients and hospital systems. Non-glycemic therapy for patients with diabetes and AMI has benefited from more conclusive data, as this population has greater morbidity and mortality than those without diabetes. For ST-elevation myocardial infarction (STEMI), reperfusion therapy with primary percutaneous coronary intervention or fibrinolysis, antithrombotic therapy to prevent acute stent thrombosis following percutaneous coronary intervention or rethrombosis following thrombolysis, and initiation of β -blocker therapy are the current standard of care. Emergency coronary artery bypass graft surgery is reserved for the most critically ill. For those with non-STEMI, initial reperfusion therapy or fibrinolysis is not routinely indicated. Overall, there have been dramatic advances for the treatment of people with AMI and diabetes. The use of continuous glucose monitoring in this population may allow better ability to safely reach glycemic targets, which it is hoped will improve glycemic control.

Introduction

THE CENTERS FOR DISEASE CONTROL and Prevention reported in 2004 that 68% of diabetes-related deaths were due to heart disease.¹ A report from the Framingham Heart Study noted that the relative risk for acute myocardial infarction (AMI) is 50% greater in men with diabetes and 150% greater in women with diabetes.² Despite some improvements in mortality from AMI during the past few decades, death rates remain higher in patients with diabetes.³

Most endocrinologists and primary care physicians are familiar with advances in coronary artery disease prevention, as reflected in national and international outpatient guidelines for dietary intervention, lipoprotein management, blood pressure control, smoking cessation, appropriate aspirin use, and glucose control. However, what is currently known about the treatment of the AMI patient with diabetes? That topic will be reviewed here as it pertains to glycemia and non-glycemia management.

Glycemic Control

Mechanisms

There is no consensus about the definition of acute hyperglycemia for patients with AMI. In most recent studies, levels of blood glucose from 180 to 198 mg/dL have been used to define acute hyperglycemia. A 2000 meta-analysis of 15 studies showed that inpatients with blood glucose levels >180–198 mg/dL had an increased risk of death with a relative risk of 1.7.⁴ However, this analysis likely does not represent the modern era of reperfusion and thrombolysis. A more relevant report from the Japanese Acute Coronary Syndrome Study (80% of patients received percutaneous coronary intervention [PCI]) noted a linear relationship between admission blood glucose level and inpatient mortality for those both with and without diabetes.⁵

Although it is still controversial whether hyperglycemia is a cause or consequence of cardiac dysfunction (or perhaps both), the experimental evidence is overwhelming that hyperglycemia exacerbates myocardial damage by several

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TABLE 1. CARDIOVASCULAR EFFECTS OF ACUTE HYPERGLYCEMIA

-
- Oxidative stress
 - Inflammation
 - Apoptosis
 - Endothelial dysfunction
 - Hypercoagulability
 - Platelet hyperactivity
 - Ischemic preconditioning
-

mechanisms (Table 1). First, hyperglycemia results in inflammatory activation. It is interesting that pulse hyperglycemia appears to cause more inflammation than stable hyperglycemia.⁶ Because the antioxidant glutathione blocks this cytokine release, it is thought that the inflammatory activation from hyperglycemia is caused by an oxidative mechanism,⁶ although there is much evidence acute hyperglycemia itself (and the variability of glucose) results in an oxidative stress that results in both micro- and macrovascular damage,⁷ in addition to cell apoptosis.⁸ This complex interrelationship of oxidative stress, inflammatory activation, and hyperglycemia helps explain the toxicity of hyperglycemia during AMI. There is also strong evidence that hyperglycemia results in endothelial dysfunction,⁹ hypercoagulability,¹⁰ and platelet hyperactivity,¹¹ all detrimental in the face of an AMI.

