Impact of diabetes on mortality and rehospitalization in acute heart failure patients stratified by ejection fraction

Mohammed Al-Jarallah1, Rajesh Rajan1*, Ibrahim Al-Zakwani2, Raja Dashti3, Bassam Bulbanat4, Mustafa Ridha3, Kadhim Sulaiman4, Alawi A. Alsheikh-Al5, Prashanth Panduranga6, Khalid F. AlHabib7, Jassim Al Suwaidi8, Wael Al-Mahmeed9, Hussam AlFaleh7, Abdelfatah Elasfar10,11, Ahmed Al-Motarreb12, Nooshin Bazargani13, Nidal Asaad14 and Haitham Amin15

1Department of Cardiology, Sabah Al Ahmed Cardiac Centre, Kuwait City13001, Kuwait; 2Department of Pharmacology & Clinical Pharmacy, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman & Gulf Health Research, Muscat, Oman; 3Division of Cardiology, Al-Dabous Cardiac Centre, Al Adan Hospital, Kuwait City, Kuwait; 4Department of Cardiology, Rosalyn Hospital, Specialized Medical Care, Ministry of Health, Muscat, Oman; 5College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates; 6Department of Cardiology, Royal Hospital, Muscat, Oman; 7Department of Cardiology, King Fahad Cardiac Centre, King Saud University, Riyadh, Saudi Arabia; 8Department of Adult Cardiology, Hamad Medical Corporation and Qatar Cardiovascular Research Centre, Doha, Qatar; 9Heart and Vascular Institute, Cleveland Clinic, Abu Dhabi, United Arab Emirates; 10Department of Adult Cardiology, King Salman Heart Centre, King Fahad Medical City, Riyadh, Saudi Arabia; 11Cardiology Department, Tanta University, Tanta, Egypt; 12Department of Internal Medicine, Faculty of Medicine, Sana’a University, Sana’a, Yemen; 13Department of Cardiology, Dubai Hospital, Dubai, United Arab Emirates; 14Department of Adult Cardiology, Hamad Medical Corporation, Doha, Qatar; 15Mohammed Bin Khalifa Cardiac Centre, Manama, Bahrain

Abstract

Aims The aim of this study is to determine the impact of diabetes mellitus on all-cause mortality and rehospitalization rates at 3 months and at 1 year in patients admitted with acute heart failure (AHF) stratified by left ventricular ejection fraction (EF).

Methods and results We analysed consecutive patients admitted to 47 hospitals in seven Middle Eastern countries (Saudi Arabia, Oman, Yemen, Kuwait, United Arab Emirates, Qatar, and Bahrain) with AHF from February to November 2012 with AHF who were admitted in Gulf CARE, a multinational registry of patients with heart failure (HF). AHF patients were stratified into three groups: HF patients with preserved EF (HFpEF) (<40%), HF with mid-range EF (HFmrEF) (40–49%), and HF patients with preserved EF (HFpEF) (≥50%). Analyses were performed using univariate and multivariate statistical techniques. The mean age of the cohort was 59 ± 15 years (ranging from 18 to 99 years), and 63% (n = 2887) of the patients were males. A total of 2258 (49%) AHF patients had diabetes mellitus. The mean EF was 37 ± 14%. A reduced EF was observed in 2683 patients (59%), whereas 962 patients (21%) had mid-range and 932 patients (20%) had preserved EF. Multivariable analyses demonstrated no significant differences in all-cause mortality between diabetics and non-diabetics in all the three types of HF; at 3 months follow-up: HFrEF (adjusted odds ratio (aOR), 1.30; 95% confidence interval (CI): 0.94–1.80; P = 0.119), HFmrEF (aOR, 0.98; 95% CI: 0.51–1.87; P = 0.952), and HFpEF (aOR, 0.69; 95% CI: 0.38–1.26; P = 0.225); and at 12-months follow-up: HFrEF (aOR, 1.25; 95% CI: 0.97–1.62; P = 0.080), HFmrEF (aOR, 1.07; 95% CI: 0.68–1.68; P = 0.783), and HFpEF (aOR, 1.07; 95% CI: 0.67–1.72; P = 0.779). There were also no significant differences in rehospitalization rates between diabetics and non-diabetics in all the three types of HF; at 3 months follow-up: HFrEF (aOR, 0.94; 95% CI: 0.74–1.19; P = 0.581), HFmrEF (aOR, 0.82; 95% CI: 0.53–1.26; P = 0.369), and HFpEF (aOR, 1.06; 95% CI: 0.64–1.78; P = 0.812); and at 12-months follow-up: HFrEF (aOR, 0.93; 95% CI: 0.73–1.17; P = 0.524), HFmrEF (aOR, 0.81; 95% CI: 0.56–1.17; P = 0.257), and HFpEF (aOR, 1.29; 95% CI: 0.82–2.05; P = 0.271).

