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Is Blood Glucose an Independent Predictor of Mortality in Acute Myocardial Infarction in the Thrombolytic Era?

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OBJECTIVES This study was designed to assess the prognostic significance of hyperglycemia in acute myocardial infarction (AMI) in the thrombolytic era using contemporary criteria for hyperglycemia.

BACKGROUND Most studies that have examined this issue were performed before the widespread use of disease-modifying therapies and varied in their definition of hyperglycemia, assessment of risk factors, and reported outcomes.

METHODS There were 1,664 consecutively hospitalized patients with AMI between October 1997 and October 1998 from a disease-specific, population-based registry. Patients were stratified according to history of diabetes mellitus and, further, according to whether they had a blood glucose >198 mg/dl (11 mmol/l). The influences of cardiac risk factors, medications, and interventions were analyzed, and multivariate logistic regression was used to determine the influence of blood glucose on mortality.

RESULTS In patients without a history of diabetes, glucose levels were ≤198 mg/dl in 1,078 patients (Group 1) and >198 mg/dl in 135 (Group 2). Of those with diabetes, glucose levels were ≤198 mg/dl in 169 patients (Group 3) and >198 mg/dl in 282 (Group 4). Compared with Group 1 patients, the odds ratios (95% confidence interval) for in-hospital mortality among those in Groups 2, 3, and 4 were 2.44 (1.42 to 4.20; p = 0.001), 1.87 (1.05 to 3.34; p = 0.035), and 1.91 (1.16 to 3.14; p = 0.011), respectively. These groups also had greater 12-month mortality.

CONCLUSIONS Hyperglycemia in AMI is associated with poor outcome even among patients without known diabetes. This finding underlines the need for aggressive glucose management in this setting and may support a more vigorous screening strategy for early recognition of diabetes. (J Am Coll Cardiol 2002;40:1748–54) © 2002 by the American College of Cardiology Foundation

Diabetes mellitus is an established major cardiovascular risk factor associated with increased prevalence of coronary artery disease (CAD) (1). Patients with diabetes often have numerous concomitant cardiac risk factors with a higher incidence of acute myocardial infarction (AMI) and congestive heart failure (CHF). Poor glycemic control and insulin resistance are associated with significant endothelial cell dysfunction, procoagulability, and diffuse multi-vessel CAD.

Patients either with or without a prior history of diabetes mellitus may present with hyperglycemia during AMI. Among patients with no prior history of diabetes, hyperglycemia may reflect previously undiagnosed diabetes, preexisting carbohydrate intolerance, stress-related carbohydrate intolerance, or a combination of these (2). Several studies have reported an association between elevated blood glucose upon admission and subsequent increased adverse events, including CHF, cardiogenic shock, and death (3–20). However, an overview of these reports (2) was critical of the varying definitions for hyperglycemia (blood sugars ranged from 119 mg/dl (6.6 mmol/l) to 200 mg/dl (11.1 mmol/l) and of the sketchy assessment of patient variables, previous medical therapy, and in-hospital interventions. Furthermore, many of the studies were conducted in the pre-thrombolytic era.

Given that the management of diabetes mellitus, other cardiac risk factors, and AMI has evolved significantly since the publication of these reports, it is uncertain whether hyperglycemia upon admission, irrespective of the diagnosis of diabetes, remains an independent predictor of in-hospital morbidity and mortality. The objective of this study was to determine whether the level of blood glucose upon admission remains associated with adverse in-hospital clinical outcomes after AMI in the contemporary era, considering

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Abbreviations and Acronyms

AMI = acute myocardial infarction
CAD = coronary artery disease
CHF = congestive heart failure
ICONS = Improving Cardiovascular Outcomes in Nova Scotia

recent advances in treatment; and we sought to take a population-based approach toward examining this question.

METHODS

Setting and study population. Nova Scotia is a province of Canada with a population of approximately 940,000 persons. The clinical implications of elevated blood glucose upon hospital admission were explored using data from the Improving Cardiovascular Outcomes in Nova Scotia (ICONS) project. This is a large, prospective-cohort disease management study whose rationale and methods have been comprehensively described elsewhere (21).