Perhaps one of the most discussed mechanisms concerning diabetes and cardiovascular disease is ischemic preconditioning.¹² This refers to a phenomenon by which one or more brief episodes of myocardial ischemia increase the ability of the heart to tolerate a subsequent prolonged period of ischemic injury. Although ischemic preconditioning has been shown to occur in both animal models and humans, the protection has been characterized by various end points of cellular injury. It has been speculated that sulfonylureas, in particular the drug tolbutamide, may have blocked ischemic preconditioning in the University Group Diabetes Program,¹³ providing a potential explanation for the excess mortality in this historic clinical trial.¹⁴

Although most of the mechanistic work has addressed the impact of hyperglycemia for cardiovascular disease and AMI, there has been a recent increase in understanding about the role of *hypoglycemia* for this population. Inflammatory activation clearly occurs from hypoglycemia,¹⁵ suggesting that the hypoglycemia documented in other studies with critically ill patients may at least be partly responsible for the negative results reported with the attempt for normoglycemia.¹⁶ Hypoglycemia also appears to reduce myocardial blood flow reserve,¹⁷ in addition to the well-known effects on QT prolongation and ventricular arrhythmias.¹⁸ Taken together, hypoglycemia during AMI may be more deleterious than previously appreciated.

Hyperglycemia management during AMI

With AMI, persistent hyperglycemia is associated with worse left ventricular function and higher mortality.^{19,20} The evidence for aggressive treatment of hyperglycemia during this AMI period is far from clear.²¹ All of the anti-hyperglycemia therapy for AMI is with insulin therapy. Fifty years ago Sodi-Pollares et al.²² raised the concept that a metabolic cocktail consisting of glucose-insulin-potassium (GIK)

may protect ischemic cardiomyocytes. In the following years Opie²³ further refined the rationale for use of this metabolic therapy when he suggested that GIK infusion resulted in a reduction in free fatty acid levels. Furthermore, intracellular potassium is depleted during acute ischemia, raising the possibility that replacing this deficiency with exogenous potassium could raise the threshold for fatal ventricular arrhythmias.

However, GIK never became a standard of care because of inconclusive data. In the “thrombolytic era” a feasibility trial with positive outcomes²⁴ resulted in a larger trial powered with the aim to observe a treatment effect.²⁵ In this latter study of over 20,000 subjects with ST-elevation myocardial infarction (STEMI), GIK infusion resulted in a neutral effect on mortality, cardiac arrest, or cardiogenic shock. It is important that at baseline, 6 h, and 24 h, plasma glucose levels in the GIK group were 162 mg/dL, 187 mg/dL, and 155 mg/dL, respectively, compared with 162 mg/dL, 148 mg/dL, and 135 mg/dL in the standard therapy group. Although statistical differences for plasma glucose were not reported, baseline highest tertile glucose levels in the standard therapy group were associated with greater mortality at 30 days (6.6% in the lowest tertile, 8.5% in the middle tertile, and 14.0% in the highest tertile).²⁵

The other major pair of randomized trials was the two DIGAMI (Diabetes and Insulin Glucose Infusion in Acute Myocardial Infarction) studies. In the first trial, 620 patients with diabetes or admission glucose above 200 mg/dL were randomized to 24-h glucose-insulin infusion followed by subcutaneous insulin or routine anti-diabetes therapy.²⁶ Relative mortality reduction with the insulin-glucose infusion group was 29% ($P=0.027$) with the greatest benefit in those with a lower cardiovascular risk profile.

The second study, DIGAMI 2, was larger and more complex.²⁷ Patients with AMI were randomized to one of three groups: (1) acute insulin-glucose infusion followed by insulin-based long-term glucose control; (2) insulin-glucose infusion followed by standard glucose control (i.e., no insulin); or (3) routine metabolic management according to the local practice. The primary end point was all-cause mortality between Groups 1 and 2 according to intention-to-treat analysis, and mortality differences between Groups 2 and 3 and morbidity differences served as secondary and tertiary end points, respectively.

Glycemic results in DIGAMI 2 noted glycosylated hemoglobin was similar among all three groups at 6.8%. Furthermore, the primary treatment target of fasting blood glucose of 90–126 mg/dL for those in Group 1 was never achieved, as fasting glucose levels were similar among groups at approximately 149 mg/dL. Because there were no differences in glucose treatment targets, there were also no differences in the mortality end points. Mortality between Groups 1 (23.4%) and 2 (22.6%) did not significantly differ. Similarly, there were no differences between Groups 2 (22.6%) and 3 (19.3%).²⁷ It is important to note the total study mortality was 18.4% compared with a predicted mortality of 22.2%. Furthermore, compared with a similar population but without diabetes, mortality in the group with diabetes did not differ. It is tempting to attribute this to the reasonable (but not normal) glucose control, but that would be speculative.