Conclusions There were no significant differences in 3 and 12 months all-cause mortality as well as rehospitalization rates between diabetics and non-diabetic patients in all the three types of AHF patients stratified by left ventricular ejection fraction.

Keywords Heart failure; Diabetes mellitus; Mortality; Middle East; Readmission

Received: 21 May 2019; Revised: 19 August 2019; Accepted: 17 September 2019

*Correspondence to: Dr Rajesh Rajan, Department of Cardiology, Sabah Al Ahmed Cardiac Centre, Kuwait City 13001, Kuwait. Tel: +965 65873326. Email: cardiology08@gmail.com

© 2019 The Authors. ESC Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
**Introduction**

Heart failure (HF) is associated with increasing incidence of diabetes in view of its insulin resistant state. Prevalence of type 2 diabetes mellitus (T2DM) remains almost the same in both HF with reduced ejection fraction (EF) (HFrEF) and HF with preserved EF (HfPEF). The prevalence of diabetes mellitus in congestive heart failure ranges between 11% and 28%. Diabetes along with racial difference and age also plays an important role in the management of HF. Most of the major trials have shown that the treatment of HF should remain the same irrespective of the presence of T2DM. Diabetes in HF is an independent predictor of mortality and frequent hospitalizations. Incidence of HF in diabetic patients is reported to be twice the rate when compared with those without diabetes. Rate of readmissions is noted relatively high in HF patients with T2DM. Early diagnosis and proper treatment plan are important to achieve favourable short-term and long-term outcomes. Anti-diabetic medications increase the metabolic risk and thereby increase the rate of mortality and HF-related hospitalizations in all patients irrespective of the presence of HF. Systematic reviews and meta-analyses have identified age, duration of DM, renal failure, and coronary artery disease (CAD) as independent risk factors for developing HF in diabetic patients.

There is scant information on the epidemiology of HF in diabetic patients in the Arabian Gulf. The aim of this study was to determine the impact of diabetes mellitus on all-cause mortality and rehospitalization rates at 3 months and at 1 year in patients admitted with acute heart failure (AHF) stratified by left ventricular ejection fraction in the Arabian Gulf.

**Methods**

Gulf CARE is a prospective, multicenter, multinational registry of AHF patients admitted to 47 hospitals in seven Middle Eastern countries (Kuwait, Oman, Qatar, United Arab Emirates, Bahrain, Saudi Arabia, and Yemen). The registry is listed in clinicaltrials.gov (number NCT01467973). Baseline and admission-based variables on demographic, co-morbidities, behavioural risk factors, clinical presentation, investigations, including medication history, and in-hospital outcomes were captured. Follow-up for all-cause mortality and rehospitalization was carried out telephonically at 3 months and either telephonically or through out-patient clinic visits at 1 year.

Data entry was carried out online using a custom designed electronic case-record form at the Gulf CARE website (www.gulfcare.org). Institutional or national ethical committee or review board approvals were obtained. Trained abstractors collected the data from medical records at each participating site, and this information was recorded using an electronic case-record form. Importantly, registry participation did not require any alteration of treatment or hospital care, and entry of the data into the registry was not contingent on the use of any particular therapeutic agent or treatment regimen.

**Definition of heart failure**

Acute heart failure (AHF) was defined according to the European Society of Cardiology as the rapid onset of symptoms and signs secondary to abnormal cardiac function, including (i) symptoms (dyspnoea at rest or on exercise, fatigue, tiredness, and ankle swelling), (ii) signs (tachycardia, tachypnoea, elevated jugular venous pressure, pulmonary rales, pleural effusion, hepatomegaly, and peripheral oedema), and (iii) objective evidence of structural or functional abnormality of the heart at rest (third heart sound, murmurs, cardiomegaly, abnormal echocardiogram, and raised natriuretic peptide concentration). AHF was further classified as either acute decompensated chronic heart failure (ADCHF) or new-onset acute HF (de novo AHF) on the basis of European Society of Cardiology guidelines. ADCHF was defined as the worsening of HF in patients with a previous diagnosis or hospitalization for HF. De novo AHF was defined as AHF in patients with no history of HF.

