

INPATIENT DIABETES: REVIEW OF DATA FROM THE CARDIAC CARE UNIT

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ABSTRACT

Objective: To review prospective and retrospective studies in an effort to assess the effect of glucose control on outcomes in critically ill populations.

Methods: Results from recent prospective and retrospective studies are presented and analyzed in detail, with an emphasis on patients with myocardial infarction.

Results: Retrospective observations show that, with the routine use of percutaneous coronary interventions, hyperglycemia continues to be a risk factor for mortality. In 2 prospective studies using glucose-insulin-potassium infusion, glucose levels did not reach target, and the results of both trials were negative with regard to the primary endpoint, mortality. However, progressive hyperglycemia was a risk factor for death in both prospective studies. It is an interesting paradox that diabetes actually may be protective for myocardial infarction. Although the reasons for this are not clear, one study showed that patients with diabetes were more likely to receive insulin for any given blood glucose level.

Conclusion: A study using variable-rate intravenous insulin infusion should be commissioned. In the meantime, clinicians should strive to achieve the best-possible glucose control in all patients with acute myocardial infarction and hyperglycemia. While we improve our understanding of the basic roles of glucose and insulin in modulating inflammation, we must aggressively treat hyperglycemia to the national goals for this population, which would substantially improve outcomes. (*Endocr Pract.* 2006;12[Suppl 3]:27-34)

Abbreviations:

AMI = acute myocardial infarction; **CI** = confidence interval; **CREATE-ECLA** = Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiológicas Latin American Study Group trial; **DIGAMI** = Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction study; **GIK** = glucose-insulin-potassium; **HbA1c** = hemoglobin A1c; **MI** = myocardial infarction

INTRODUCTION

In 2001, Van den Berghe and colleagues published a landmark study noting a dramatic benefit from providing enough insulin to keep blood glucose levels in the normal range for a surgical intensive care unit population (1). Importantly, this was mostly a nondiabetic population. Since then, there have been other studies, both prospective and retrospective, for other populations of patients (both with and without diabetes), including those having myocardial infarction (MI). This topic is important to emphasize, especially because heart disease and stroke account for approximately 65% of deaths in people with diabetes (2). This review will focus mostly on what has been recently observed about glucose control, particularly for individuals who are admitted with MI.

RECENT RETROSPECTIVE REPORTS

There have been various recent observations on the relationship between glucose control and outcomes for individuals admitted with MI. These recent analyses differ from earlier reports because of newly available advances in cardiac care, particularly the introduction of reperfusion therapy. For example, Ishihara et al (3) noted that acute hyperglycemia, but not diabetes, was a predictor for inpatient mortality after acute MI. "Acute hyperglycemia" was defined as a plasma glucose level of 198 mg/dL on admission, regardless of diabetes status. Percutaneous coronary

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intervention was performed in 72% of these 1,253 patients. For those with acute hyperglycemia, the mortality rate was 16%, compared with 6% for those without hyperglycemia ($P < 0.001$). Mortality rates did not differ between those with diabetes, yet acute hyperglycemia was present more frequently in both populations (without diabetes, 24% versus 6%; $P < 0.001$; with diabetes, 10% versus 5%; $P < 0.039$). It appears that being “labeled” with diabetes prior to admission for acute MI is not a risk factor for mortality. Whether mortality is related to previously undiagnosed diabetes or to stress hyperglycemia is not clear. This is a difficult issue to clarify because undiagnosed diabetes and impaired glucose tolerance are common in this population (4).

Similarly, Timmer et al (5) investigated long-term clinical outcome for 356 consecutive nondiabetic patients with ST-elevated MI treated with reperfusion therapy. The mortality rate correlated directly with the tertile of glucose level (Fig. 1). Higher glucose levels also correlated with infarct size ($P < 0.01$) and reduced residual left ventricular function ($P < 0.05$). Since both MI and heart failure are known inflammatory states, these data should not be surprising, because glucose is known to be pro-inflammatory (6).

