The prognostic impact of hyperglycemia on clinical outcomes of acute heart failure: Insights from the heart function assessment registry trial in Saudi Arabia

Alwaleed Aljohar a, Khalid F. Alhabib b, Tarek Kashour b, Ahmad Hersi b, Waleed Al Habeeb b, Anhar Ullah b, Abdelfatah Elasfar c, Ali Almasood d, Abdullah Ghabashi e, Layth Mimish f, Saleh Al Habeeb b, Anhar Ullah b, Abdelfatah Elasfar c, Ali Almasood d, Mushabab Al-Murayeh k, Hussam AlFaleh b,

a Department of Internal Medicine, King Saud University Medical City, King Saud University, Riyadh; b Department of Cardiac Sciences, King Fahad Cardiac Center, College of Medicine, King Saud University, Riyadh; c Department of Cardiovascular Medicine, King Salman Heart Center, King Fahd Medical City, Riyadh; d Adult Cardiology Department, Prince Sultan Cardiac Center, Riyadh; e Adult Cardiology Department, Prince Sultan Cardiac Center, Hafouf; f Department of Internal Medicine/Cardiovascular Unit, King Abdulaziz University Hospital, Jeddah; g Department of Cardiology, Madina Cardiac Center, AlMadina AlMonaoarah; h Department of Cardiology, National Guard Hospital, Jeddah; i Department of Cardiology, North West Armed Forces Hospital, Tabuk; j Department of Internal Medicine, Armed Forces Hospital Southern Region, Khamis Mushayt

Background: The prognostic impact of hyperglycemia (HG) in acute heart failure (AHF) is controversial. Our aim is to examine the impact of HG on short- and long-term survival in AHF patients.

Methods: Data from the Heart Function Assessment Registry Trial in Saudi Arabia (HEARTS) for patients who had available random blood sugar (RBS) were analyzed. The enrollment period was from October 2009 to December 2010. Comparisons were performed according to the RBS levels on admission as either <11.1 mmol/L or ≥11.1 mmol/L. Primary outcomes were hospital adverse events and short- and long-term mortality rates.

Results: A total of 2511 patients were analyzed. Of those, 728 (29%) had HG. Compared to non-HG patients, hyperglycemics had higher rates of hospital, 30-day, and 1-year mortality rates (8.8% vs. 5.6%; p = 0.003, 10.4% vs. 7.2%; p = 0.007, and 21.8% vs. 18.4%; p = 0.04, respectively). There were no differences between the two groups in 2- or 3-year mortality rates. After adjustment for relevant confounders, HG remained an independent predictor for hospital and 30-day mortality [odds ratio (OR) = 1.6; 95% confidence interval (CI) 1.07–2.42; p = 0.021, and OR = 1.55; 95% CI 1.07–2.25; p = 0.02, respectively].

Conclusion: HG on admission is independently associated with hospital and short-term mortality in AHF patients. Future research should focus on examining the impact of tight glycemic control on outcomes of AHF patients.

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* Corresponding author at: Department of Cardiac Sciences, King Fahad Cardiac Center, College of Medicine, King Saud University, Post Office Box 7805, Riyadh 11472, Saudi Arabia.
E-mail address: halfaleh@ksu.edu.sa (H. AlFaleh).

P.O. Box 2925 Riyadh – 11461KSA
Tel: +966 1 2520088 ext 40151
Fax: +966 1 2520718
Email: sha@sha.org.sa
URL: www.sha.org.sa

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1. Introduction

Acute heart failure (AHF) continues to be a burdensome problem to healthcare systems and is a leading cause of frequent hospitalizations and long-term medical care [1]. Multiple illnesses coexist with HF and influence its prognosis [2–4]. Diabetes mellitus (DM) is known as one of the most commonly associated comorbidities in HF patients with a prevalence ranging from 25% to 40% [5,6]. Data from major HF registries indicate that DM worsens hospital outcomes and increases short-term mortality rates [6–11]. Although the impact of DM on HF outcomes is known, the role of hyperglycemia (HG), whether new-onset or in the context of a preexisting DM, remains controversial [12–20]. Several reports have suggested a negative impact of HG on AHF mainly affecting hospital outcomes and overall survival [12–18], yet others have not shown similar findings [19,20].