Briefly, the ICONS study protocol received ethics review and approval at the Queen Elizabeth II Health Sciences Centre in Halifax and at several other institutions across Nova Scotia. Since October 15, 1997, extensive data have been compiled through primary chart abstraction on all Nova Scotia residents consecutively hospitalized in a Nova Scotia health care facility with, among other conditions, AMI. Daily patient lists, sorted by admission ward, are obtained from the admitting or health records departments at all provincial adult care hospitals. These are scanned, and charts are requested on patients who might be having an AMI. Similarly, lists of patients sorted by discharge diagnosis (ICD-9-CM codes 410–414) are obtained from health records departments. All diagnosis types (including most responsible diagnosis, primary diagnosis, secondary diagnoses, and complications) are requested, and charts are reviewed. This process ensures high sensitivity for identifying all patients with a clinical diagnosis of AMI. The ICONS investigators defined cases on the basis of clinical diagnosis, as opposed to specific electrocardiographic and enzymatic criteria for two reasons: first, to enable comparisons with published reports using administrative data sets, and second, to avoid missing events in an era when more sensitive enzyme markers of myocardial injury are redefining case definition (22). For the present study, information was collected pertaining to the 12-month interval between October 15, 1997, and October 14, 1998, which was the baseline phase of the parent study.

Data collection. Specially trained nurses and medical record technologists abstracted detailed information from each inpatient chart, including documentation of modifiable cardiac risk factors, particularly diabetes. Data were also collected pertaining to comorbid illnesses, admission medications, the results of investigations (including the first blood glucose upon admission), processes of care in the hospital, and outcomes. The outcomes of interest included in-hospital mortality as determined from chart review, and one-year mortality obtained through record linkage to the Nova Scotia Vital Statistics Registry.

Data quality control. Data collection for the ICONS study commenced only after an accuracy level of at least 95% for data abstraction was achieved. This required the implementation of several quality control mechanisms, described elsewhere (21), including random reabstraction of charts, software logic checks built around key fields, and periodic review of a random sample of entered cases.

The death registration process in Nova Scotia involves numerous quality checks, including upon completion of death registration by division registrars, at input into the computer registration system, as a "pending" file, at file "completion," and before microfilming. Data sent to Statistics Canada are assigned an ICD code via machine coding, enhancing consistency at a national level. Coded data returned to Nova Scotia are rechecked and rematched with provincial data, including against such clinical registries as the one maintained by Cancer Care Nova Scotia. Nova Scotia Vital Statistics sends periodic database information, corrections, updates, and queries to Statistics Canada for further verification. Although all these steps ensure a high degree of data accuracy, ICONS study research staff additionally screen the obituary sections of provincial newspapers and continuously monitor those patients enrolled for longitudinal out-of-hospital follow-up in the parent study (about 50% of the total hospitalized).

Data analysis. Although it is not the preferred method, carbohydrate intolerance can be diagnosed on the basis of two consecutive elevated blood sugars and associated symptoms (23). Consequently, hyperglycemia was defined in the current study as a random blood glucose at admission that was >198 mg/dl (11 mmol/l) as per the 2002 and 1998 guidelines of the American and Canadian Diabetic Associations, respectively (23,24). Patients were stratified into four groups, based on their history of diabetes mellitus and the blood glucose level at admission:

Group 1: No previous diagnosis of diabetes and random blood sugar ≤198 mg/dl;

Group 2: No previous diagnosis of diabetes and random blood sugar >198 mg/dl;

Group 3: Known diabetes and random blood sugar ≤198 mg/dl;

Group 4: Known diabetes and random blood sugar >198 mg/dl.

This is an observational study, and the data are reported using simple descriptive statistics. The chi-squared test was used to assess differences in the distribution of categorical variables; *t* tests or analysis of variance were used to compare continuous variables. Multivariate analysis was performed using stepwise logistic regression in order to identify independent predictors of in-hospital mortality. A significance

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Table 1. Patient Characteristics According to Diagnosis of Diabetes and Glycemic Status

Variable	Group 1* (n = 1,078)	Group 2† (n = 135)	Group 3‡ (n = 169)	Group 4§ (n = 282)	p Value
Age (yrs)	64.7	69.9	68.6	68.2	< 0.0001
Male (%)	68.5	51.1	62.7	56.7	< 0.0001
Glucose (mmol/l)	7.3	21.0	8.6	19.0	< 0.0001
Creatinine (mmol/l)	110.5	133.8	125.7	125.8	0.0001
Smoker (%)	64.8	52.6	60.9	57.5	0.0112
Hypertension (%)	45.1	49.6	63.3	64.5	< 0.0001
Hyperlipidemia (%)	33.3	23.7	44.4	36.9	0.0013
Prior myocardial infarction (%)	24.2	25.9	34.3	33.0	0.0028
Prior heart failure (%)	6.9	18.5	17.2	19.5	< 0.0001
Peripheral vascular disease (%)	3.1	0.7	5.9	4.3	0.0647