RECENT PROSPECTIVE REPORTS

In 1997, Malmberg and colleagues (7) published the long-awaited Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. In this study, subjects with type 2 diabetes and acute myocardial infarction (AMI) were randomized to received intravenous insulin or glucose for at least 24 hours, followed by outpatient diabetes management of a multi-dose insulin regimen ($N = 306$, baseline hemoglobin A1c (HbA1c) = 8.2%). The comparator group was standard diabetes management both peri-infarction and after discharge from the hospital ($N = 314$, baseline HbA1c = 8.0%). Overall reduction in absolute mortality was 11% (with a 28% relative risk reduction), compared with 15% for subjects at low risk for MI who were not taking insulin before randomization (with a relative risk reduction of 51%) (7).

The second DIGAMI study (DIGAMI 2) was a larger one with a different protocol (8). The purpose of this trial was to further explore the potential benefit of insulin-based regimens for a similar population of patients, as seen in the first DIGAMI trial. However, the populations were not similar. In DIGAMI 2, diabetes control at baseline was im-

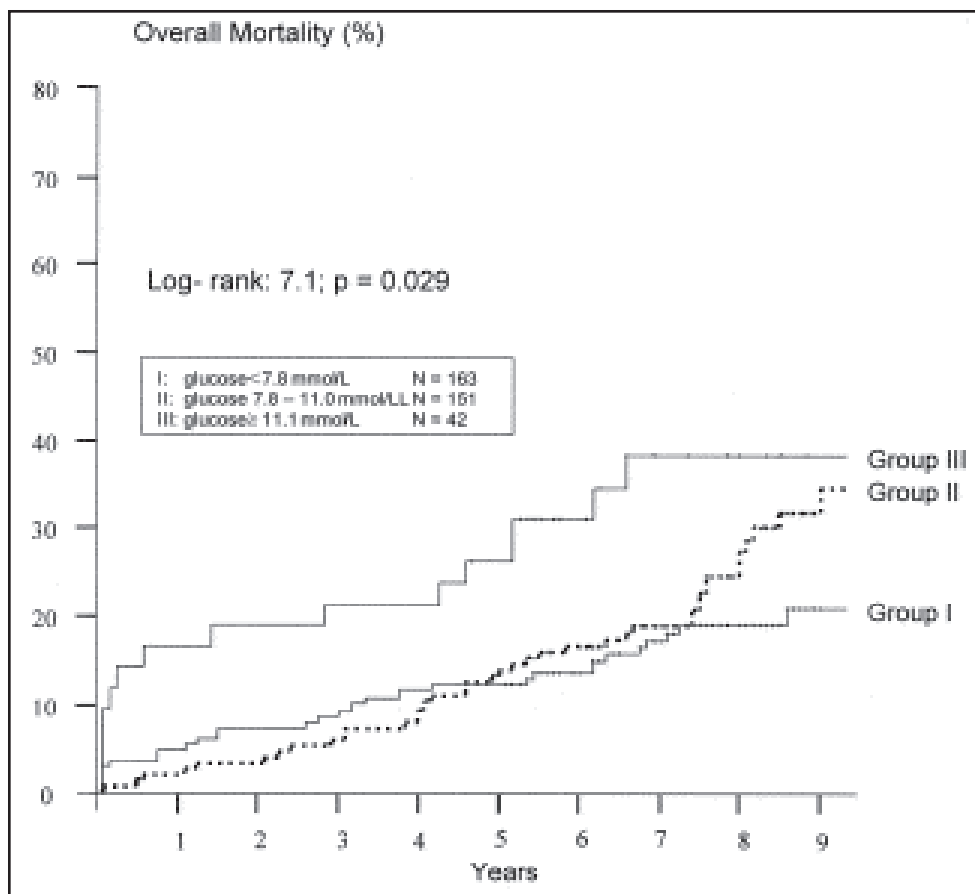


Fig. 1. Kaplan-Meier curves showing mortality rates of the 3 glucose tertiles. From Timmer et al (5). Reprinted with permission.