HG in acute coronary syndromes (ACS) has been widely investigated. The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial showed a survival benefit in ACS patients with tight glycemic control [21]. This was later confirmed in other major trials [22–24]. Currently, the 2013 American Heart Association/American College of Cardiology guidelines recommend targeting sugar levels <180 mg/dL [25]. Glycemic control has become an integral part of the standard management of ACS, however the impact of extrapolating this evidence across the spectrum of all cardiovascular diseases is yet to be determined.

We sought to determine the relationship between HG and hospital adverse outcomes, as well as short- and long-term mortality rates in AHF patients using data from the Heart Function Assessment Registry Trial in Saudi Arabia (HEARTS).

2. Materials and methods

HEARTS protocol has been described previously [26,27]. Briefly, HEARTS is a prospective registry that enrolled 2609 consecutive patients with a primary admission diagnosis of AHF. Eighteen tertiary care centers in different regions of Saudi Arabia participated in this registry. Enrollment took place between October 2009 and December 2010, with clinical follow-up until January 2013. The definition of HF was according to the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF [28]. The study was approved by the institutional review board at each participating hospital and complied with the Declaration of Helsinki.

Patients were eligible for this analysis if baseline random blood sugar (RBS) values were available. The diagnosis of DM was based on medical records documentation, patient self-reporting, or if the patient was taking diabetic medications. Patients were labeled as having HG if their RBS was ≥11.1 mmol/L, according to the American Diabetes Association guidelines [29]. We described patients’ baseline characteristics, therapies, hospital course, and hospital mortality rates. Additionally, we obtained the vital status after 30 days, 1 year, 2 years, and 3 years following hospital discharge by a telephone interview and verified these data as needed using hospital records.
2.1. Statistical analysis

Categorical data were summarized with absolute numbers and percentages. Numeric data were summarized with mean and standard deviation (SD) or median and interquartile range (IQR). Comparisons between different groups were performed using Chi-square test or Fisher's exact for categorical variables and independent sample t test or Mann–Whitney U test for continuous variables. Kaplan–Meier analysis was applied to plot the cumulative survival and differences between curves were assessed using the log-rank test. We used logistic regression models to estimate unadjusted and adjusted odds ratios (OR) for mortality rates. We adjusted for age, sex, estimated glomerular filtration rate (eGFR), ACS, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), AHF type, ejection fraction (EF), dyslipidemia (DLD), anemia, hypertension (HTN), and DM. Logistic regression with interaction terms was used to test the statistical significance of the interaction between HG and other baseline factors. To estimate the strength of association in subgroups we used OR with 95% confidence intervals (CI). A two-sided p value <0.05 was considered statistically significant. All analyses were performed using SAS/STAT software, version 9.2 (SAS Institute Inc., Cary, NC, USA.) and R software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Of the 2609 patients enrolled in HEARTS, 2511 (96.2%) patients were eligible for the present analysis. A total of 1783 (71%) were in the non-HG group, while 728 (29%) had HG at baseline. HG patients were generally older and had higher BMIs. Further, they were more likely to be diabetic, hypertensive, and dyslipidemic (p < 0.001 for all comparisons; Table 1).

Compared with patients with HG, non-HG patients were more likely to have a history of HF, valvular heart diseases (rheumatic and

| Table 1. Baseline characteristics. |
|-----------------------------------|
| Overall 2511 | Non-HG 1783 (71%) | HG 728 (29%) | p |
| Demographics | | | |
| Age | 61.34 ± 15 | 60.65 ± 15.6 | 63.38 ± 12.4 | <0.001 |
| Saudi | 2135 (85) | 1521 (85.3) | 614 (84.3) | 0.539 |
| Male | 1653 (65.8) | 1207 (67.7) | 446 (61.3) | 0.002 |
| Body mass index | 29.2 ± 6.7 | 29 ± 6.7 | 29.7 ± 6.7 | 0.028 |
| Risk factors | | | |
| Diabetes mellitus | 1629 (65.1) | 955 (53.8) | 674 (92.7) | <0.001 |
| Smoker/ex-smoker | 844 (33.6) | 614 (34.4) | 230 (31.6) | 0.171 |
| Hypertension | 1781 (71.4) | 1195 (67.4) | 586 (81.3) | <0.001 |
| Dyslipidemia | 870 (36.8) | 550 (32.5) | 320 (47.8) | <0.001 |
| History of cardiovascular diseases | | | |
| Heart failure | 1607 (64.2) | 1179 (66.3) | 428 (59) | <0.001 |
| Ischemic heart disease | 1342 (54) | 908 (51.6) | 434 (59.9) | <0.001 |
| TIA/stroke | 241 (9.6) | 156 (8.8) | 85 (11.7) | 0.025 |
| PAD | 97 (3.9) | 60 (3.4) | 37 (5.1) | 0.044 |
| PCI | 326 (13) | 222 (12.5) | 104 (14.3) | 0.219 |
| CABG | 257 (10.3) | 175 (9.8) | 82 (11.3) | 0.282 |
| RHD | 172 (6.9) | 137 (7.7) | 35 (4.8) | 0.010 |
| Other VHD | 359 (14.4) | 271 (15.3) | 88 (12.2) | 0.045 |
| Atrial fibrillation | 390 (15.6) | 313 (17.6) | 77 (10.6) | <0.001 |
| VT/VF | 60 (2.4) | 50 (2.8) | 10 (1.4) | 0.033 |
| ICD | 216 (8.6) | 179 (10.1) | 37 (5.1) | <0.001 |
| CRT | 81 (3.2) | 67 (3.8) | 14 (1.9) | 0.018 |
| History of other chronic medical illnesses | | | |
| Anemia | 1116 (44.6) | 781 (44) | 335 (46.2) | 0.308 |
| CKD on dialysis | 70 (9.5) | 45 (8.7) | 25 (11.4) | 0.256 |
| CKD not on dialysis | 668 (90.5) | 473 (91.3) | 195 (88.6) | 0.055 |
| Chronic lung disease | 179 (7.1) | 131 (7.4) | 48 (6.6) | 0.505 |