HFrEF was diagnosed when patients with symptoms and signs of HF had a measured EF <40%. HF with mid-range EF (HfMrEF) was diagnosed when patients with symptoms and signs of HF had a measured EF between 40% and 49%. HfPEF was diagnosed when patients with symptoms and signs of HF had a measured EF between ≥50%.

Patients with HF who were discharged from the emergency room without admission were excluded from the registry. Patients with no available record of EF were also excluded from the analysis.

**Data variables**

Coronary artery disease (CAD) was diagnosed if any of the following conditions were present: at least one major epicardial coronary artery determined by coronary angiography to have >70% obstruction, history of myocardial infarction associated with wall motion abnormality seen on echocardiography or gated blood pool imaging, and/or stress testing (with or without imaging) results that are diagnostic of CAD. Hypertension was defined when any of the following conditions were present: at least one major epicardial coronary artery determined by coronary angiography to have >70% obstruction, history of myocardial infarction associated with wall motion abnormality seen on echocardiography or gated blood pool imaging, and/or stress testing (with or without imaging) results that are diagnostic of CAD. Hypertension was defined when any of the following conditions were present:

- Blood pressure ≥140/90 mmHg on repeated measurements on at least 2 occasions
- Hypertension medications
- History of hypertension

ESC Heart Failure 2020; 7: 298–306
DOI: 10.1002/ehf2.12538
conditions were present: untreated systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥105 mmHg for at least 3 months and/or hypertension requiring at least two drugs for control for ≥5 years.16

Type 2 diabetes was diagnosed on the basis of fasting plasma glucose levels ≥126 mg/dL (7.0 mmol/L). 2 h plasma glucose levels (2 h PG) ≥200 mg/dL (11.1 mmol/L) during oral glucose tolerance test, and HbA1c ≥6.5% (48 mmol/mol).17

**Results**

A total of 4457 HF patients with a diagnosis of AHF were recruited to the study; 63% (n = 2887) of the patients were male. The mean age was 59 ± 15 years, ranging from 18 to 99 years. Forty-nine percent (n = 2258) of the patients had diabetes mellitus. A total of 2762 (60%) had CAD, 2783 (61%) patients had hypertension, and 1646 (36%) patients had known dyslipidaemia. Atrial fibrillation was observed in 559 patients (12%), and chronic kidney disease or those requiring dialysis was observed in 670 (15%) patients.

The mean EF of the cohort was 37 ± 14%. A reduced EF (<40%) was observed in 2683 patients (59%), whereas 962 patients (21%) had mid-range (40–49%) EF while 932 patients (20%) had preserved EF (≥50%). At hospital discharge, the aetiology of HF was recorded as being acute coronary syndrome in 1259 (28%) patients, primary cardiomyopathy in 854 (19%) patients, hypertensive heart disease in 697 (15%) patients, primary valve pathology in 441 (9.6%) patients, and pulmonary hypertension in 116 (2.5%) patients. The median duration of hospitalization was 7 (4–10) days. The overall in-hospital mortality was 5.2% (n = 236).

Acute heart failure (AHF) diabetic patients were older (63 vs. 55 years; P < 0.001) with higher body mass index (30 vs. 27 kg/m²; P < 0.001) but less likely to be male (60% vs. 66%; P < 0.001), smokers (18% vs. 26%; P < 0.001), khatt users (9.3% vs. 28%; P < 0.001), and alcohol consumers (3.0% vs. 4.1%; P = 0.032). AHF diabetic patients were also more likely to present with CAD (73% vs. 48%; P < 0.001), peripheral vascular disease (7.2% vs. 1.6%; P < 0.001), stroke/transient ischaemic attack (11% vs. 5.0%; P < 0.001), hypertension (82% vs. 41%; P < 0.001), dyslipidaemia (54% vs. 18%; P < 0.001), chronic kidney disease/dialysis (23% vs. 6.3%; P < 0.001), sleep apnoea requiring therapy (3.2% vs. 0.8%; P < 0.001), and ACHF type (60% vs. 51%; P < 0.001). They were also associated with higher serum creatinine (143 vs. 117 μmol/L; P < 0.001) and systolic blood pressure (142 vs. 132 mmHg; P < 0.001). There were no significant differences mean left ventricular ejection fraction between diabetics and non-diabetics (37% vs. 37%; P = 0.259); however, diabetics were less likely to be associated with HFrEF compared with non-diabetics (56% vs. 61%; P = 0.002). Other clinical characteristics are outlined in Table 1.