*Group 1 = No previous diagnosis of diabetes and random blood glucose ≤198 mg/dl (11 mmol/l). †Group 2 = No previous diagnosis of diabetes and random blood glucose >198 mg/dl. ‡Group 3 = Known diabetes and random blood glucose ≤198 mg/dl. §Group 4 = Known diabetes and random blood glucose >198 mg/dl.

level of $p < 0.2$ in univariate analysis was specified for maintaining variables in the multivariate model. Only those variables that remained significant at $p < 0.05$ were retained in the final model. The strength of association of glycemic status was assessed by comparison of the three groups with a disordered blood glucose profile to the "normal" (Group 1) patients not previously diagnosed with diabetes and with a random blood sugar ≤198 mg/dl.

RESULTS

There were 1,664 patients hospitalized with AMI in Nova Scotia during the 12 months of interest: 1,103 (66.3%) with non–ST-segment elevation AMI and 561 (33.7%) with ST-segment elevation AMI or left bundle branch block. In-hospital mortality rates were 12.9% for patients with non–ST-segment elevation AMI and 10.9% for those with ST-segment elevation AMI or left bundle branch block, whereas cumulative mortality at one year was 18.1% and 13.3%, respectively.

The majority of patients (72.9%) did not have a history of diabetes. The reference (Group 1) cohort made up 64.8% of the overall population. Patients who were not previously known to have diabetes but who were hyperglycemic upon admission made up 8.1% of the total. Patients with known diabetes and with normal blood glucose upon presentation represented 10.2%, whereas diabetic patients whose blood glucose levels exceeded 198 mg/dl contributed the remaining 16.9%.

Patient characteristics stratified by the four study subgroups are shown in Table 1. Patients known to have diabetes were significantly older than "normals," yet the oldest group of patients had hyperglycemia but no known history of diabetes. Males made up almost 70% of the normal-glucose non-diabetic group, but only half of the non-diabetic hyperglycemic group. Predictably, creatinine was higher in both diabetic cohorts by comparison to "normals," but the highest creatinine levels were seen in hyperglycemic patients not previously known to have diabetes. Other major cardiac risk factors had a varied distribution across groups, and those with known diabetes were most likely to have sustained a previous myocardial infarction independent of glucose level. However, a prior history of CHF was most common among the patients with abnormally elevated admission blood sugars independent of diabetic status.

Admission medications are shown in Table 2. In general, patients with diabetes were most likely to be receiving efficacious, cardiovascular disease-modifying drugs such as

Table 2. Admission Medication According to Diagnosis of Diabetes and Glycemic Status

Admission Medication	Group 1* (n = 1,078)	Group 2† (n = 135)	Group 3‡ (n = 169)	Group 4§ (n = 282)	p Value
Oral hypoglycemic (%)	0	0	50.3	62.8	< 0.0001
Insulin (%)	0	0	20.7	27.7	< 0.0001
Aspirin (%)	31.1	25.2	33.1	35.1	0.2128
ACEI (%)	18.9	23.0	30.8	34.8	< 0.0001
ARB (%)	1.9	0	2.4	4.6	0.0145
Beta-blocker (%)	31.1	25.2	41.4	37.2	0.0042
CCB (%)	5.1	10.4	14.8	9.9	< 0.0001
HMG CoA (%)	15.1	5.2	17.8	16.0	0.0093
Nitrates (%)	21.6	26.7	30.2	34.8	< 0.0001
Digoxin (%)	3.4	6.7	7.1	7.1	0.0126

*Group 1 = No previous diagnosis of diabetes and random blood glucose ≤198 mg/dl (11 mmol/L). †Group 2 = No previous diagnosis of diabetes and random blood glucose >198 mg/dl. ‡Group 3 = Known diabetes and random blood glucose ≤198 mg/dl. §Group 4 = Known diabetes and random blood glucose >198 mg/dl.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMG CoA = hydroxymethylglutaryl-coenzyme A reductase inhibitor.