proved compared with the earlier study: mean HbA1c was 7.2% to 7.3%. In DIGAMI 2, subjects with type 2 diabetes were randomized to 1 of 3 groups. Groups 1 and 2 received an insulin-and-glucose infusion, with the objective of maintaining blood glucose between 126 and 180 mg/dL. The infusion lasted for at least 24 hours, although no details are provided about how frequently bedside blood glucose measurements were obtained, the degree of glucose control during those 24 hours, or the number of subjects who were eating. Group 3 subjects received anti-hyperglycemic treatment based on local practice. In group 1, subcutaneous insulin was initiated after cessation of the insulin-glucose infusion (regular insulin given before meals; intermediate or long-acting basal insulin administered at bedtime [no analogue insulin was available]). The fasting blood glucose target was 90 to 126 mg/dL, with a nonfasting goal of less than 180 mg/dL. No specifics were provided for addressing the frequency of home blood glucose monitoring or for determining whether the nonfasting target should be the 1- or 2-hour postprandial glucose level. Moreover, there was no mention of the frequency of intervention with nurse educators or nutritionists. Groups 2 and 3 received anti-diabetes therapy based at the discretion of their local physicians.

The median study duration was 2.1 years (8). At the end of the first 24 hours, groups 1 and 2 had the lowest blood glucose levels, each at 164 mg/dL, whereas the blood glucose for group 3 was 180 mg/dL. After discharge, multi-dose insulin therapy (≥ 3 daily injections) was provided to only 42% of group 1 patients, compared with 15% and 13% of group 2 and 3 patients, respectively. By the end of the

study, HbA1c levels were the same for the 3 groups (approximately 6.8%), and the target fasting glucose for group 1 was not met (mean glucose level, 144 mg/dL).

Total mortality rate for the population was 18.4%. The primary endpoint, mortality between groups 1 and 2, did not differ. Likewise, the secondary endpoint, mortality between groups 2 and 3, did not differ (Fig. 2). This may not be surprising because there were no differences in blood glucose levels. However, in an epidemiologic analysis, blood glucose was found to be a strong independent risk factor for mortality (8).

Although “the DIGAMI 2 trial confirms that glucose level is a strong independent predictor of long-term mortality following MI in patients with type 2 diabetes” (8), the primary endpoint was negative. However, the investigators acknowledged that several important issues must be considered. First, the study operated with few resources, and recruitment was less than 50% of what was calculated from the initial power calculation. Second, only 42% of subjects in group 1 received “intensive therapy,” defined as 3 or more daily injections of insulin. Even for the minority who did receive this therapy, 1 of the 3 meals was not treated with prandial insulin, which suggests that basal insulin (most likely neutral protamine Hagedorn) was used to cover meal requirements. Therefore, few of these subjects were provided the tools to prevent postprandial hyperglycemia and more severe glycemic variability, problems found in those with insulin deficiency, which appear to be strongly related to vascular disease (9,10). Also not provided are any specific data for the frequency of self-monitoring of blood