Data are presented as n (%) or mean ± SD.
CABG = coronary artery bypass grafting; CKD = chronic kidney disease; CRT = cardiac resynchronization therapy; HG = hyperglycemia; ICD = implantable cardioverter defibrillator; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; RHD = rheumatic heart disease; SD = standard deviation; TIA = transient ischemic attack; VF = ventricular fibrillation; VHD = valvular heart disease; VT = ventricular tachycardia.
nonrheumatic), arrhythmias (both atrial and ventricular), and to have undergone cardiac device implantation. However, vascular comorbidities such as ischemic heart disease (IHD), strokes/transient ischemic attacks, and peripheral arterial disease were significantly higher among patients with HG (Table 1).

Table 2 demonstrates the types, etiologies, and exacerbating factors of AHF. HG patients were more likely to present with acute de novo HF while non-HG patients were more likely to present with acute on chronic HF \((p < 0.001\) for group comparison). IHD was the prime etiology for AHF in patients with HG, while nonischemic etiologies of AHF were seen more often in non-HG patients \((p < 0.001\) for group comparison). ACS and uncontrolled HTN were the main reasons for AHF exacerbation among HG patients, and had occurred more frequently compared to the non-HG group.

Patients with HG had a higher mean baseline SBP (134.5 vs. 126.6, \(p < 0.001\)), higher rates of positive troponin levels (51.3\% vs. 32.6\%, \(p < 0.001\)), and a higher proportion of low eGFR defined as <60 mL/min/1.73 m\(^2\) (60.2\% vs. 51.0\%, \(p < 0.001\)). Non-HG patients were more likely to have severe left ventricular systolic dysfunction (50.6\% vs. 39.7\%; \(p < 0.001\)). Among the patients who underwent coronary angiogram during the same admission \((n = 720)\), significant left main, three-vessel, and double-vessel disease were more frequently seen in patients with HG. Further comparisons in clinical presentations and baseline investigations are depicted in Table 3.

Hospital therapies and discharge medications are shown in Fig. 1. β-blockers and aldosterone antagonists use was higher in non-HG patients, both prior to hospital admission, and upon discharge, while aspirin and statin therapy were prescribed more frequently in HG patients upon discharge.

Hospital procedures, complications, as well as hospital, short-, and long-term mortality rates are shown in Table 4. Compared to HG patients, the non-HG group were more likely to receive device therapies (implantable cardioverter defibrillators and cardiac resynchronization therapy) and were less likely to require mechanical ventilation. Apart from a higher rate of hospital recurrence of AHF in patients with non-HG (33.1\% vs. 28.2\%; \(p = 0.015\)), there were no differences in the rate of hospital complications between the two groups.