One other possibility is that the benefit of GIK infusion would be enhanced by much earlier administration (i.e., in the

Diagnosis: check one box: ☐ Type 1 DM ☐ Type 2 DM ☐ Stress Hyperglycemia

Goal Blood Glucose (BG) Range – check one box:

Acute Care Unit OR Intensive care unit (ICU): ☐ 100-180 mg/dL **ICU ONLY:** ☐ 100-140 mg/dL

Insulin Infusion Orders: ICU: Initiate insulin infusion when BG is ☐ >180 X2; ☐ >140 X2

Acute care unit: Initiate insulin infusion when ordered.

☒ **Discontinue all previous insulin orders.**

☒ **Start Insulin Infusion:** 100 units insulin/ 100 mL NS given IV infusion, at:

☐ **Algorithm 1:** Start here for most patients.

☐ **Algorithm 2:** Start here if s/p CABG surgery, solid organ transplant, receiving glucocorticoids, or patient receiving >80 units/day of insulin as an outpatient.

- NO PATIENT STARTS AT ALGORITHM 3 OR 4.

☒ See back of form for the algorithms and instructions: *"Insulin Infusion Algorithm Decision Tree"*

☒ Transition to SubQ. Give specified basal insulin dose SubQ, then discontinue insulin infusion in 2 hours.

Fluid Orders: Indicate source of Dextrose: ☐ IVF ☐ Continuous tube feedings ☐ TPN

☒ **ICU patient refer to ICU fluid orders (See back for recommendations)**

☒ **Acute Care patients:**

☐ D₁₀W with 20 meq/L KCl given IV at a rate of 100mL/hour (=10 gm of carbohydrate/hour or 960 calories/day)

☐ D₅½NS with 20 meq/L KCl given IV at a rate of 100mL/hour (=5 gm of carbohydrate/hour or 480 calories/day)

Patient Monitoring:

☒ Check BG every 1 hour until it is within **goal** range for 4 hours. Then decrease BG checks to every 2 hours. ALWAYS resume hourly checks if BG exits goal range.

☒ If BG is below 110mg/dL or decreases more than 100mg/dL in previous hour, check BG in 20-30 minutes

▶ Hourly monitoring may be indicated for critically ill patients or patients having medical or surgical procedures even if they have stable BG. Consult with Charge nurse to plan for BG monitoring if patient must be transported off the unit. Patients with T1DM should never have the insulin infusion turned off for >1 hour.

FIG. 1. General instructions for University of Washington intravenous insulin infusion protocol. BG, blood glucose; D₅½NS, dextrose 5% in 0.45% NaCl; D₁₀W, dextrose 10% in water; DM, diabetes mellitus; HMC, Harborview Medical Center; ICU, intensive care unit; IV, intravenously; IVF, intravenous fluid; NS, normal saline; s/p CABG, status post-coronary artery bypass graft; SubQ, subcutaneous; T1DM, type 1 diabetes mellitus; TPN, total parenteral nutrition.

Notify the Physician:

- ☒ For any BG increase >100 mg/dL from a stable baseline
- ☒ For 2 consecutive BG decreases of >100 mg/dL
- ☒ For any hypoglycemia which results in loss of consciousness **OR** does not resolve within 20 min of implementing the hypoglycemia protocol below
- ☒ Failure of algorithm 4 for 3 consecutive hours (Consider adding HMC High Dose Insulin Infusion Orders)

Treatment of Hypoglycemia (BG <70 mg/dL) or symptoms of hypoglycemia or below BG goal:

- ☒ **Turn off** insulin infusion for any BG below goal **AND**
- ☒ Give 25 mL (1/2 amp) of 50% dextrose IV if BG 50-69 mg/dL **OR**
- ☒ Give 50 mL (1 amp) of 50% dextrose IV if BG < 50 mg/dL.
- ☒ Recheck BG every 20-30 minutes until BG $\geq$ 100 mg/dL
 - IF BG is <70 mg/dL repeat 25 mL (1/2 amp) 50% dextrose
 - WHEN BG is $\geq$ 100 mg/dL, restart the insulin infusion at a lower dose by using one algorithm **LEFT** from previous algorithm (see *"Insulin Infusion Algorithm Decision Tree"* section).

