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Prevalence of diabetes mellitus in large acute coronary syndrome studies in a Middle Eastern country: The road to “GLORY”
AYMAN HAMMOUDEH, MD, FACCC; AKRAM SALEH, MD; MAHMOUD IRAIQ, MD; HAZEM HAMDAN, MD; MOHAMMAD BAKRI, MD; ABDULNASSER NAQIY, MD; ASSEM NAMMAS, MD, FACCC; AZMI AHMAD, MD; IMAD ALHADDAD, MD, FACCC FOR THE JOHARTS AND JCC GROUPS AMMAN, JORDAN
Measuring A1C is by far the most widely accepted tool used to assess long-term glycemic control. It is also assumed to be closely related to the risk of diabetes-related long-term complications. The vast majority of epidemiologic studies and clinical trials use A1C also as a tool for assessment and outcome, almost all diabetes organizations do consider the establishment of specific A1C targets for diabetes care with the goal of preventing or delaying the development of long-term complications.

Diabetes treatment is adjusted based on the A1C results, expressed as the percentage of hemoglobin that is glycated. The vast majority of assays have been standardized worldwide, through the National Glycohemoglobin Standardization Program, to the assay used in the Diabetes Control and Complications Trial (DCCT), which established the relationship between A1C levels and risk for long-term diabetes complications.

A new, more stable and specific method of standardization of the A1C assay, which is not intended for routine assays, has been developed and proposed to be used for global standardization by the International Federation of Clinical Chemists. However, the new method results in values that are 1.5 – 2.0 percentage points lower than current National Glycohemoglobin Standardization Program values, potentially causing confusion for patients and health care providers. Moreover, the International Federation of Clinical Chemists results would be expressed in new units (millimoles per mole), which would add to the confusion. Chronic glycemia (A1C) is usually expressed as a percentage of hemoglobin that is glycated, whereas the day-to-day monitoring and therapy of diabetes are based on acute glucose levels expressed as milligrams per deciliter or millimoles per liter. This discrepancy has always been problematic. If we could reliably report chronic metabolic control and long-term management goals as average glucose (AG), i.e., in the same units of measurement as acute glycemia, it may be of help in avoiding this confusion.

The relationship between A1C and chronic glycemia has been explored in several studies that have supported the association of A1C with AG levels over the preceding 5–12 weeks.

The results of a recent study translating the A1C assay into estimated average glucose values was just published in Diabetes Care (1). The investigators identified the A1C levels obtained at the end of 3 months and measured in a central laboratory were compared with the AG levels during the previous 3 months. AG was calculated by combining weighted results from at least 2 days of continuous glucose monitoring performed four times, with seven-point daily self-monitoring of capillary (finger stick) glucose performed at least 3 days per week. The results indicated that the linear regression equations did not differ significantly across subgroups based on age, sex, diabetes type, race/ethnicity, or smoking status. They concluded that A1C levels can be expressed as eAG for most patients with type 1 and type 2 Diabetes.

The answer of the question: A1C or eAG may be clear from this study. I myself could support this conclusion despite we need more evidence!!

Mahmoud Ashraf Ibrahim, MD
Editor, Middle East Edition

Reference
(1) DAVID M. NATHAN, JUDITH KUENEN, RIKKE BORG, HUI ZHENG, DAVID SCHOENFELD, ROBERT J. HEINE, FOR THE A1C- DERIVED AVERAGE GLUCOSE (ADAG) STUDY GROUP, Translating the A1C Assay Into Estimated Average Glucose Values, Diabetes Care 31:1473–1478, 2008

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Prevalence of diabetes mellitus in large acute coronary syndrome studies in a Middle Eastern country: The road to “GLORY”

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Introduction

Cardiovascular disease (CVD) is the commonest cause of death worldwide and in the Middle East. Diabetes mellitus (DM) is major risk factor for CVD and its incidence is rising in our region. Compared with the general population, diabetics face a two- to fourfold increased risk of CVD (1). In this context, we will discuss the prevalence of DM in 5 Jordanian studies and registries (2-5) that involved 5645 ACS patients (18). In 5 Jordanian studies and registries that involved 5645 ACS patients, the overall prevalence of diabetes was 48%, which is similar to that found by a registry of ACS patients in the Arab Gulf countries (45%), but much lower than that found in western studies (see table 2). This rate of prevalence in Jordanian studies varies from one study to another and ranges between 35% and 58%. Moreover, age and gender are two important variables that determine the prevalence of diabetes among ACS patients. In every study, women had higher DM prevalence than men, and older patients had higher prevalence than young patients. Among patients with ACS who are < 30 years of age, DM prevalence was 17% among men and 33% among women; and among those older than 66 years of age, DM prevalence was 39% among men and 71% among women (2). DM prevalence was not different among patients with the 3 subtypes of ACS; 40% in those with unstable angina, 44% in non STEMI, and 41% in STEMI patients (5).

