Prevalence of Newly Diagnosed Diabetes in Clinical Settings

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A substantial number of patients being evaluated or treated for cardiovascular disease are found to have glucometabolic disorders. Identification of such patients is important because treatment for coronary artery disease and stroke needs to be individualized. Hyperglycemia on admission or during hospitalization regardless of whether diabetes mellitus is known to exist in these patients is associated with increased morbidity and mortality. Despite the fact that this has been known for some time, various strategies to reduce hyperglycemia have had mixed results in cardiac outcomes. Another important factor is that a new diagnosis of diabetes mellitus in these patients should result in the patient's triage to appropriate healthcare professionals to optimize glycemic control. The prevalence of hyperglycemia in patients admitted with acute cardiovascular disease and the effect of hyperglycemia on outcome are reviewed.
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The in-hospital mortality after acute myocardial infarction in the 1950s was approximately 30% for all patients and nearly 50% for those with diabetes mellitus (DM). By the late 1990s, numerous advances in the treatment of acute myocardial infarction including, most recently, the use of fibrinolytic therapy and percutaneous coronary intervention, has greatly reduced early mortality today to less than 10% (Figure 1).[1] However, despite this significant progress in the treatment of acute coronary syndromes, patients

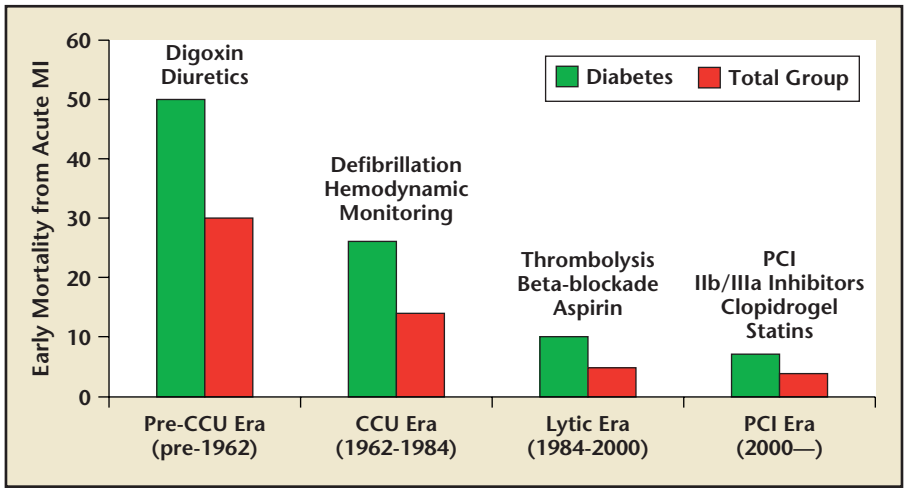

Figure 1. *Effect of diabetes mellitus on mortality of acute myocardial infarction, pre-1962 to 2000. MI, myocardial infarction; PCI, percutaneous coronary intervention; CCU, cardiac care unit. Adapted from Braunwald E.*[1]

with DM still have approximately twice the 30-day mortality rate of patients without DM. This gap in survival between patients with and without DM suggests that the mechanisms by which diabetes causes heart disease are poorly understood and not totally corrected by current treatment strategies for acute myocardial infarction.

Recently there has been a new appreciation of the prevalence and role of hyperglycemia as a factor accounting for the increased risk of mortality in acute myocardial infarction.[2] Elevated glucose on admission is now recognized as a risk factor for a wide variety of in-hospital adverse outcomes.[3] Hyperglycemia is not only a feature of patients with known DM, but is also seen in patients without a history of DM. The association of either hyperglycemia or glycosuria in patients with diabetes with myocardial infarction was noted many years ago. It was not clear at that time whether the recognized disorder of glucose metabolism was a cause or effect of the acute cardiac event. Furthermore, the finding of admission hyperglycemia in a patient without a diagnosis of DM was largely a clinical curiosity and not regarded as a target for treatment.