At hospital discharge, diabetic patients were less likely to receive aldosterone antagonists (36% vs. 53%; P < 0.001), digoxin (20% vs. 33%; P < 0.001), beta blockers (71% vs. 74%; P < 0.001), and angiotensin-converting-enzyme inhibitors (57% vs. 66%; P < 0.001) but more likely to receive ivabradine (7.0% vs. 3.6%; P < 0.001) and angiotensin

**Statistical analysis**

Descriptive statistics were used to summarize the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analysed using Pearson’s χ² test. For continuous variables, mean and standard deviation were used to summarize the data while analysis was performed using Student’s t-test.

Multivariable logistic regression models, utilizing the simultaneous method, were performed to evaluate the impact of HF (HFrEF, HfMRF, and HFpEF) on all-cause mortality and rehospitalization (primary outcomes) at 3 months and and 1 year post-hospital discharge. The multivariate logistic models were adjusted for age, gender, body mass index, smoking, khatt chewing, peripheral vascular disease, hypertension, diabetes mellitus, prior stroke/transient ischaemic attack, systolic blood pressure, diastolic blood pressure, serum creatinine, in-hospital percutaneous coronary intervention or coronary artery bypass graft, admission diagnosis, New York Heart Association class, in-hospital course (included non-invasive ventilation, intubation/ventilation, cardiogenic shock, inotropes, intra-aortic balloon pump, acute dialysis/ultrafiltration, atrial fibrillation requiring therapy, major bleeding, blood transfusion, stroke, and systemic infection requiring therapy), and discharged medications [diuretics, digoxin, oral nitrates, CCBs, beta blockers, aldosterone antagonist, ACEIs, ARBs, aspirin, and Iβ channel blocker (ivabradine)].

The goodness of fit of the multivariable logistic model was examined using the Hosmer and Lemeshow goodness-of-fit statistic. Based on the χ² distribution, a Hosmer and Lemeshow statistic with a P > 0.05 is considered a good fit. The discriminatory power of the logistic model was assessed by the area under the receiver operating characteristics curve also known as C-index. A model with perfect discriminative ability has a C-index of 1.0; an index of 0.5 provides no better discrimination than chance. Models with area under the receiver operating characteristics curve of >0.7 are preferred. An a priori two-tailed level of significance was set at P < 0.05. Statistical analyses were conducted using STATA version 13.1 (STATA Corporation, College Station, TX, USA).
### Table 1: Patient characteristics of the Gulf CARE cohort stratified by diabetes mellitus (DM) (N = 4577)

| Characteristic | All (N = 4577) | DM | P-value |
|---------------|----------------|----|---------|
| **Demographic** |                |    |         |
| Age, mean ± SD, years | 59 ± 15 | 55 ± 17 | 63 ± 11 | <0.001 |
| Male gender | 2887 (63%) | 1525 (66%) | 1362 (60%) | <0.001 |
| Smoking | 1020 (22%) | 607 (26%) | 413 (18%) | <0.001 |
| Khatt | 849 (19%) | 639 (28%) | 210 (9.3%) | <0.001 |
| Alcohol | 163 (3.6%) | 96 (4.1%) | 67 (3.0%) | 0.032 |
| BMI, mean ± SD, kg/m² | 28 ± 6 | 27 ± 6 | 30 ± 7 | <0.001 |
| **Medical history** |                |    |         |
| CAD | 2762 (60%) | 1104 (48%) | 1658 (73%) | <0.001 |
| PVD | 2045 (45%) | 1013 (44%) | 1032 (46%) | 0.169 |
| Palpitation | 1427 (31%) | 858 (37%) | 569 (25%) | <0.001 |
| Ascites | 653 (14%) | 370 (16%) | 283 (13%) | 0.001 |
| Heart failure type |                |    |         |
| AHF | 2047 (45%) | 1147 (49%) | 900 (40%) | <0.001 |
| ADCHF | 2530 (55%) | 1172 (51%) | 1358 (60%) |         |
| ECG |                |    |         |
| Sinus status | 3749 (82%) | 1858 (80%) | 1891 (84%) | 0.003 |
| Sinus rhythm | 628 (14%) | 358 (15%) | 270 (12%) |         |
| CHB | 49 (1.1%) | 30 (1.3%) | 19 (0.8%) |         |
| Paced | 68 (1.5%) | 27 (1.2%) | 41 (1.8%) |         |
| SVT | 26 (0.6%) | 14 (0.6%) | 12 (0.5%) |         |
| Others | 57 (1.3%) | 32 (1.4%) | 25 (1.1%) |         |
| LV hypertrophy | 1434 (31%) | 737 (32%) | 697 (31%) | 0.506 |
| ST-depression/T-inversion | 2053 (45%) | 940 (41%) | 1113 (41%) | <0.001 |
| STEMI | 487 (11%) | 255 (11%) | 232 (10%) | 0.429 |
| Pathological Q waves | 1110 (24%) | 487 (21%) | 623 (28%) | <0.001 |
| QRS duration ≥ 0.12 msec | 3602 (79%) | 1813 (78%) | 1789 (79%) | 0.256 |
| No | 616 (13%) | 330 (14%) | 286 (13%) |         |
| LVEF, mean ± SD, % | 37 ± 14 | 37 ± 14 | 37 ± 13 | 0.259 |
| LVEF | 2683 (59%) | 1415 (61%) | 1268 (56%) |         |
| HFrEF | 962 (21%) | 447 (19%) | 515 (23%) | 0.002 |
| HFP EF | 932 (20%) | 457 (20%) | 475 (21%) |         |