Beyond the higher prevalence issue compared with western studies, we found that DM was an independent risk factor for death during hospitalization and combined nonfatal MI and mortality at 1 year in Jordanians with ACS compared with nondiabetics (odds ratio 3.18, 95% confidence interval 0.33-30.6, p<0.001) (4). Furthermore, hypertension was present in 49% of diabetics compared with 21% of nondiabetics. Coexistence of DM and smoking was associated with worse coronary involvement (severe infarct-related artery disease, and more multivessel disease) in patients with STEMI compared with non diabetics who do not smoke (11). The incidence of anterior wall MI in diabetics was more than that of non-anterior wall MI (56% vs. 44%, p=0.01) while the incidence of both type of infarctions was similar in prevalence of DM, but also will study the prevalence of glucometabolic (prediabetic) states in patients with ACS and the impact of these states on prognosis after 1 year of admission (see table 1). The adverse impact of DM on coronary arteries is attributed to several factors including endothelial dysfunction, platelet hyperactivity, hypercoagulability, atherogenic dyslipidemia, vascular smooth muscle migration and proliferation, monocyte adhesion, insulin resistance, and plaque inflammation (7-10). Moreover, coexistence of DM with other coronary risk factors in the same individual compiles worse cardiovascular complications. For example, cigarette smoking in a diabetic individual adds worse impact on serum dyslipidemia and coronary arteries compared with a nonsmoking diabetic with more incidence of multivessel coronary artery disease (CAD) (11). Likewise, coexistence of hypertension with DM triples the already high risk of CAD (12).

Compared with nondiabetics, diabetics tend to have worse outcome when they present with ACS. They have higher short- (30 days) and long-term (1 year) prognosis (13,14). Diabetics also suffer more complications when they undergo coronary diagnostic and revascularization procedures and are subject to higher restenosis rate after percutaneous angioplasty and stent implantation (15,16). Hence, diabetics deserve an aggressive therapeutic strategy that includes the use of triple antiplatelet therapy (aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors), early invasive diagnostic catheterization and revascularization, and using beta blockers, ACE inhibitors/ angiotensin II receptor blockers, and statins when they present with ACS in order to lower their short- and long-term cardiovascular events.

Prevalence of diabetes in cardiac patients

Various western ACS studies showed a variable prevalence rate of diabetes ranging from 20% to 30% of patients with STEMI (17), and 17% of patients with non ST elevation ACS (18). In 5 Jordanian studies and registries that involved 5645 ACS patients, the overall prevalence of diabetes was 48%, which is similar to that found by a registry of ACS patients in the Arab Gulf countries (45%), but much lower than that found in western studies (see table 2). This rate of prevalence in Jordanian studies varies from one study to another and ranges between 35% and 58%. Moreover, age and gender are two important variables that determine the prevalence of diabetes among ACS patients. In every study, women had higher DM prevalence than men, and older patients had higher prevalence than young patients. Among patients with ACS who are < 30 years of age, DM prevalence was 17% among men and 33% among women; and among those older than 66 years of age, DM prevalence was 39% among men and 71% among women (2). DM prevalence was not different among patients with the 3 subtypes of ACS; 40% in those with unstable angina, 44% in non STEMI, and 41% in STEMI patients (5).
nondiabetics (6). Anterior wall MI patients tend to have larger infarction size and are prone to more incidence of complications especially heart failure.

The criteria for diagnosing diabetes in these studies were similar to the European studies, i.e., according to the EUROSPINE criteria (19). DM was defined as the prior history of DM as diagnosed by another physician, or the use of insulin or oral antidiabetic agents. It is evident that this widely used definition will underestimate the true prevalence of DM because (a) it avoids looking at those with no prior DM diagnosis or prior use of antidiabetic agents who have hyperglycemia upon admission with ACS, and (b) it does not address the issue of how to evaluate prediabetic states such as impaired fasting glucose and impaired glucose tolerance in patients with blood sugar levels that fall between nondiabetic and diabetic values.

**Glucometabolic states in ACS: GLORY study**

Insulin resistance often precedes the onset of DM and already exists in the prediabetic states including impaired fasting glucose and impaired glucose tolerance (19). Patients who are admitted with ACS have markedly elevated levels of “stress-related” mediators such as adrenalin and cortisol. This stressful state can expose latent diabetes in individuals who were never diagnosed to have diabetes in the past, or it simply can allow diagnosing an already existing, but undiagnosed, disease. Glucose blood levels might be very high on admission and reach frank diabetes levels, or they can fit in the category of impaired fasting glucose. This is what our ongoing GLORY (The Glucometabolic abnOrmalities in acute coronaRY syndrome study) aims at evaluating. To date (mid June 2008), GLORY has enrolled about 300 patients (of a target of 1000) admitted with ACS to 5 hospitals (1 university, 2 teaching, and 2 private). Patients will be followed up for one year after the index admission. Risk of mortality and nonfatal MI will be evaluated in relation to the diabetic and nondiabetic state each patient has on admission.

Several studies have shown that hyperglycemia in patients admitted with ACS is common and is associated with a markedly increased mortality rate and heart failure (20). Mechanisms responsible for hyperglycemia include relative insulin deficiency and resultant excess of free fatty acids, and an excess of stress mediators such as cortisol or catecholamines (21). Impaired glucose regulation in the absence of frank DM is considered a risk factor (22).