Hyperglycemia in the setting of an acute cardiac illness is due to several factors.[4] Stress during illness leads to a release of counter-regulatory hormones (catecholamines, glucagons, cortisol, growth hormone) and mediators of inflammation such as cytokines. These hormones cause hyperglycemia by gluconeogenesis and glycogenolysis, principally in the liver. In addition, peripheral insulin resistance can be induced acutely in response to these counter-regulatory hormones as well as a consequence of the increase in plasma level of free fatty acids. The release of tumor necrosis factor–alpha, an important mediator of inflammation, also can cause "acute" insulin resistance in patients under these circumstances. Patients with DM may exhibit a greater glycemic response to these hormones because such patients will have an inadequate release of insulin due to beta cell dysfunction and already have some degree of insulin resistance made only worse by these acute metabolic phenomena. During the course of hospitalization, numerous other factors can contribute to hyperglycemia. In a patient with known DM, insufficient insulin administration typically due to an inadequate individualized sliding scale can lead to hyperglycemia. The use of dextrose in parenteral infusions (as nutrition and in solution with drugs) in acutely ill patients may lead to excessive glucose exposure. Refeeding a patient with excessive calories can elevate glucose levels. The use of steroids and sympathomimetics can cause hyperglycemia. Sliding scales often play "catch up" once any of these factors intervenes. In prolonged hospitalizations, hyperglycemia may indicate infection often not clinically evident.

In general, the presence of DM is associated with a greater likelihood of pre-hospital death in patients with acute myocardial infarction[5] as well as a higher rate of reinfarction after successful percutaneous coronary intervention (PCI). Furthermore, these patients tend to have impairment of coronary blood flow despite successful PCI[6] and also may experience reactivation of ischemia before discharge typically once antithrombotic therapies are withdrawn. Diabetic patients are also thought to lack the benefit of ischemic preconditioning that can limit infarct size.[7] Early and late congestive heart failure is also more common in these patients after myocardial infarction,

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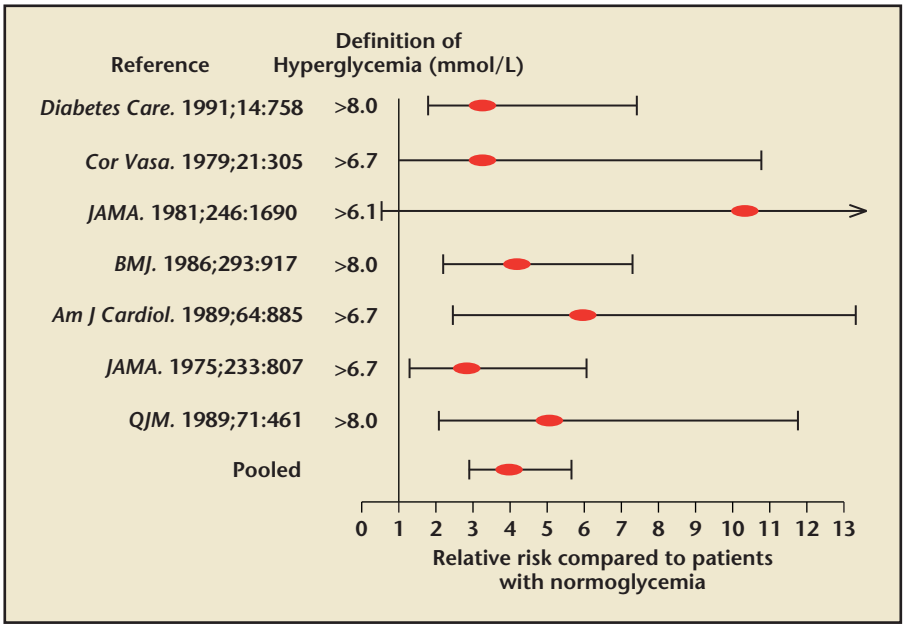
resulting in longer intensive care unit and hospital stays.[8] All of these adverse events occur despite the fact that patients with DM experience similar patency rates after PCI as patients without DM. In the past the reason explaining this increased relative risk associated with DM was the fact that these patients presented with more extensive coronary disease at the time of their myocardial infarction. At least 2 studies have shown that even after statistical adjustment for the extent of coronary artery disease, patients with DM still exhibit twice the mortality compared to patients without DM. In the Global Utilization of Streptokinase and tPA for Occluded Coronary arteries trial, which examined the efficacy of fibrinolytic therapy with streptokinase in patients with acute MI, an angiographic substudy found that even after adjusting for clinical factors known to affect outcome such as previous myocardial infarction, age, gender, congestive heart failure, and so on, and angiographic measures such as extent of coronary artery disease, the likelihood of 30-day mortality associated with DM remained significantly elevated (odds ratio 2.0: $P = .02$).[9] Most recently, the Fragment and Fast Revascularization During Instability in Coronary Disease Trial, which examined invasive versus conservative management of acute coronary artery disease and efficacy of a low-molecular-weight heparin, dalteparin, a multivariate analysis found that the strongest independent risk factor for early mortality was a diagnosis of DM and that multivessel disease was not a significant independent predictor of mortality in the analysis even though diabetic patients tended to present with more double, triple, and left main coronary artery disease.[10] In this study, the mortality risk ratio associated with a diagnosis of diabetes was 5.42 after controlling for other clinical variables and the extent of coronary artery disease.