Table 3. Admission Electrocardiogram and Course in Hospital According to Diagnosis of Diabetes and Glycemic Status

Variable	Group 1* (n = 1,078)	Group 2† (n = 135)	Group 3‡ (n = 169)	Group 4§ (n = 282)	p Value
STEMI/LBBB (%)	36.0	30.4	25.4	31.6	0.0301
Thrombolysis (%)	36.7	30.4	28.4	26.6	0.0035
Heart failure (%)	13.3	32.6	18.9	35.5	< 0.0001
PCI (%)	11.9	8.2	6.5	5.7	0.0049
CABG (%)	4.1	4.4	4.7	5.3	0.8319
Mean length of stay (days)	10	11	13	12	0.0465

*Group 1 = No previous diagnosis of diabetes and random blood glucose ≤198 mg/dl (11 mmol/l). †Group 2 = No previous diagnosis of diabetes and random blood glucose >198 mg/dl. ‡Group 3 = Known diabetes and random blood glucose ≤198 mg/dl. §Group 4 = Known diabetes and random blood glucose >198 mg/dl.

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; STEMI/LBBB = ST-elevation myocardial infarction/left bundle branch block.

aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and hydroxymethylglutaryl-coenzyme A reductase inhibitors. By contrast, patients who were hyperglycemic with no previous history of diabetes tended to have the lowest rates of these therapies upon presentation.

Differences were noted across groups in terms of their hospital course (Table 3). The "normal" group had a greater propensity to receive thrombolytic therapy, possibly because ST-segment elevation or left bundle branch block was more commonly seen on their admission electrocardiograms. These patients were most likely to undergo percutaneous coronary intervention in the hospital, whereas patients with diabetes were least likely to receive this therapy. However, there was no difference in the rate of in-hospital bypass surgery across groups. Length of hospital stay tended to be longer for patients with diabetes compared to those without, although this difference was of only marginal significance. Rates of heart failure during the index hospitalization were similar across the hyperglycemic cohorts and in each instance were about double those documented in the corresponding euglycemic groups.

Multivariate analysis identified several variables that were independently associated with in-hospital mortality (Table 4). Diabetic status, irrespective of glucose level upon admission, was a predictor of adverse outcome; but patients with hyperglycemia and no history of diabetes had an even worse outcome, with more than a twofold higher risk. Patients known to have diabetes and those with hyperglycemia without a history of diabetes continued to suffer a relatively worse outcome even up to one year (Fig. 1). Variables associated with lower in-hospital mortality include exposure to disease-modifying drugs known to be associated with long-term benefit.

To assess whether it was blood sugar alone or, alternatively, hyperglycemia as part of a metabolic syndrome that was associated with adverse outcome, multivariate analysis was repeated first with body mass index and then with individual lipid levels included as additional variables. Height and weight information was available for 916 patients (55%), and these were stratified into three groups of body mass index based on World Health Organization criteria with 18.5 to 24.9 kg/m^2, 25 to 29.9 kg/m^2, and ≥30 kg/m^2 representing normal, overweight, and obese individuals, respectively. In the resulting model, body mass index was not linked with outcome, although the three groups with deranged glucose profiles (Groups 2 to 4) continued to be independently associated with prognosis. Total cholesterol/high density lipoprotein cholesterol ratio, low-density lipoprotein cholesterol, and triglyceride levels were also considered, but neither these variables nor a history of hyperlipidemia correlated independently with outcome.

DISCUSSION

Our study suggests that patients presenting with an AMI who are hyperglycemic upon admission represent a high-risk population. The worst outcomes occurred among those without a prior history of diabetes. This may relate to hyperglycemia being associated with several high-risk features, including older age, female gender, and a prior history of CHF. However, an elevated blood sugar upon admission was correlated with more in-hospital CHF and greater in-hospital and one-year mortality independent of a history

Table 4. Independent Predictors of Outcome

Variable	Odds Ratio	95% CI	p Value
Group 1*	1.00	—	—
Group 2†	2.44	1.42–4.20	0.0013
Group 3‡	1.87	1.05–3.34	0.0346
Group 4§	1.91	1.16–3.14	0.0105
Peripheral vascular disease	4.33	1.88–9.96	0.0006
Insulin on admission	2.05	1.07–3.92	0.0299
Age (per 10 years)	1.89	1.58–2.24	< 0.0001
Prior heart failure	1.81	1.09–3.00	0.0219
Prior myocardial infarction	1.95	1.28–2.98	0.0020
Female	1.66	1.31–2.43	0.0096
Creatinine (per 10 mmol/l)	1.04	1.02–1.05	0.0001
Aspirin on admission	0.53	0.33–0.86	0.0101
ACEI on admission	0.46	0.26–0.79	0.0052
Beta blocker on admission	0.25	0.14–0.44	< 0.0001
Digoxin on admission	0.13	0.04–0.47	0.0018
HMG CoA on admission	0.06	0.01–0.46	0.0067

*Group 1 = No previous diagnosis of diabetes and random blood glucose ≤198 mg/dl (11 mmol/l). †Group 2 = No previous diagnosis of diabetes and random blood glucose >198 mg/dl. ‡Group 3 = Known diabetes and random blood glucose ≤198 mg/dl. §Group 4 = Known diabetes and random blood glucose >198 mg/dl.