TPN/ Enteral feeding:

- ☒ If TPN/ Enteral feeding is stopped or significantly reduced, decrease insulin infusion rate by moving **LEFT** one algorithm. Then, use *"Insulin Infusion Algorithm Decision Tree"* to determine subsequent rate changes **AND** check BG every 1 hour x 4 hours.

FIG. 1. (Continued).

pre-hospital setting). A very recent, randomized trial has reported on *pre-hospital* GIK administration by paramedics to patients with high probability of acute coronary syndromes based on symptoms and electrocardiographic findings.²⁸ GIK administration was associated with lower risks for a combined end point of cardiac arrest plus in-hospital mortality, both in the whole acute coronary syndrome cohort ($n=871$, odds ratio 0.56, $P=0.01$) and in the subset presenting with STEMI ($n=357$, odds ratio 0.63, $P=0.01$).²⁸ In those receiving GIK, circulating free fatty acid levels were suppressed acutely approximately 40%, and median infarct size at 30 days was smaller. Diabetes was present in just under 30% of trial participants; the magnitude of GIK reduction in outcomes appeared to be similar in those with and without diabetes.²⁸ Although intriguing, this study clearly bears replication before pre-hospital GIK administration could become a standard of care.

So how can all of this be translated to the clinician? It seems clear that although there may be some theoretical basis for the classic GIK infusion, from a practical point of view it is too cumbersome to use with quickly changing insulin requirements as the insulin concentration needs to be altered every time a change in insulin infusion rate is needed. Therefore, for the nothing-by-mouth hyperglycemic patient (with or without a prior history of diabetes), using a variable-rate intrave-

nous insulin infusion seems the most reasonable strategy of insulin delivery.

Glycemic targets are more complicated because, other than the trials noted above, there are no intervention studies in the current era of thrombolytic therapy that target AMI. It should also be noted there are no studies using short-term glycemic markers such as fructosamine or 1,5-anhydroglucitol to use as other measures of glycemic targets. The most publicized trial, NICE-SUGAR,¹⁶ assessing tight glucose control in 6,104 critically ill patients, did not include patients with AMI. Still, the results are noteworthy in that the intensive therapy group had mean weighted glucose (115 ± 18 mg/dL) significantly lower than the conventional therapy group (144 ± 23 mg/dL) but with more hypoglycemia less than 40 mg/dL (6.8% vs. 0.5%). The primary end point, 90-day mortality, was greater in the intensive therapy group (27.5% vs. 24.9%) ($P=0.02$). A recent meta-analysis for both medical and surgical critically ill patients noted similar findings.²⁹ Perhaps this is not surprising as we learn about the impact of hypoglycemia on inflammatory activation.³⁰ This concern may even be more relevant for a patient with AMI because of the negative impact of hypoglycemia on ischemia³¹ and arrhythmia.³²

Because high-level evidence for glycemic targets in AMI is not available and hypoglycemia is likely as dangerous if not

more so in this population, we believe the current American Association of Clinical Endocrinologists (AACE)/American Diabetes Association (ADA) targets of 140–180 mg/dL for critically ill patients are reasonable.³³ This would include initiating insulin therapy when blood glucose rises above 180 mg/dL. There are no data with the use of a subcutaneous insulin pump or continuous glucose monitoring for use during AML.