The real question that remains, however, is what factor specific to diabetes is responsible for this increased relative risk. More recently attention has turned to the possibility that it may be hyperglycemia itself that drives the risk and that this is more likely to occur in patients with diabetes when acute myocardial infarction occurs. A review of the literature by Capes and colleagues in 2000 showed that stress hyperglycemia in acute myocardial infarction increased the risk of mortality in patients without a history of diabetes (Figure 2).[2,11-17] The increased relative risk was quite dramatic and varied from 2- to 10-fold compared to patients with normoglycemia on admission. This relative risk may be somewhat exaggerated in this study because there was not a complete adjustment for other factors typically seen in these patients that could have accounted for this increased risk. Hyperglycemia could have been a manifestation of undiagnosed DM, or a marker of other factors, such as hypertension, dyslipidemia, and obesity, that would tend to cluster in these patients who undoubtedly are insulin resistant. In 1986 an interesting study by Oswald and colleagues[18] showed that infarct size measured by peak aspartate transaminase was loosely related to the plasma glucose on admission. For many years, clinicians have thought that the level of glycemia seen during acute myocardial infarction was a direct result of the size of myocardial injury and an index of stress hyperglycemia due to the release of counter-regulatory hormones, as mentioned previously. Admission hyperglycemia probably reflects a combination of several factors, only one of which is the "stress" component. An insulin-resistant patient will develop higher glucose levels for any degree of cardiovascular stress than a patient who is not insulin resistant.

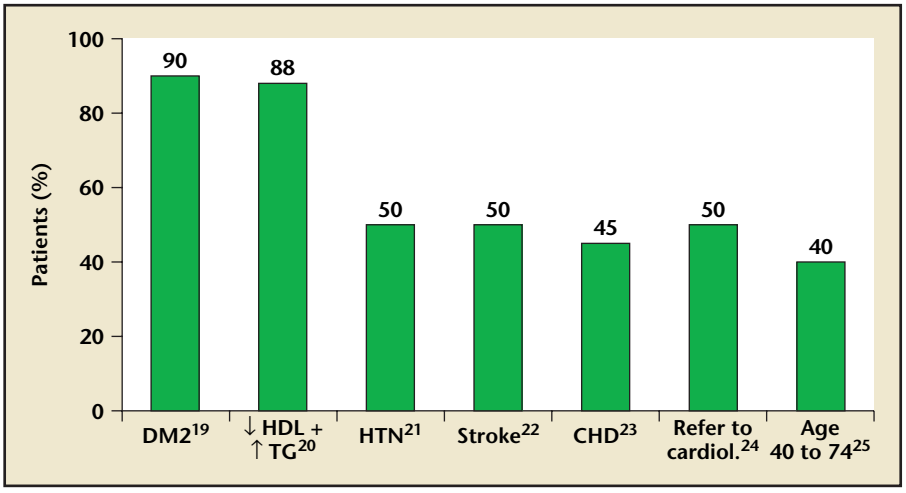
Figure 2. *Mortality risk for stress hyperglycemia in patients without diabetes mellitus. Data from references 11-17.*