ACEI = Angiotensin-converting enzyme inhibitor; CI = confidence interval; HMG CoA = hydroxymethylglutaryl-coenzyme A reductase inhibitor.

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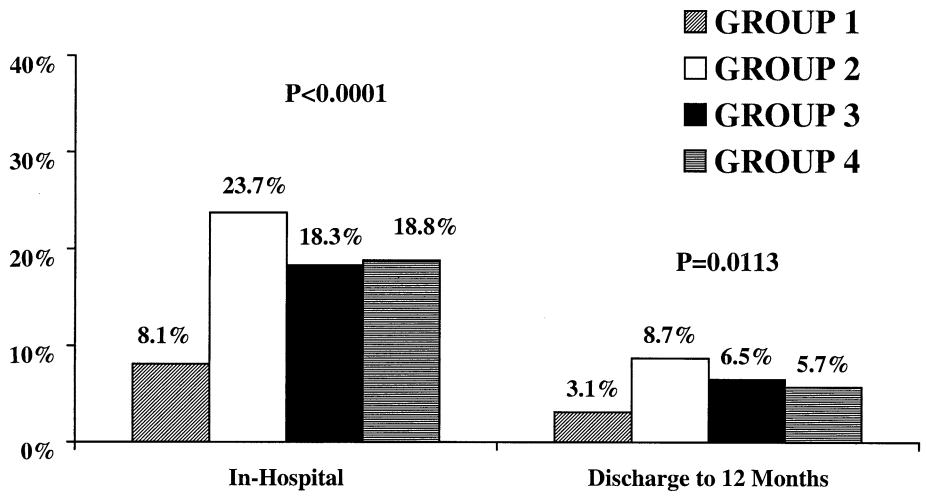

Figure 1. Mortality in the hospital and from discharge to one year, by diabetes and glycemic status. Group 1: no previous diagnosis of diabetes and random blood glucose ≤198 mg/dl (11 mmol/l); Group 2: no previous diagnosis of diabetes and random blood glucose >198 mg/dl; Group 3: known diabetes and random blood glucose ≤198 mg/dl; Group 4: known diabetes and random blood glucose >198 mg/dl.

of diabetes mellitus or of any of the high-risk features listed earlier. Furthermore, hyperglycemia conferred risk independent of body mass index or history of hyperlipidemia, suggesting that glucose status itself may be contributing to, or is a key marker of, adverse outcome.

Hyperglycemia and unrecognized diabetes mellitus. Hyperglycemia in non-diabetic patients most likely represents undiagnosed diabetes. In Canada, the incidence of known diabetes is 5%, but it has been estimated that at least another 5% of the population has this condition yet remains undiagnosed (24). The 8.1% incidence of hyperglycemia seen in the present study among patients hospitalized with AMI and not known to have diabetes is consistent with the published estimates and the hypothesis that many of these individuals have unrecognized diabetes.

Although several reports have equated acute hyperglycemia with glucose intolerance or frank diabetes mellitus, this has not been a universal finding, and clarification has been limited by differing definitions of hyperglycemia (19,25–27). Even if the hyperglycemic "non-diabetic" population did represent individuals with undiagnosed diabetes, their relatively worse outcomes vis-à-vis diagnosed diabetic patients still warrant an explanation. It is likely that such individuals are in fact undiagnosed and hence untreated diabetic patients, with potentially many years of uncontrolled elevated blood sugar resulting in increased endothelial damage and thus greater risk for macro- and micro-vascular morbidity. Overt diabetes likely represents one end of the spectrum of carbohydrate intolerance and increasing cardiovascular risk (28). However, whereas recognized diabetics with vigorous glycemic control may be to some extent protected against the additional metabolic stresses associated with AMI, diabetic patients who are undertreated do poorly and fare better only by comparison with those patients who, by virtue of their undiagnosed state, are receiving no diabetic therapy whatsoever.