At the University of Washington Medical Center, we started using an inpatient intravenous insulin infusion protocol in 1992. There have been several major revisions to our protocols over the years. Our current intravenous insulin algorithms are presented in Figures 1–3. It is important to note we use our protocol when appropriate for the patient not eating in both the intensive care unit and non-intensive care unit setting. Our most recent version is noted in Figures 1–3. Note the lower end of our targets is below the AACE/ADA recommendations because of our longstanding experience of safety using intravenous insulin in our institution.³⁴

Non-Glycemia Management

Atherosclerotic plaque morphology and myocardial infarction risk in diabetes

Disruption of the structural integrity of a preexisting atherosclerotic plaque is thought to be the primary initiator of AMI. The most common mechanisms include fibrous cap rupture or ulceration, which exposes the blood to thrombogenic plaque contents, such as macrophages and lipid. This

stimulates formation of a thrombus in the lumen of the coronary artery that may propagate to occlude blood flow, resulting in downstream myocardial ischemia and myocardial infarction (MI). Based on this paradigm, the risk for MI would be increased by three sets of factors, all of which are increased in those with diabetes. These include the following: (1) Increases are found in those with diabetes in plaque macrophages and lipid,^{35,36} both of which promote plaque instability.³⁷ Plaque lipids not only undermine plaque structural integrity³⁸ but also promote influx of macrophages, which secrete enzymes^{39,40} that degrade plaque structural proteins, including collagen. (2) A generalized increase is observed in arterial stiffness, clinically manifest as an increase in pulse pressure, which results in increased transmission of hemodynamic forces to plaque fibrous caps. In experimental models, diabetes has been associated with both increased arterial collagen^{41,42} and decreased arterial elastin.⁴³ (3) A prothrombotic milieu occurs, which in those with diabetes includes increases in plaque content of the prothrombotic molecule and plasminogen activator inhibitor-1,⁴⁴ as well as greater plasma hypercoagulability,¹⁰ including platelet dysfunction¹¹ and increased levels of fibrinogen.⁴⁵

Risks for MI complications in those with diabetes

Diabetes is associated with dramatic increases in risk for death from MI, both during the index hospitalization and following hospital discharge. Early in the thrombolytic era,

FIG. 2. Insulin infusion algorithm decision tree used to guide insulin infusion rates at the University of Washington Medical Center. BG, blood glucose; TPN, total parenteral nutrition.

Algorithm 1		Algorithm 2		Algorithm 3		Algorithm 4	
BG	Units/hr	BG	Units/hr	BG	Units/hr	BG	Units/hr
<70 = Hypoglycemia (See page 1 for treatment)							
70-99: Off x 20-30 minutes & recheck BG							
100-110 Recheck BG in 20-30 minutes, consider moving left one Algorithm							
100-120	0.5	100-120	1.	100-120	1.5	100-120	2
121-140	0.8	121-140	1.5	121-140	2.5	121-140	3.5
141-160	1.2	141-160	2	141-160	3	141-160	4.5
161-180	1.5	161-180	2.5	161-180	4	161-180	6
181-210	2	181-210	3	181-210	5	181-210	7.5
211-240	2.5	211-240	4	211-240	6.5	211-240	9.5
241-270	3	241-270	5	241-270	8	241-270	11.5
271-300	3.5	271-300	6	271-300	9	271-300	13.5
301-330	4	301-330	6.5	301-330	10.5	301-330	15
331-360	4.5	331-360	7.5	331-360	12	331-360	17
>360	5	>360	8.5	>360	14	>360	19

FIG. 3. Column-based insulin infusion protocols. For individuals who require higher doses, a higher infusion rate can be administered. BG, blood glucose.

the GUSTO-I trial found a near doubling in the 30-day post-MI mortality rate in those with diabetes.⁴⁶ More recently, a U.S. registry involving >80,000 MI cases found diabetes to be associated with a 33% increase in in-hospital mortality.⁴⁷ Diabetes also is associated with increases in longer-term risks for death following MI. Post hoc analyses of the SAVE⁴⁸ and VALIANT⁴⁹ trials both found a diabetes-associated 50% in risk of death at 3.5–5 years following post-MI hospital discharge. The pathophysiology of this dramatic, diabetes-associated increased risk of death is likely multifactorial and involves increased risks for recurrent coronary occlusion,⁴⁶ congestive heart failure (CHF) and cardiogenic shock,⁵⁰ and arrhythmias.