The majority of patients entering the hospital for evaluation of cardiovascular disease typically have clustering of risk factors indicative of insulin resistance (Figure 3).[19-25] Many of these patients meet criteria for metabolic syndrome, impaired glucose tolerance (IGT), or DM. Data from the Bruneck study show that when "common" risk factors such as low high-density lipoprotein, hypertension, or hypercholesterolemia occur together in a patient, the likelihood of insulin resistance as measured by homeostasis model assessment is very high.[26] In a series of men without known DM referred for coronary angiography, oral glucose tolerance testing (OGTT) showed that as the severity of coronary artery disease increased so did the discovery of undiagnosed IGT or DM so that patients with double or triple vessel coronary disease had nearly a 50% likelihood of having either IGT or a new diagnosis of DM.[27] These data were corroborated in the GAMI study, which evaluated the prevalence of IGT in DM in patients with acute myocardial infarction.[28] Subjects were excluded if they had a previous diagnosis of DM or if they had a markedly elevated glucose on admission (> than 11.1 mm/L). The prevalence of IGT in this group was 34%, and 33% had a new diagnosis of DM. One might think that the acuity of the illness might cause a "temporary" dysglycemia in this study and that the diagnosis of IGT or type II DM was transient, but when patients were retested 12 months later, 40% were found to have IGT and 25% retained a diagnosis of DM. These data indicate that IGT and type II DM are commonly discovered in patients presenting with coronary artery disease syndromes. One of the most comprehensive analyses of this issue was carried out by Norhammar and colleagues.[29] This group performed an oral glucose tolerance test at discharge on 181 patients presenting with acute myocardial infarction without known DM. At discharge 35% of the patients were found to have IGT and 31% had a new diagnosis of DM. When the same patients were tested 3 months later, 40% had IGT and 25% retained a diagnosis of DM. Preliminary findings from a study by Chung and colleagues demonstrated that approximately 50% of patients with myocardial infarction who were younger than 45 years of age met criteria for metabolic syndrome.[30] Similar findings were seen in a large community hospital with the same prevalence of metabolic syndrome in young heart attack victims.[31] In summary, insulin resistance syndromes occur in the majority of people seen by the cardiologist, and these patients are likely to have hyperglycemia on admission.

The level of glucose on admission in patients with type II DM experiencing acute myocardial infarction does relate to the degree of glycemic control before the event, so that patients with lower A1Cs on admission will present with lower admission glucose levels compared to those patients with a high A1C.[32] In patients presenting with admission hyperglycemia, 2 other factors specific to glycemia appear important in determining the prognosis. In an evaluation of 735 patients with acute myocardial infarction without a diagnosis of DM, blood glucose level on admission as well as within 24 hours after an 8-hour fast were measured in each patient. The fasting glucose 24 hours after admission was a more powerful independent predictor of outcome at 30 days than the admission level of glucose.[33] The CARDINAL study analyzed 1469 patients with acute myocardial infarction with both baseline and 24-hour glucose measurements (Figure 3). Baseline glucose and the 24-hour change in glucose (24-hour glucose level subtracted from the baseline glucose) were included in multivariate models for 30- and 180-day mortality.

Figure 3. *Insulin resistance is relatively common in clinical practice, as indicated by results shown here. As expected, the vast majority of patients with DM are also insulin resistant. Insulin resistance is highly prevalent among patients with low levels of high-density lipoprotein cholesterol (HDL-C) and high triglyceride (TG) levels. Approximately half of all patients referred to a cardiologist are also insulin resistant, as are many patients with stroke and congestive heart failure (CHD). Forty percent of patients aged 40 to 74 years, as well as at least half of patients with hypertension (HTN), are also insulin resistant. Data from references 19-25.*



In patients without a history of DM, higher baseline glucose predicated higher mortality, and a greater 24-hour change in glucose predicted lower mortality.[34] Taken together, these 2 studies indicate that the overall degree and time course of glucometabolic derangement impacts the outcome. The failure of glucose to decrease in a patient with admission hyperglycemia is a poor prognostic sign and is one of the strongest pieces of evidence suggesting that therapeutic intervention in these patients could change outcome.