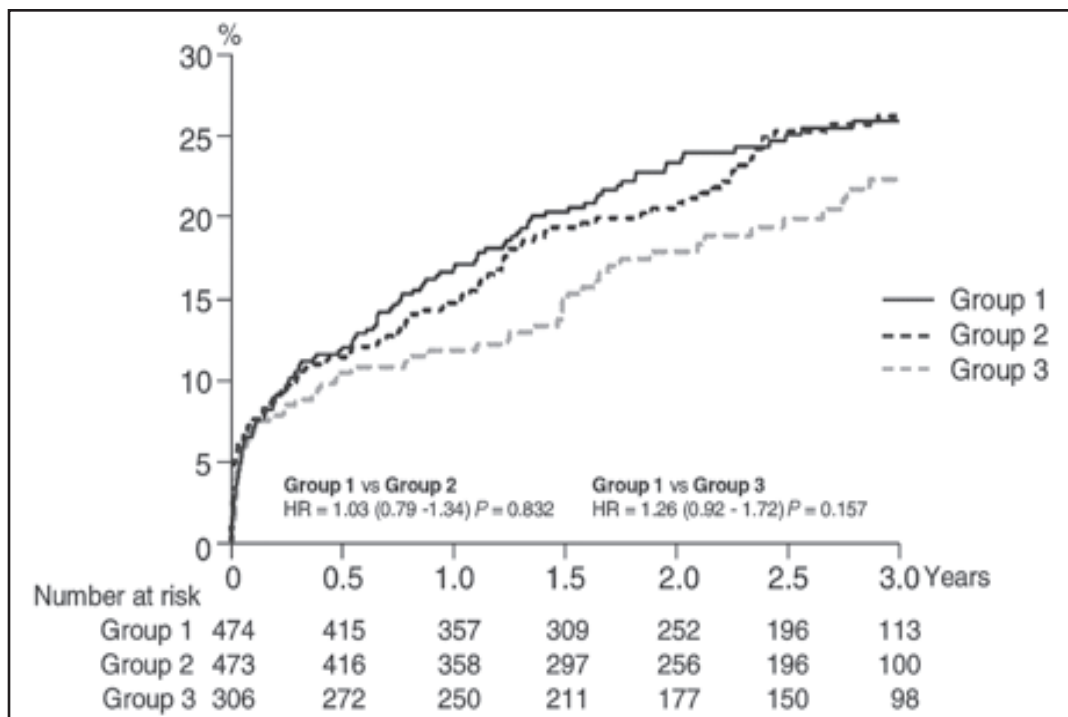


Fig. 2. Mortality rates for DIGAMI 2. Data are shown for all 3 groups in the intention-to-treat analysis.

glucose, nor the protocols used to manage insulin regimens in these outpatients. Were patients seen by diabetes nurse educators and nutritionists? Were endocrinologists involved with the insulin management for those in group 1? We don't have answers to these important questions. What we do know is that glycemic endpoints did not differ between the groups. Is it any wonder there were no differences in mortality?

The other important study published in 2005, which used glucose-insulin-potassium (GIK) infusion for AMI, was the CREATE-ECLA (Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiológicas Latin American Study Group) trial (11). In this study, subjects presenting with ST-elevation MI (17% with type 2 diabetes) were randomized to receive GIK infusion for 24 hours plus usual care (n = 10,091) or usual care alone (n = 10,110). The primary endpoint was mortality, cardiac arrest, cardiogenic shock, and reinfarction 30 days after randomization.

As shown in Figure 3, there were no differences in death or the composite of death or nonfatal cardiac arrest (11). Likewise, cardiac arrest and cardiogenic shock did not differ between the groups ($P = 0.51$ and 0.38 , respectively). As with DIGAMI 2, this was a negative study, showing a neutral effect between groups. Also similar to DIGAMI 2, when the control group was subdivided into baseline glucose tertiles, the highest glycemia group was found to have the highest mortality rate (14%), whereas subjects in the lowest tertile group had the lowest rate (6.6%). Additionally, even though the 2 groups had identical blood glucose levels at randomization, these levels were higher in the GIK group during the 24 hours on the infusion (Table

1). If we accept that hyperglycemia itself is an inflammatory stimulus (3,12), one could argue that it is surprising that GIK was not associated with a higher mortality rate. As with DIGAMI 2, if treatment goals are not met, it is unlikely that differences in outcomes will be observed.

GIK infusion does more than simply control glucose. For example, in another recent study using GIK, it was shown that when the infusion rate was slower (1/3 of that used in the CREATE-ECLA study), the incidence of 1-month major adverse cardiac events was reduced from 32.5% to 10% (RR 0.24, 95% confidence interval (CI), 0.09 to 0.63; $P = 0.0043$) (13). In this study, there was also improvement in left ventricular ejection fraction after 1 year (13).

Another earlier study using GIK for AMI did not show a reduction in mortality among its 940 subjects (14). However, a subgroup analysis of 856 patients (91% of the study population) without signs of heart failure did show that GIK infusion correlated with improvement in the mortality rate (1.2% versus 4.2%; RR = 0.28; 95% CI, 0.1 to 0.75).