CHF and cardiogenic shock. Diabetes is a well-recognized risk factor for CHF, with a twofold increase in risk for prevalent CHF,² CHF hospitalization,⁵¹ and idiopathic cardiomyopathy.⁵² Echocardiography has shown associations of diabetes with increased left ventricular mass and impaired cardiac relaxation (i.e., diastolic dysfunction), both of which not only precede the development of impaired cardiac contractile function (i.e., systolic dysfunction) but also are independent of hypertension and increased body mass index.⁵³ Baseline diastolic dysfunction may be present in up to 50–60% of those with diabetes.^{53,54} It is interesting that a higher prevalence of diastolic dysfunction has been correlated with both poorer glycemic control and more severe albuminuria.⁵⁵ Diabetes is associated with increased myocardial fibrosis⁵⁶

and with metabolic disturbances, including increased oxidative stress and altered energy substrate utilization,⁵⁷ all of which likely contribute to impaired cardiac relaxation.

Against this background of diabetes-associated abnormalities in cardiac *relaxation*, it is not surprising that the acute superimposition of an acute decrease in *contractility* of the infarcted segment of myocardium is more likely to precipitate clinical CHF or even cardiogenic shock. The degree of contractile dysfunction during MI is further exacerbated by the lack of compensatory hyperkinesis in non-infarcted segments.⁴⁶ Thus, an 80,000-participant PCI registry documented that diabetes is associated with a much higher risk for cardiogenic shock at presentation.⁵⁰

Arrhythmias. Whether diabetes is associated with increased risk for ventricular arrhythmias has been somewhat controversial, as studies have suggested a decreased risk for ventricular arrhythmias with coronary occlusion in rats,⁵⁸ as well as post-primary PCI for AMI in humans.⁵⁹ However, one recent study found that an admission glucose level of >180 mg/dL was associated with a 50% increase in “high-risk” ventricular arrhythmias.⁶⁰ Moreover, those with diabetes have several risk factors for arrhythmias, which include myocardial fibrosis and electrolyte disturbances, such as hyperkalemia and hypomagnesemia from type IV renal tubular acidosis. However, the greatest theoretical and practical risk for ventricular arrhythmias for those with diabetes and MI may be that of severe hypoglycemia,¹⁸ which has multiple pro-arrhythmic

effects, including adrenergic activation, induction of coronary ischemia,³¹ and increases in the QT interval⁶¹ and QT dispersion.³² Thus, avoidance of hypoglycemia, targeting glucose levels to a range of 140–180 mg/dL,³³ may be a key factor in avoiding arrhythmias during AMI in those with diabetes.

General Approach to MI Care in Those with Diabetes

AMI therapies

STEMI. Acute treatment of STEMI is outlined in the 2004 American College of Cardiology / American Heart Association guidelines⁶² as well as in a 2009 focused update⁶³ and includes the following: (1) ischemic pain relief with supplemental oxygen and intravenous morphine, as necessary; (2) assessment of the hemodynamic state and correction of abnormalities, including hypertension, tachycardia, pulmonary congestion, and/or hypoperfusion and shock; (3) prompt reperfusion therapy with primary PCI or fibrinolysis; (4) antithrombotic therapy to prevent acute stent thrombosis following PCI or rethrombosis following thrombolysis; and (5) initiation of β -blocker therapy to prevent ventricular arrhythmias and recurrent ischemia.

Unstable angina/non-STEMI. Acute management of those presenting with unstable angina or non-STEMI differs primarily in that, as opposed to STEMI management, initial reperfusion therapy with PCI or fibrinolysis is *not* routinely indicated. Instead, stratification of risk for complications should be performed to help guide whether an individual patient should be managed conservatively with medical therapy or with an early invasive strategy with angiography and either PCI or referral for coronary artery bypass graft (CABG) surgery, as guided by coronary anatomy.⁶⁴

Specific considerations for non-glycemic MI therapies in diabetes

Relief of ischemic pain. Therapies for management of ischemic pain are similar in those with and without diabetes and include supplemental oxygen, especially in those with arterial O₂ saturation <90%, as well as intravenous morphine, as necessary to control pain.

Assessment of hemodynamic state. This requires particular attention to signs and symptoms of congestion, including dyspnea, rales, and increased jugular venous pressure, as well as signs of hypoperfusion beyond low blood pressure, such as cold, clammy extremities, diminished peripheral pulses, and decreased mentation. Because of the increased risks for CHF and cardiogenic shock in those with diabetes, attention to these potential signs and symptoms should be heightened.