Percentages might not add up to 100% due to rounding off. Analyses were performed using Student’s t-test or Pearson’s χ² test, whenever appropriate.

SD, standard deviation; smoking, includes chewing tobacco and/or smoking water-pipe; alcohol, drinking daily; BMI, body mass index; kg, kilogram; CAD, coronary artery disease; PVD, peripheral vascular disease; Afib, atrial fibrillation; TIA, transient ischaemic attack; CKD, chronic kidney disease; Abd, abdominal; BG, peripheral admission blood glucose; Crea, creatinine; SBP, systolic blood pressure; AHF, acute new-onset heart failure; ADCHF, acute decompensated chronic heart failure; ECG, electrocardiography; CHB, complete heart block; SVT, supraventricular tachycardia; LV, left ventricular; STEMI, ST-segment elevation myocardial infarction; LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, intra ventricular conduction delay; LVEF, LV ejection fraction; HFrEF, Heart failure (HF) with reduced ejection fraction (EF) (<40%); HFrEF, HF with mid-range EF (40–49%); HFP EF, HF with preserved EF (≥50%).
receptor blockers (57% vs. 66%; \( P < 0.001 \)). Other pre-admission and discharged medications are shown in Table 2.

As shown in Table 3, there were no significant differences in cumulative all-cause mortality and rehospitalization rates, neither at 3 months nor at 1 year follow-up, in all the three types of HF (all \( P \)-values were \( >0.05 \)).

**Discussion**

The data extracted from GULF CARE registry demonstrated that there were no significant differences in 3 and 12 months all-cause mortality as well as rehospitalization rates between diabetics and non-diabetic patients in all the three types of AHF patients stratified by left ventricular ejection fraction in the Arabian Gulf. The findings are contrary to many studies that have shown poor outcomes in those HF patients with elevated HbA1c.\(^{18} \) A moderate difference between HFrEF and HFP EF diabetic patients in terms of in-hospital mortality has been observed.\(^ {19} \) Interestingly, young diabetic HF patients have also been reported to have higher risk ratio for mortality.\(^ {20} \) An observational study had suggested that optimal glycaemic control, blood pressure control, and the addition of ACE inhibitors in the treatment regimen may reduce the mortality risk in HF patients.\(^ {1,2,22} \) CAD and renal impairment have also been reported to increase the risk of mortality in HF.\(^ {23} \)

International data have reported up to 40% incidence of diabetes in AHF patients and 25% in chronic HF patients.\(^ {24} \) In our study, an incidence of 49% of diabetes mellitus has been observed in AHF patients in the Arabian Gulf. In the setting of HF and diabetes, many randomized controlled trials have shown no benefits with strict glycaemic control.\(^ {25} \) In the CHARM trial, the cardiovascular mortality and rate of