The observed hospital, 30-day, and 1-year mortality rates were significantly higher in patients with HG (8.8\% vs. 5.5\%; \(p = 0.003\), 10.4\% vs. 7.2\%; \(p = 0.007\), and 21.8 vs. 18.4; \(p = 0.049\), respectively). There were no differences in the 2- and 3-year mortality rates between the two groups. After adjusting for important confounders, HG remained an independent predictor for hospital and 30-day mortality (OR = 1.61; 95\% CI 1.07–2.42, \(p = 0.022\), and OR = 1.55; 95\% CI 1.07–2.25, \(p = 0.021\), respectively), Table 5. A Kaplan–Meier plot comparing survival rates between the groups showed that patients with HG had significantly lower survival rates compared with patients with non-HG (log-rank test \(p = 0.038\)), Fig. 2.

### Table 2. Heart failure types, etiologies, and exacerbating factors for acute heart failure.

|                         | Overall 2511 | Non-HG 1783 (71%) | HG 728 (29%) | \(p\)       |
|-------------------------|--------------|-------------------|-------------|----------|
| **Acute heart failure type** |              |                   |             |          |
| Acute de novo HF        | 904 (36)     | 604 (33.9)        | 300 (41.2)  | <0.001   |
| Acute on Chronic HF     | 1607 (64)    | 1179 (66.1)       | 428 (58.8)  |          |
| **Etiology**            |              |                   |             |          |
| Ischemic                | 1419 (56.5)  | 937 (52.5)        | 482 (66.2)  | <0.001   |
| Nonischemic             | 1092 (43.5)  | 846 (47.4)        | 246 (33.8)  |          |
| **HF exacerbation factors** |           |                   |             |          |
| NSTACS                  | 702 (28)     | 440 (24.7)        | 262 (36)    | <0.001   |
| STEMI                   | 266 (10.6)   | 164 (9.2)         | 102 (14)    | <0.001   |
| Uncontrolled hypertension | 506 (20.1)   | 332 (18.6)        | 174 (23.9)  | 0.003    |
| Noncompliance to HF medications | 523 (20.8) | 403 (22.6) | 120 (16.5) | <0.001 |
| Noncompliance to diet   | 628 (25)     | 493 (27.6)        | 135 (18.5)  | <0.001   |
| Worsening renal failure | 443 (17.6)   | 341 (19.1)        | 102 (14)    | 0.002    |
| Arrhythmia              | 275 (10.9)   | 210 (11.8)        | 65 (8.9)    | 0.038    |
| Infections              | 524 (20.9)   | 363 (20.4)        | 161 (22.1)  | 0.326    |
| COPD exacerbation       | 94 (3.7)     | 74 (4.1)          | 20 (2.7)    | 0.093    |

Data are presented as \(n\) (%).

COPD = chronic obstructive pulmonary disease; HF = heart failure; HG = hyperglycemia, NSTACS = non-ST elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.
The interaction between HG and mortality was assessed in several patient subgroups. Subgroups assessed included patients stratified by age (≥70 years vs. <70 years), sex (males vs. females), prior diagnosis of DM, use of insulin, HF etiology (ischemic vs. nonischemic), type of AHF (de novo vs. acute on chronic), eGFR (≥60 mL/min/1.73 m² vs. <60 mL/min/1.73 m²), EF (≥40% vs. <40%), SBP (≥90 mmHg vs. <90 mmHg), and history of anemia. A significant interaction between HG and EF was observed, where the negative impact of HG on 30-day mortality was worse in patients with an EF < 40% (EF < 40%, OR = 1.69; 95% CI 1.18–2.42, p = 0.003, vs. EF ≥ 40%, OR = 0.72; 95% CI 0.37–1.39, p = 0.331, p value for interaction = 0.025). This interaction between HG and EF was not seen in hospital or 1-year mortality. Additionally, a strong interaction was observed between HG and anemia. Anemic patients with HG had a higher hospital mortality compared with nonanemic patients (anemia present, OR = 2.69; 95% CI 1.62–4.46, p < 0.001 vs. anemia absent, OR = 1.10; 95% CI 0.71–1.73, p = 0.66, p for interaction = 0.01). This interaction between anemia and HG also impacted short- and long-term mortality (data not shown).

4. Discussion
To our knowledge, this is the first report from the Arab Middle East examining the impact of glycemic status on the outcomes of patients with AHF. We found that almost 30% of our patients had HG upon hospital admission. Irrespective of their diabetic status and other comorbidities, these patients had a worse prognosis. Data on the impact of HG on AHF outcomes are inconsistent [12–20]. Some reports have suggested that HG is independently associated with hospital [12–16], 30- [17,18], and 60-day [14] mortality. However, this association with mortality was less robust in the long term [12,13,19,20]. Conversely, other reports did not show an association between HG and short-term mortality [19,20] but rather an
association with long-term mortality [18]. Our data agree with the general pattern of these reports where HG is more likely to be related to short-term mortality. The discrepancy in the findings of these studies could be explained by the diverse methods and inclusion and exclusion criteria that were used, such as the exclusion of diabetic patients [14,16,19], using different blood sugar measurements (random and/or fasting) and cut-offs, or selecting patients under special circumstances such as AHF patients admitted to the intensive care only [15,19].