Reperfusion. Based on evidence demonstrating a >40% reduction in risk for death, non-fatal re-infarction, or stroke for “primary” PCI (i.e., PCI as first reperfusion therapy) versus intravenous fibrinolytic therapy,⁶⁵ primary PCI is the preferred initial reperfusion strategy in most patients presenting with AMI. Guidelines have established a goal of opening the infarct artery within 90 min of first contact with medical personnel at a facility with PCI capability.⁶³ Facilities without on-site PCI should have protocols for rapid transfer

to PCI centers for primary PCI.⁶³ Emergency CABG surgery is reserved for those failing reperfusion with PCI or fibrinolytics, cardiogenic shock or life-threatening arrhythmias, and severe, multivessel, or left main disease.⁶² In addition to the higher rates of cardiogenic shock in those with diabetes,⁵⁰ data from GUSTO-IB suggest these patients have a higher rate of failed reperfusion.⁴⁶ Patients with diabetes are more likely to present with multivessel coronary artery disease and therefore more likely to be candidates for extensive revascularization with CABG surgery; however, it may be preferable to defer surgery for several days in those without emergency indications in order to minimize risk of reperfusion injury. CABG surgery is generally preferred over PCI in those with diabetes requiring multivessel revascularization,⁶⁶ likely because more complete revascularization is associated with better clinical outcomes.⁶⁷

Antiplatelet therapy. Antiplatelet therapy with full-dose aspirin (325 mg/day) and a thienopyridine (clopidogrel, prasugrel, or ticagrelor) is essential to prevent re-occlusion of the infarct-related artery following reperfusion with PCI or fibrinolytics. Moreover, older data demonstrate similar *relative* efficacy of long-term aspirin in those with and without diabetes.⁶⁸ Although those with diabetes have increased rates of re-occlusion,⁴⁶ there is no evidence supporting use of aspirin doses above 325 mg/day, and some theoretical concern exists that higher doses could promote vasoconstriction by inhibiting prostacyclin production. There is some debate about the relative clinical efficacy of clopidogrel versus prasugrel or ticagrelor, but an analysis across multiple comparative trials concluded that the latter two agents are clearly associated with increased risks for bleeding and are substantially more expensive than clopidogrel.⁶⁹

β -Blockers. Oral β -blocker therapy, preferably with a β -1-selective agent, is an essential component of non-glycemic therapy in those with MI. As in those without diabetes, contraindications to β -blocker use include heart failure, low output state, or high risk for cardiogenic shock, bradycardia, and heart block.⁶² Older data suggest that the relative risk reduction associated with in-hospital β -blocker therapy may be even greater in those with diabetes compared with those without diabetes (37% vs. 13%).⁷⁰ A relative risk reduction of 40% with post-MI β -blocker therapy in diabetes was confirmed in a large Medicare database.⁷¹ In addition, it appears that many patients with chronic obstructive pulmonary disease may be safely treated with β -blockers post-MI and also achieve significant reduction in mortality.⁷¹ One important consideration with β -blocker therapy is that the predominant hypoglycemic symptoms are shifted from sympathetic (e.g., tremulousness) to parasympathetic (e.g., diaphoresis), though with no adverse change in the level of hypoglycemic awareness.⁷²

Conclusions

Although there have been dramatic improvements in the understanding of the basic pathophysiology of AMI in patients with diabetes, evidence for improved outcomes has been significantly greater in the area of non-glycemic management. In general, non-glycemic therapies considered standard of care for treatment of AMI in those without

diabetes appear to have similar, and in some cases greater, relative benefits to those seen in those without diabetes. On the other hand, we lack appropriate evidence from intervention trials to identify ideal glycemic targets. Because of both epidemiologic data and newer data on the general dangers of hypoglycemia, we believe that the current general glycemic targets for inpatient hyperglycemia management are appropriate for patients with AMI. It is hoped that newer technology (specifically continuous glucose monitoring) will provide improved safety to allow clinical trials to assess the impact of normoglycemia for this population.

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Author Disclosure Statement

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