| Medication, n (%) | All (\( N = 4577 \)) | DM No (\( n = 2319 \)) | Yes (\( n = 2258 \)) | \( P \)-value |
|------------------|----------------------|----------------------|----------------------|-------------|
| Pre-admission    |                      |                      |                      |             |
| Diuretics        | 2642 (58%)           | 1175 (51%)           | 1468 (65%)           | <0.001      |
| Aldosterone antagonist | 784 (17%)     | 406 (18%)            | 378 (17%)            | 0.491       |
| Digoxin          | 798 (17%)            | 461 (20%)            | 337 (15%)            | <0.001      |
| Nitrates         | 1208 (26%)           | 425 (18%)            | 783 (35%)            | <0.001      |
| CCB              | 589 (13%)            | 158 (6.8%)           | 431 (19%)            | <0.001      |
| Hydralazine      | 201 (4.4%)           | 43 (1.9%)            | 158 (7.0%)           | <0.001      |
| Aspirin          | 2863 (63%)           | 1167 (50%)           | 1696 (75%)           | <0.001      |
| Clopidogrel      | 883 (19%)            | 281 (12%)            | 602 (27%)            | <0.001      |
| Statin           | 2,350 (51%)          | 789 (34%)            | 1561 (69%)           | <0.001      |
| Oral anticoagulant | 571 (12%)           | 312 (13%)            | 259 (11%)            | 0.042       |
| Iubradine        | 108 (2.4%)           | 32 (1.4%)            | 76 (3.4%)            | <0.001      |
| Anti-arrhythmic  | 117 (2.6%)           | 50 (2.2%)            | 67 (3.0%)            | 0.082       |
| Beta blocker     | 2061 (45%)           | 859 (37%)            | 1202 (53%)           | <0.001      |
| ACEI             | 1993 (44%)           | 978 (42%)            | 1015 (45%)           | 0.058       |
| ARB              | 589 (13%)            | 184 (7.9%)           | 405 (18%)            | <0.001      |
| UFH/LMWH         | 210 (4.6%)           | 86 (3.7%)            | 124 (5.5%)           | 0.004       |
| At discharge\(^ {a} \) |                      |                      |                      |             |
| Diuretics        | 3970 (94%)           | 2000 (93%)           | 1970 (95%)           | 0.073       |
| Aldosterone antagonist | 1885 (45%)     | 1141 (53%)           | 744 (36%)            | <0.001      |
| Digoxin          | 1109 (26%)           | 701 (33%)            | 408 (20%)            | <0.001      |
| Nitrates         | 1619 (38%)           | 604 (28%)            | 1019 (49%)           | <0.001      |
| CCB              | 637 (15%)            | 185 (8.6%)           | 451 (22%)            | <0.001      |
| Hydralazine      | 309 (7.3%)           | 86 (4.0%)            | 223 (11%)            | <0.001      |
| Aspirin          | 3454 (82%)           | 1628 (76%)           | 1826 (88%)           | <0.001      |
| Clopidogrel      | 1608 (38%)           | 657 (31%)            | 951 (46%)            | <0.001      |
| Statin           | 3064 (73%)           | 1271 (59%)           | 1793 (86%)           | <0.001      |
| Oral anticoagulant | 816 (19%)           | 479 (22%)            | 337 (16%)            | <0.001      |
| Iubradine        | 223 (5.3%)           | 78 (3.6%)            | 145 (7.0%)           | <0.001      |
| Anti-arrhythmic  | 207 (4.9%)           | 100 (4.2%)           | 107 (5.2%)           | 0.476       |
| Beta blocker     | 3067 (73%)           | 1586 (74%)           | 1481 (71%)           | 0.036       |
| ACEI             | 2606 (62%)           | 1418 (66%)           | 1188 (57%)           | <0.001      |
| ARB              | 720 (17%)            | 319 (15%)            | 401 (19%)            | <0.001      |
| UFH/LMWH         | 153 (3.6%)           | 58 (2.7%)            | 95 (4.6%)            | 0.001       |

Analyses were performed using Pearson’s \( \chi^2 \) test.

CCB, calcium channel blocker; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; UFH, unfractionated heparin; LMWH, low molecular weight heparin.

\(^ {a} \)Medications at discharge excluded those that died (\( n = 236; 5.16\% \)) as well as those that left against medical advice (\( n = 122; 2.67\% \)) (LAMA) (\( N = 4219 \)).
hospitlizations were found higher with HFrEf than HFrEf.\textsuperscript{26} The ALLHAT trial has shown that diabetes mellitus had a two-fold rise in risk for HF hospitalizations as well as mortality.\textsuperscript{31} The Framingham Heart study has shown a 34% mortality at 1 year for diabetic patients who were diagnosed to have HF.\textsuperscript{28} The SOLVD trial also demonstrated higher rates of hospitalizations, mortality in asymptomatic ischaemic cardiomyopathy patients with diabetes.\textsuperscript{29} The Framingham study has shown that the rate of incidence of HF was five-fold higher in women and 2.4-fold higher in men with diabetes.\textsuperscript{30} Incidence of diabetes was found to be 67% in AHF patients with cardiorenal anaemia syndrome in Gulf Care registry.\textsuperscript{31} A new risk calculator for HFrEf (https://www.hfriskcalc.in/) has been suggested.\textsuperscript{32}