The conclusion from these and other studies is that there are many factors impacting the success of this therapy. First, GIK is cumbersome to use, especially compared with variable-rate insulin infusion. GIK infusion actually can cause more hyperglycemia (as seen in CREATE-ECLA), defeating its purpose. It is also difficult to use GIK in a population that is eating, which appears to be the case in many studies (little attention is given to this problem). Postprandial hyperglycemia generally is ignored for patients in the hospital, and it could be argued that the AMI population should have the best after-meal glucose

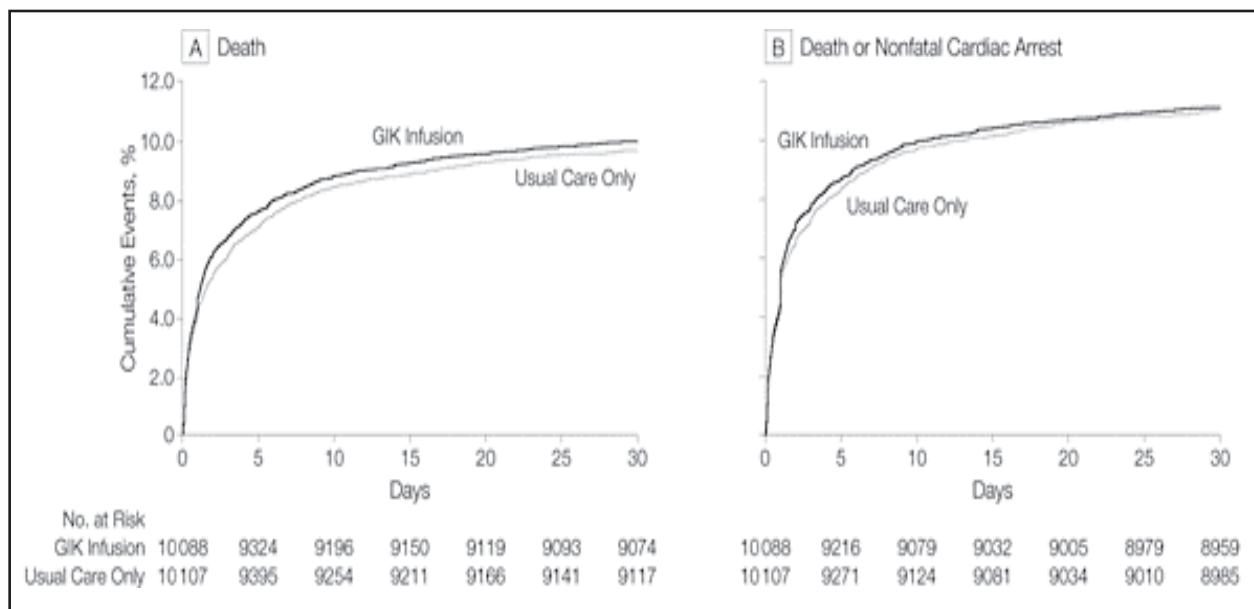


Fig. 3. Cumulative hazard rates (HR) of death and death/nonfatal cardiac arrest within 30 days. For death, the HR was 1.03 [95% confidence interval (CI), 0.95 to 1.13; $P = 0.45$]. For death/nonfatal cardiac arrest, HR was 1.01 (95% CI, 0.93 to 1.10); $P = 0.73$). From Kosiborod et al (17). Reprinted with permission.

Table 1
Blood Glucose Levels During the 24 Hours
After Randomization to the Control or the
Glucose-Insulin-Potassium Group

	Baseline	6 hours	24 hours
Control	162	148	135
GIK	162	187	155

Data from the CREATE-ECLA Group Investigators (11).

control (15). Differences in volume of fluid infused and degree of heart failure also appear to influence outcome. Nevertheless, the literature does contain positive studies with GIK infusion; and indeed, a meta-analysis from 1997 showed a benefit (16). It appears that, if GIK infusion can be provided to restore near-normal glycemia in patients who are not volume overloaded, it could be used successfully. However, from a practical point of view, few institutions would be able to accomplish this.