Stress hyperglycemia. It is unclear whether so-called stress hyperglycemia predisposes to a worse outcome or is simply a marker of poor prognosis. Though inconclusive, studies suggest that stress hyperglycemia may be a marker of extensive myocardial damage (29). Better established through both in-vitro and in-vivo studies is the fact that an elevated blood glucose level, whether acute or chronic, adversely affects endothelium-dependent vasodilation and impairs macrophage and lymphocyte function (30–32). Hyperglycemia during AMI may reflect a compromised metabolic state and is associated with a surge of serum catecholamines and decreased insulin sensitivity that increases the turnover of potentially harmful free fatty acids (13). As well, hyperglycemia may promote an osmotic diuresis, leading to a reduced circulating volume and decreased end-diastolic and stroke volumes through interference with the Frank-Starling mechanism of myocardial contractility (33,34).

If stress hyperglycemia indeed reflects an underlying dysglycemic state, then this would be expected to correlate with a higher overall risk for more extensive CAD and would explain a worse prognosis after AMI (35). Thus, elevated plasma glucose would both reflect the acute stress and predict an increased propensity for long-term cardiovascular events (2). Prior studies have shown that an elevated admission blood glucose in AMI correlates with an increased incidence of CHF, cardiogenic shock, and in-hospital mortality (7,11,12,36). In contrast, the utility of hemoglobin A_1C in predicting adverse outcomes in the setting of AMI remains uncertain, considering the varying results of studies (7,36,37).

Hyperglycemia as a trigger for more aggressive management. If hyperglycemia predicts adverse events, then identifying it and the metabolic milieu from which it arose, as well as managing these, might be expected to attenuate risk in both the short and long term. Malmberg and associates

(38,39) showed that the use of insulin-glucose therapy in hyperglycemic AMI patients resulted in a 30% relative risk reduction in one-year mortality. However, there was no demonstrable short-term benefit, with in-hospital survival being similar in treatment and control groups. Several questions are raised by these results, including whether there are high-risk patient subgroups that could benefit in the short term with intensive insulin-glucose therapy or whether comparable long-term benefit could be achieved through the use of insulin in non-diabetic patients (38,39). Many of the variables independently associated with adverse outcome in our study, including peripheral vascular disease, increasing age, previous AMI, previous CHF, renal insufficiency, and insulin upon admission, can reflect significant systemic atherosclerosis, decreased myocardial reserve, and preceding metabolic abnormality. Patients at highest risk for both in-hospital and 12-month mortality were those with prior AMI, heart failure, and increased age. Yet, although high-risk patients can generally expect to derive more benefit from aggressive treatment, there is insufficient evidence to support the use of insulin-glucose infusion therapy in all patients, regardless of admission blood glucose (40–42).

Study limitations. This study is observational and nonrandomized. However, it does reflect the "real world" population in that it includes all consecutive patients hospitalized with AMI in a self-contained health care system and thus provides important insights into the treatment and outcomes of such patients when stratified according to their glycemic status. We could not determine the true incidence of diabetes mellitus, especially among persons without a prior history of this condition. However, an admission diagnosis of diabetes probably has high specificity, considering that any individuals declaring this condition very likely had it. Because hemoglobin A_1C levels are not routinely measured in patients with AMI, we are unable to comment on the impact of chronically impaired glucose control in our study population. Finally, no attempt was made to analyze sequential glucose levels in the hospital, and thus we have no information on the outcome of patients who may have developed hyperglycemia later in their hospital course. However, studies such as that of Malmberg et al. (39) have determined the efficacy of aggressive glucose management on the basis of admission blood glucose.

Conclusions. Independent of diabetic status, the occurrence of hyperglycemia during AMI is associated with a sub-population of patients at particularly high risk for an adverse clinical outcome. In general, these patients are older, have multiple cardiac risk factors, and are more likely to have a prior history of CHF. Even with the highly efficacious treatment strategies currently available, persons presenting with AMI and hyperglycemia are at increased risk for CHF or death in hospital; all-cause mortality at one year is also higher.

At the time of diagnosis, patients with diabetes have an increased prevalence of micro- and macro-vascular complications regardless of symptoms. Expert consensus recommends screening of all asymptomatic individuals beginning at age 45 (23,24), although there is controversy over the cost-effectiveness of this approach (23,43). Even though Tuomilehto et al. (44) demonstrated the beneficial effect of lifestyle modification on the incidence of type 2 diabetes in patients at high risk, it is uncertain whether earlier diagnosis and additional years of treatment result in fewer diabetes-related events. However, the poor cardiovascular outcomes of hyperglycemic patients in our study, particularly among those not previously known to be diabetic, lend support for aggressive screening strategies aimed at the early recognition of diabetes.

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