Our subgroup analysis suggests an interaction between HG and an anemic status as well as with EF. The test of interaction is hypothesis generating and may suggest colinearity between HG and anemia on one hand, and HG and an EF < 40% on the other hand. Alternatively, anemia and a low EF such as HG simply reflect disease severity. Therefore, a risk score for AHF that combine all potential risk factors for worse prognosis is essential for targeted therapy and hospital disposition. In addition, the high readmission and mortality rates in AHF patients further necessitate conducting trials focusing on risk score designing and validation [30]. Indeed, there have been many proposed risk scores that correlate with hospital and postdischarge mortality [31–33]. However, none of them is implemented as a standard-of-care in current clinical practice.

Whether HG in AHF serves as a marker of disease severity or a direct cause for adverse outcomes remains unclear. Some have suggested that chronic elevation of blood sugar as evident by an elevated HbA1c could cause direct injury to the myocardium [34]. In addition, persistent hyperglycemia (e.g., Type I DM) may lead to an insulin-resistant state [35] and impaired glucose uptake by the myocardium shifting the energy generation pathway towards utilization and oxidation of free fatty acids by the myocardium [36,37] which in turn may promote arrhythmogenesis [38]. Finally, HG may impart the cardiac function through various mechanisms such as oxidative stress [39,40], endothelial atherogenesis, and vascular inflammation [41]. However, HG in AHF can simply be stress-induced. The normal physiological response to stress insults leads to high glucose levels as a result of sympathetic nervous system activation and/or excessive release of stress hormones such as cortisol [42,43]. The fact that HG seemed to be an independent predictor of short- rather than long-term mortality might support the premise that HG is merely a marker of severity rather than a direct cause of mortality.

The clinical implications of our findings are numerous. Firstly, the measurement of RBS in the Emergency Department is simple and provides very useful information in predicting the hospital course and prognosis of AHF. Therefore, it can potentially be used as a tool amongst other tools for risk stratification in AHF patients. Secondly, HG in the context of AHF was found to be predictive of the development of new-onset DM [18]. Similar findings were observed in critically ill patients [44], and patients with ACS [45]. This should encourage treating physicians to screen patients with abnormal glucose levels for DM following the acute phase of HF. Finally, as HG is an independent predictor of short-term adverse outcomes in the context of AHF, this should raise interest in studies examining the efficacy of aggressive glycemic control on the outcomes of AHF patients. Despite the general recommendation by the American Diabetes Association to aim for strict glycemic control in any hospital admission regardless of the primary diagnosis [46], the evidence for this practice in AHF is weak.
This study suffered from several limitations. Data on hospital readmission rates were not collected in the HEARTS registry, therefore, the impact of HG on AHF readmissions rates and postdischarge disease deterioration could not be assessed. In addition, the registry only recorded all-cause mortality, and thus we are unable to comment on the rates of cardiovascular mortality. Finally, HbA1c data were not collected systematically. Hence, we could not determine if HG is a new event or simply a reflection of an undiagnosed DM.

5. Conclusion

Our study highlights the deleterious short-term prognostic impact of HG in AHF patients.
findings should prompt the design of clinical trials addressing the impact of tight glycemic control in AHF on clinical outcomes.

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References

[1] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239.

[2] Dahlof U. Frequent noncardiac comorbidities in patients with chronic heart failure. Eur J Heart Fail 2005;7:309–16.

[3] Brown AM, Cleland JG. Influence of concomitant disease on patterns of hospitalization in patients with heart failure discharged from Scottish hospitals in 1995. Eur Heart J 1998;19:1063–9.

[4] Triposkidakis FK, Skoularigis J. Prevalence and importance of comorbidities in patients with heart failure. Curr Heart Fail Rep 2012;9:354–62.

[5] MacDonald MR, Petrie MC, Hawkins NM, Petrie JR, Fisher M, McKelvie R, et al. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. Eur Heart J 2008;29:1224–40.

[6] Greenberg BH, Abraham WT, Albert NM, Chiswell KL, Clare R, Stough WG, et al. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J 2007;154(277):e1–8.