Admission Glucose, AMI, and the Elderly

Another important study published in 2005 was the Cooperative Cardiovascular Project, a nationally representative community-based sample of elderly patients (N = 141,680) hospitalized with AMI between 1994 and 1996

(17). The frequency of diabetes in this population was 30.4%, with a mean glucose level on admission (for the entire group) of 150 mg/dL. Hyperglycemia was common in those without known diabetes (e.g., 58% of patients with admission glucose levels between 170 and 240 mg/dL, and 26% for those with glucose levels above 240 mg/dL). Still, in each glucose category, those with known diabetes were more likely to receive insulin therapy during the admission (Fig. 4). For all patients, both crude 30-day and 1-year mortality rates rose as glucose levels increased (Fig. 5). However, glucose-associated mortality rates differed for those with and without diabetes. Admission hyperglycemia was associated with a steep increase in 30-day and 1-year mortality rates for those without known diabetes, yet this relationship was not present for those with established diabetes (Fig. 6). Mortality for those with known diabetes was increased only at the highest glucose level (>240 mg/dL). It is tempting to speculate that the greater attention to hyperglycemia (with insulin treatment) for those with diabetes was partly responsible for this observation, but this would only be speculative.

SUMMARY AND CONCLUSION

As we enter the second half of the first decade of the millennium, it is clear that the epidemiologic evidence supports a strong relationship between hyperglycemia and mortality for AMI. Although specific mechanisms cannot be determined from these studies, data continue to accu-

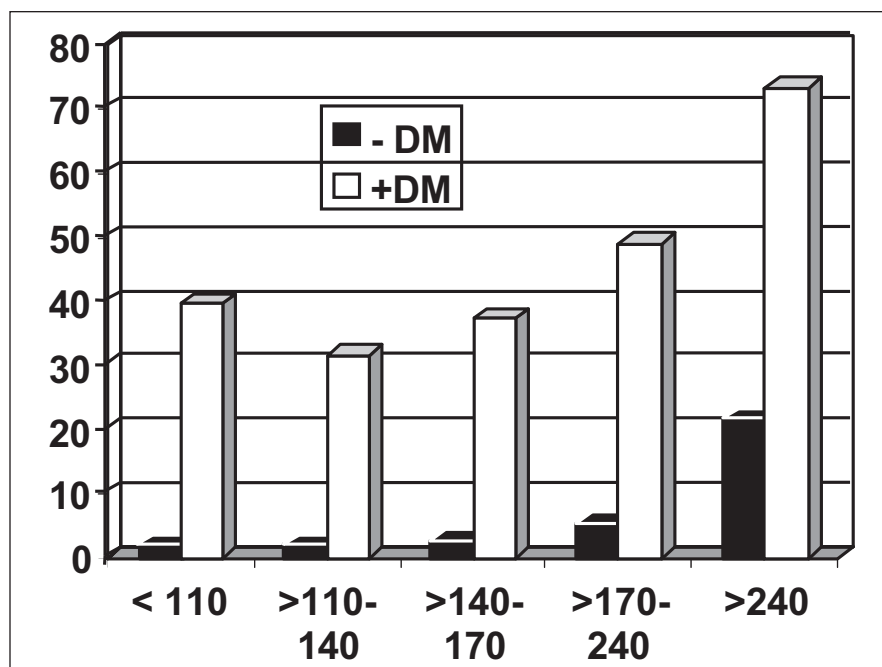


Fig. 4. Insulin administration rates during hospitalization in patients with and without recognized diabetes. For comparison between patients with and without diabetes, $P < 0.001$ for each of the admission glucose groups. From Kosiborod et al (17). Adapted with permission.