Interim analysis of the ongoing GLORY study shows 48% have known DM, 14% have new-onset DM, 14% have impaired fasting glucose, and 24% are nondiabetics. This indicates that 76% have one form of glucometabolic state. This is an alarmingly high percentage that is higher than that among a patient population enrolled in a European study that found known DM in 31%, new-onset DM in 15%, and impaired glucose regulation in 22% (23). The same study found that the prognosis of patients with new-onset DM and old history of DM was worse than that of nondiabetics (hazard ratios [HR] 2.0 and 2.4, respectively); however, prognosis in patients with prediabetic states was not different from that of nondiabetics (HR 1.1).

**Controlling blood sugar in patients with ACS**

It is strongly recommended to control blood sugar in patients admitted with ACS. There is no consensus, however, on the best approach to control blood sugar. In the EUROHEART survey 28% of the patients did not receive therapy to control blood sugar, and poor control with treatment “was common” (23). The previous enthusiasm to the glucose-insulin-potassium (GIK) infusion in AMI patients has been lost recently. A recent study compared 3 strategies to control blood sugar in ACS patients: (a) local experience of the treating physicians, (b) glucose insulin infusion followed by subcutaneous insulin injections on the long term, and (c) glucose insulin infusion fol-

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Study</th>
<th>Number of Patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>JoHARTS</td>
<td>Jordan Hyperlipidemia And Related Targets Study</td>
<td>5000</td>
<td>2,24-26</td>
</tr>
<tr>
<td></td>
<td>- ACS*</td>
<td>946</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- No ACS</td>
<td>4054</td>
<td></td>
</tr>
<tr>
<td>SMART</td>
<td>Survey of Management and Assessment of coRonary hearT disease patients</td>
<td>2765</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>- Impact of DM and smoking on coronary lesions in AMI**</td>
<td>470</td>
<td>4</td>
</tr>
<tr>
<td>CAPRIS</td>
<td>CRP And PRognosis In Acute coronary Syndrome</td>
<td>502</td>
<td>5</td>
</tr>
<tr>
<td>MINTOR</td>
<td>Myocardial INfarction Triggers and Onset in JoRdan</td>
<td>962</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Total number of patients</td>
<td>9969</td>
<td></td>
</tr>
<tr>
<td>GLORY</td>
<td>GLucometabolic abnOrmalities in acute coronaRY syndrome</td>
<td>(1000)</td>
<td>(ongoing)</td>
</tr>
</tbody>
</table>

*ACS=acute coronary syndrome, ** AMI=acute myocardial infarction.
lowed by "usual" glucose control. The study found no difference between the 3 strategies. An ad hoc analysis concluded that patients who were sent home on insulin had higher risk compared with those sent home on metformin (17).

GLORY study, when finished, will be the first of its kind in our region to answer so many questions about DM and glucometabolic states in ACS patients: prevalence, distribution among men and women, distribution in various age groups, in-hospital complications, long-term prognosis, and whether these result are similar to or different from data from the west.

Acknowledgment
We are very grateful to Prof. Kamel Ajlouni, Director of the National Center for Diabetes, Endocrinology and Genetics /Jordan University, Amman for his invaluable advice during the planning of the GLORY study and its progress. We also thank Hikma Pharmaceuticals, Amman for fully supporting the study.

References

Table 2.
Prevalence of diabetes in Jordanian and non Jordanian cardiovascular disease studies/registries

<table>
<thead>
<tr>
<th>Study</th>
<th>Diabetics, n (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jordanian studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JoHARTS Overall</td>
<td>1410/5000 (28%)</td>
<td>2,24-26</td>
</tr>
<tr>
<td>ACS</td>
<td>378/946 (40%)</td>
<td></td>
</tr>
<tr>
<td>No ACS</td>
<td>1032/4054 (25%)</td>
<td></td>
</tr>
<tr>
<td>SMART</td>
<td>1604/2765 (58%)</td>
<td>3</td>
</tr>
<tr>
<td>DM and smoking in AMI</td>
<td>164/470 (35%)</td>
<td>4</td>
</tr>
<tr>
<td>CAPRIS</td>
<td>207/502 (41%)</td>
<td>5</td>
</tr>
<tr>
<td>MINTOR</td>
<td>344/962 (38%)</td>
<td>6</td>
</tr>
<tr>
<td>Total ACS</td>
<td>2679/5645 (48%)</td>
<td></td>
</tr>
<tr>
<td><strong>Non Jordanian Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swedish Heart</td>
<td>3123/14873 (21%)</td>
<td>13</td>
</tr>
<tr>
<td>TIMI Trials (meta-analysis, 11 studies)</td>
<td>10613/62036 (17%)</td>
<td>18</td>
</tr>
<tr>
<td>Gulf RACE (Arab Gulf Countries)</td>
<td>669/1484 (45%)</td>
<td>27</td>
</tr>
<tr>
<td>Euro Heart Survey</td>
<td>1425/4676 (30%)</td>
<td>28</td>
</tr>
</tbody>
</table>