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The situation is very similar in the setting of acute stroke. In general, the prevalence of IGT or undiagnosed DM is seen somewhat less than in the setting of an acute myocardial infarction but nevertheless indicates that vascular disease in general is associated with recognized and unrecognized disorders of glucose metabolism. For instance, Matz and coworkers[35] showed that in 238 patients presenting with acute thromboembolic stroke submitted to OGTT that 23% had a diagnosis of IGT and 16% had a new diagnosis of type II DM. In another study,[36] Kernan and coworkers submitted 98 patients without a previous diagnosis of DM who had experienced a recent transient ischemic attack or ischemic stroke to an oral glucose tolerance test at a mean of 105 days after hospitalization. IGT was found in 28% and a new diagnosis of type II DM was confirmed in 24%. In the Glucose Infusion in Stroke Trial in which patients with acute stroke were given OGTT 12 weeks after discharge, a blood glucose level greater than or equal to 6.1 mmol/L combined with a glycosylated hemoglobin level greater than or equal to 6.2% on admission accurately predicted the presence of DM.[37] Continuous glucose monitoring in 59 patients with acute hemispheric ischemic stroke for up to 88 hours indicated that there are early and late hyperglycemia phases in both nondiabetic and diabetic patients despite current treatments. Hyperglycemic patients also had a worse neurologic outcome and a higher rate of infectious complications. Furthermore, a retrospective study of patients discharged with a diagnosis of ischemic stroke indicated that admission hyperglycemia was associated with a higher mortality rate but normalization of glucose (< 130 mg/dL) was associated with a 4.6-fold reduction in mortality risk compared to the group whose blood glucose did not fall in the first 48 hours of hospitalization.[38] Given the prevalence and risk of glucometabolic disorders in these patients, some have suggested that there is an urgent need to apply insulin infusions to reduce hyperglycemia in patients with thromboembolic stroke.[39] The rationale for the insulin infusion in these patients is based on the fact that hyperglycemia may impair cerebral blood flow (see article by Dr. Dandona in this issue) and worsen ischemia/reperfusion injury to brain tissue through hyperglycemia's vasoconstrictive, pro-thrombotic, and pro-inflammatory effects.[40] Acute hyperglycemia in this setting has been implicated in lower tissue plasminogen activator–induced recanalization rates in stroke patients with intracranial artery occlusion.[41]

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Another situation in which blood glucose concentration is related to outcomes is in the setting of coronary artery bypass grafting (CABG). Similar to acute myocardial infarction, CABG is associated with acute vascular and myocardial injury, and it is not surprising that the toxic effect of hyperglycemia plays an important role in the outcome in patients undergoing this procedure. Although it has been known for some time that DM increases the likelihood of poor outcomes in patients undergoing bypass surgery, it is not clear whether this was due to diabetes per se or to the hyperglycemia triggered at the time of CABG. In the Society of Thoracic Surgeons database,[42] the incidence of mortality following CABG was 4.5% among patients with DM, and 2.7% among those without DM. In the Portland Diabetic Project,[43] a strong relationship between post-CABG mortality and plasma glucose concentration was described.

In the multivariate analysis of this database, the blood glucose concentration in the perioperative period as well as in the 2 days following surgery was independently associated with high risk for adverse outcome even after adjustment for clinical variables such as cardiogenic

shock, age, left ventricular function status, history of atrial fibrillation, and the use of pressors. Interestingly, blood glucose concentration after the third postoperative day was not as significant an independent predictor of increased mortality nor was the preoperative blood glucose level or the state of glycemic control (hemoglobin A1C) measured before DM. This situation resembles that of acute myocardial infarction during which the glucose level at the time of the cardiac insult has a direct effect on outcome; the glucotoxic effect may be more important than the presence or absence of DM per se. Institution of a continuous infusion of insulin in hyperglycemic patients at the time of CABG in the Portland Diabetic Project reduced postoperative mortality of 5.3% to 2.5% when management was changed from subcutaneous insulin to continuous infusion of insulin. Cardiac-related mortality was also significantly reduced for all patients undergoing coronary artery bypass graft surgery from 4.4% with subcutaneous insulin to 1.6% with continuous infusion of insulin. Management of hyperglycemia during this 3-day period has resulted in a similar outcome following CABG for patients with and without DM and signifies the important causative role of hyperglycemia. The mechanisms by which continuous infusion of insulin and rigorous control of hyperglycemia lead to better outcomes are outlined in other articles in this supplement issue to *Reviews in Cardiovascular Medicine*.

In conclusion, emerging guidelines[44,45] indicate that cardiologists need to become more familiar with detecting and treating hyperglycemia in acutely ill patients. Furthermore, almost one third of patients presenting with acute coronary syndromes will have a new diagnosis of DM and another one third will have IGT. The cardiologist has a responsibility to diagnose such conditions because earlier intervention in type II DM can prevent diabetes-related end organ complications. ■

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Main Points

- Hyperglycemia on admission or during hospitalization for cardiovascular disease, regardless of whether diabetes mellitus is known to exist in these patients, is associated with increased morbidity and mortality.
- Various strategies to reduce hyperglycemia have had mixed results in cardiac outcomes.
- The prevalence of hyperglycemia in patients admitted with acute cardiovascular disease and the effect of hyperglycemia on outcome are reviewed.
- Cardiologists need to become more familiar with detecting and treating hyperglycemia in acutely ill patients; almost one third of patients presenting with acute coronary syndromes will have a new diagnosis of diabetes mellitus and another one third will have impaired glucose tolerance.

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