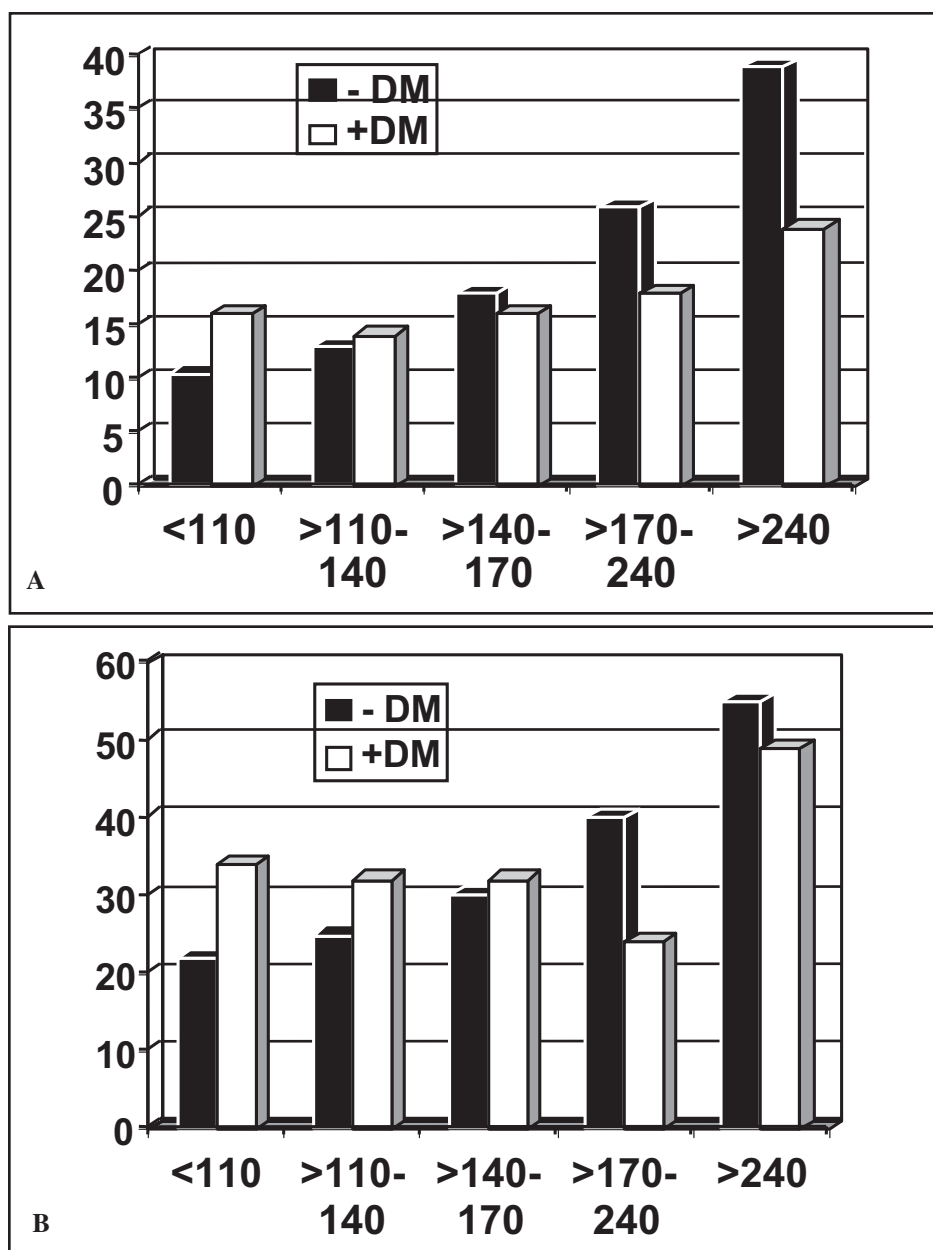


Fig. 5. (A) Relationship between admission glucose levels and crude 30-day mortality in patients with and without recognized diabetes. (B) Relationship between admission glucose and crude 1-year mortality in patients with and without recognized diabetes. From Kosiborod et al (17). Adapted with permission.

mulate that glucose and insulin co-modulate inflammation (6,18-21). Hyperinsulinemia is anti-inflammatory with euglycemia (18-20). However, high insulin levels appear to be pro-inflammatory when in a hyperglycemic environment (21). Therefore, it is not surprising that the 2 recently published intervention trials with the GIK infusion for AMI (DIGAMI 2 and CREATE/ECLA) both had negative results. Primary study endpoints cannot be met if treatment targets are not reached. On the other hand, both of these trials showed that hyperglycemia has a negative impact on mortality, similar to the retrospective data. It appears that

the GIK infusion is too cumbersome to consistently reach euglycemic targets, and thus variable-rate intravenous insulin infusion should be used instead.