[7] Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ. Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. J Am Coll Cardiol 2001;38:421–8.

[8] Kamalesh M, Subramanian U, Sawada S, Eckert G, Temkit M, Tierney W. Decreased survival in diabetic patients with heart failure due to systolic dysfunction. Eur J Heart Fail 2006;8:404–8.

[9] MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur Heart J 2008;29:1377–85.

[10] Parissis JT, Rafoulis-Stergiou P, Mebazaa A, Ikonomidis I, Bistola V, Nikolaou M, et al. Acute heart failure in patients with diabetes mellitus: clinical characteristics and predictors of inhospital mortality. Int J Cardiol 2012;157:108–13.

[11] Smooke S, Horwich TB, Fonarow GC. Insulin-treated diabetes is associated with a marked increase in mortality in patients with advanced heart failure. Am Heart J 2005;149:168–74.

[12] Helfand BK, Maselli NJ, Lessard DM, Yarzebski J, Gore JM, McManus DD, et al. Elevated glucose levels and survival after acute heart failure: a population-based perspective. Diab Vasc Dis Res 2015;12:119–25.

[13] Targher G, Dauriz M, Tavazzi L, Temporelli PL, Lucci D, Urso R, et al. Prognostic impact of in-hospital hyperglycemia in hospitalized patients with acute heart failure: results of the IN-HF (Italian Network on Heart Failure) Outcome registry. Int J Cardiol 2015;203:587–93.

[14] Barsheshet A, Garty M, Grossman E, Sandach A, Lewis BS, Gottlieb S, et al. Admission blood glucose level and mortality among hospitalized nondiabetic patients with heart failure. Arch Intern Med 2006;166:1613–9.

[15] Lazzeri C, Valente S, Chiostri M, D’Alfonso MG, Spini V, Angelotti P, et al. Admission glycaemia and acute insulin resistance in heart failure complicating acute coronary syndrome. Heart Lung Circ 2015;24:1074–80.

[16] de Miguel-Yanes JM, Gonzalez-Hernando C, Munoz-Rivas N, Mendez-Bailon M, Cava-Valenciano F, Torres-Macho J. First plasma glucose value after urgent admission and inhospital mortality in acutely decompensated heart failure. Heart Lung Circ 2015;44:137–40.

[17] Mebazaa A, Gayat E, Lassus J, Meas T, Mueller C, Maggioni A, et al. Association between early blood glucose and outcome in acute heart failure: results from an international observational cohort. J Am Coll Cardiol 2013;61:820–9.

[18] Sud M, Wang X, Austin PC, Lipscombe LL, Newton GE, Triposkiadis FK, Skoularigis J. Prevalence and importance of comorbidities in patients with heart failure. Curr Heart Fail Rep 2011;8:97–104.

[19] D’Alfonso MG, Spini V, Angelotti P, et al. Admission glycaemia and acute insulin resistance in heart failure complicating acute coronary syndrome. Heart Lung Circ 2015;24:1074–80.

[20] Kosiborod M, Inzucchi SE, Spertus JA, Wang Y, Masoudi FA, Havranek EP, et al. Elevated admission glucose and mortality in elderly patients hospitalized with heart failure. Circulation 2009;119:1899–907.

[21] Malmberg K, Ryden L, Elendir S, Herlitz J, Nicol P, Mardenstrom A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995;26:57–65.

[22] Mehta SR, Yusuf S, Diaz R, Zhu J, Pias P, Xavier D, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. JAMA 2005;293:437–46.

[23] van der Horst IC, Zijlstra F, van’t Hof AW, Doggen CJ, de Boer MJ, Suryapranata H, et al. Glucose-insulin-potassium infusion inpatients treated with primary angioplasty for acute myocardial infarction: the glucose-insulin-potassium study: a randomized trial. J Am Coll Cardiol 2003;42:784–91.

[24] Selker HP, Beshansky JR, Sheehan PR, Massaro JM, Griffith JL, D’Agostino RB, et al. Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial. JAMA 2012;307:1925–33.

[25] O’Gara PT, Kushner FG, Ascheim DD, Casey Jr DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:e36–425.

[26] AlShabibi KF, Elsaffar AA, AlBacker H, AlFaleh H, Hersi A, AlShaer F, et al. Design and preliminary results of the heart function assessment registry trial in Saudi Arabia (HEARTS) in patients with acute and chronic heart failure. Eur J Heart Fail 2011;13:1178–84.