A community-based study showed that advanced NYHA class was associated with higher incidence of diabetes.\textsuperscript{33} A Scottish retrospective study has shown that South Asians had a higher rate of HF hospitalizations and death than Caucasians.\textsuperscript{34} In the SOLVD trial, African Americans with HFrEf were at higher risk of developing AHF compared with Whites.\textsuperscript{35} A study evaluating diabetic cardiomyopathy showed diabetes in Blacks were associated with reduced end diastolic volume and stroke volume with an increased left ventricular mass.\textsuperscript{36}

In the Middle East, AHF patients were a decade younger when compared with those in the Western world.\textsuperscript{37} A systemic review has shown that the use of metformin was associated with a 13% reduction in readmissions for HF in diabetic patients.\textsuperscript{38} Another study has shown metformin to be associated with a reduction in mortality and major adverse cardiovascular events.\textsuperscript{39} The DECLARE-TIMI 58 trial has demonstrated that diabetic HF patients will benefit with dapagliflozin treatment in terms of reduced all-cause mortality and cardiovascular death in HFrEF. Furthermore, there was also a noted reduction in HF-related hospitalizations in both HFrEF and HFrEF patients.\textsuperscript{40} SGLT2 inhibitors were associated with reductions in HF hospitalizations in diabetic patients.\textsuperscript{41} The SAVOR-TIMI 53 trial has shown that saxagliptin increases the risk of HF hospitalizations.\textsuperscript{42} Newer molecules, nephrilysin inhibitors, have shown nephro protective and anti-diabetic effects.\textsuperscript{43} In our study, we found that diabetics has no impact on mortality or rehospitalization rates at 3 months or at 12 months in all the types of HF.

The limitation of this study is its nature of being a registry, which may have introduced bias through confounding by variables not controlled for or measured (such as iron levels and history of chronic anaemia). In some countries, only a few hospitals took part in the registry; hence, the results might not entirely generalizable. Reasons for underuse of medications or procedures were not known in this study. The recording of natriuretic peptides was optional as not all variables not controlled for or measured (such as iron levels and history of chronic anaemia). In some countries, only a few hospitals took part in the registry; hence, the results might not entirely generalizable. Reasons for underuse of medications or procedures were not known in this study. The recording of natriuretic peptides was optional as not all hospitals routinely measure them. Echocardiographic interpretation was at the discretion of the person performing the study; no centralized evaluation was performed. Patients’ renal function at discharge is unknown, and there are no data regarding the frequency of patients with improvement of renal function. This study did not record the cognitive status and the disability status in patients with stroke, which obviously have a major impact on morbidity and mortality and only 1 year mortality. Mortality rates at 3 months and at 1 year follow-up were only recorded without the specification of the exact date of death of each patient, and hence, the Kaplan–Meier curves could not have been performed. Finally, because this was HF registry, diabetic medications were not routinely captured. Future studies need to overcome these limitations.

| Table 3 | Impact of diabetes mellitus on mortality and rehospitalization rates (at 3 months and at 1 year follow-up) by multiple logistic regression stratified by left ventricular ejection fraction (LVEF) (N = 4577) |
|---------|-------------------------------------------------------------------------------------------------|---|---|---|---|---|---|---|
| Outcome | Mortality | Rehospitalization |
| 3 months | aOR [95% CI] | aP-value | HL | ROC | aOR [95% CI] | aP-value | HL | ROC |
| HFrEF (n = 2683) | 1.30 [0.94–1.80] | 0.119 | 0.042 | 0.79 | 0.94 [0.74–1.19] | 0.581 | 0.390 | 0.62 |
| HFrEF (n = 962) | 0.98 [0.51–1.87] | 0.952 | 0.020 | 0.79 | 0.82 [0.53–1.26] | 0.369 | 0.322 | 0.73 |
| HFrEF (n = 932) | 0.69 [0.38–1.26] | 0.225 | 0.101 | 0.81 | 1.06 [0.64–1.78] | 0.812 | 0.545 | 0.70 |
| 12 months | | | | | | | | |
| HFrEF (n = 2683) | 1.25 [0.97–1.62] | 0.080 | 0.292 | 0.76 | 0.93 [0.73–1.17] | 0.524 | 0.864 | 0.62 |
| HFrEF (n = 962) | 1.07 [0.68–1.68] | 0.783 | 0.527 | 0.75 | 0.81 [0.56–1.17] | 0.257 | 0.357 | 0.63 |
| HFrEF (n = 932) | 1.07 [0.67–1.72] | 0.779 | 0.482 | 0.75 | 1.29 [0.82–2.05] | 0.271 | 0.161 | 0.65 |