Ideally, a similar study to DIGAMI2 or CREATE/ECLA should be commissioned, using variable-rate intravenous insulin infusion. In the meantime, clinicians should strive for the best glucose control possible, in all patients with AMI and hyperglycemia, as noted in the guidelines of both the American College of Endocrinology (22) and the American Diabetes Association (23).

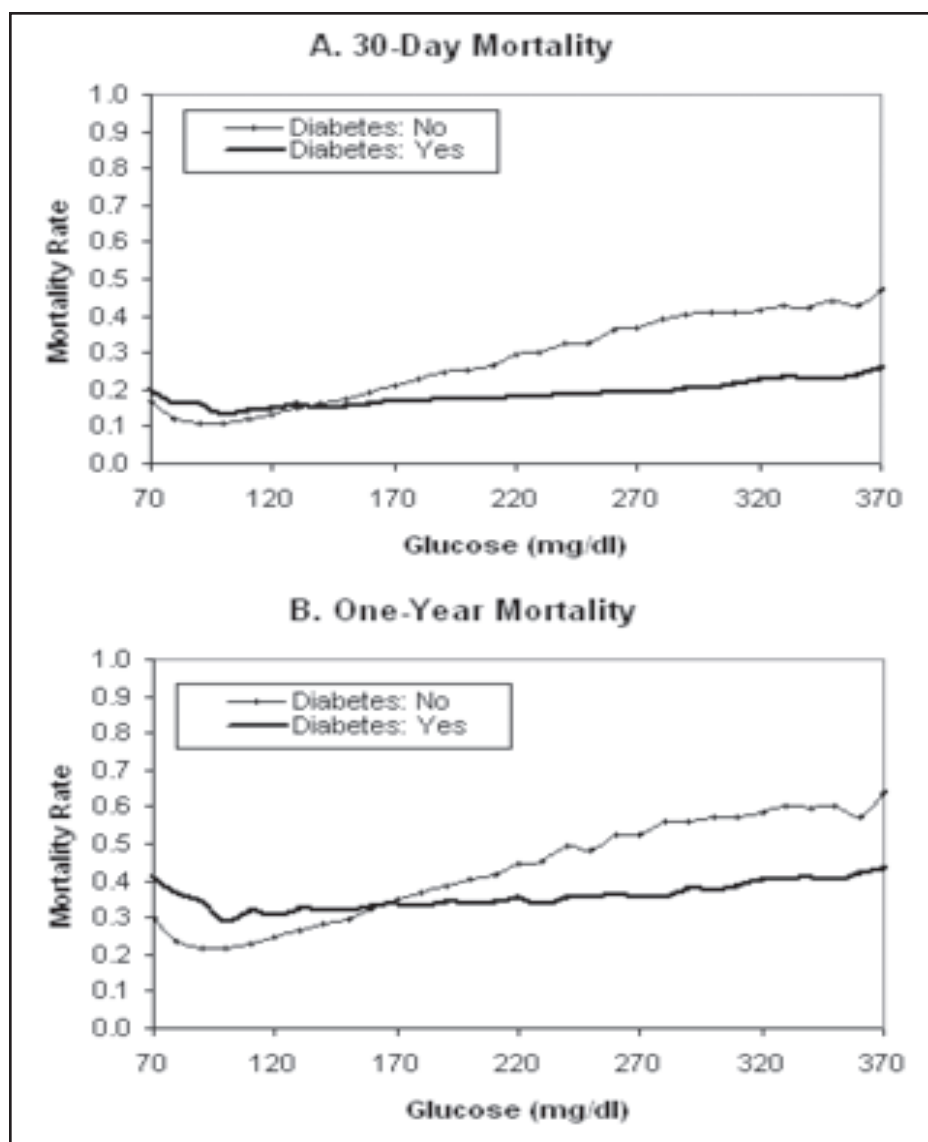


Fig. 6. Direct comparison of risk adjusted 30-day mortality (A) and 1-year mortality (B) in patients with and without recognized diabetes across range of glucose values. From Kosiborod et al (17). Adapted with permission.

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