Multivariate analyses were conducted using logistic regression model utilizing stepwise-backwards elimination method adjusting for age, gender, smoking, khatt use, alcohol, body mass index, coronary artery disease, peripheral vascular disease, prior stroke/transient ischaemic attack, hypertension, dyslipidaemia, chronic kidney disease or dialysis, sleep apnoea requiring therapy, vulvar heart disease, abdominal lower limb swelling, weight gain, serum creatinine, systolic blood pressure on admission, admission blood glucose, sinus status, prior medications (diuretics, digoxin, oral nitrates, calcium channel blockers, beta blocker, aldosterone antagonist, angiotensin-converting-enzyme inhibitor, angiotensin receptor blocker, aspirin, clopidogrel, and ivabradine) for the in-hospital model while for the 3 and 12 months logistic models, medications at hospital discharge were used aOR, adjusted odds ratio; aP-value, adjusted P-value; CI, confidence interval; HL, Hosmer and Lemeshow P-value; ROC, area under the receiver operating curve also known as c-statistic; HFrEf, heart failure (HF) with reduced ejection fraction (EF) (<40%); HFrEF, HF with mid-range EF (40–49%); HFrEF, HF with preserved EF (≥50%).

DOI: 10.1002/ehf2.12538
Conclusions

There were no significant differences in 3 and 12 months all-cause mortality and rehospitalization rates between diabetics and non-diabetic patients in all the three types of AHF stratified by left ventricular ejection fraction.

Acknowledgements

Gulf CARE is an investigator-initiated study conducted under the auspices of the Gulf Heart Association and funded by Servier, Paris, France, and (for centres in Saudi Arabia) by the Saudi Heart Association.

Conflict of interest

The authors declare that they have no competing interests.

Author Contributions

M.A.J. participated in analysis and manuscript preparation. R. B.B. participated in data acquisition and manuscript preparation. A.Z. did the statistical analysis and manuscript review. R.D. participated in the data analysis and drafting of manuscript. B.B. participated in data acquisition and manuscript preparation. All authors had access to data and take responsibility for the integrity of data and the accuracy of data analysis. All authors have read and approved the manuscript.

References

1. Banerjee D, Biggs ML, Mercer L, Mukamal K, Kaplan R, Barzilay J, Kuller L, Kizer JR, Djuusse L, Tracy R, Zieman S, Lloyd-Jones D, Siscovick D, Carnethon M. Insulin resistance and risk of incident heart failure: cardiovascular health study. *Circ Heart Fail* 2013; 6: 364–370.
2. Diabetes Canada Clinical Practice Guidelines Expert Committee, Connelly KA, Gilbert RE, Liu P. Treatment of diabetes in people with heart failure. *Can J Diabetes* 2018; 42: S196–S200.
3. Elder DH, Singh JS, Levin D, Donnelly LA, Choy A, George J, Struthers AD, Doney AS, Lang CC. Mean HbA1c, and mortality in diabetic individuals with heart failure: a population cohort study. *Eur J Heart Fail* 2016; 18: 94–102.
4. Tee LH, Nordin RB, Abdul Rahim AA. Influence of race in the association of diabetes and heart failure. *US Cardiol* 2018; 12: 17–21.
5. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Rajda M, Swiggum E, Virani SA, Ziero Z, Al-Hesayen A, Cohen-Solal A, D'Aoust M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Koz S, LeBlanc MH, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 Comprehensive update of the Canadian cardiovascular society guidelines for the management of heart failure. *Can J Cardiol* 2017; 33: 1342–1433.
6. Thomas MC. Perspective review: type 2 diabetes and readmission for heart failure. *Clin Med Insights Cardiol* 2018; 12: 1179546818779588.
7. Campbell P, Krim S, Ventura H. The bi-directional impact of two chronic illnesses: heart failure and diabetes—a review of the epidemiology and outcomes. *Card Fail Rev* 2015; 1: 8–10.
8. Fadini GP, Avogaro A, Degli Esposti L, Russo P, Saragoni S, Buda S, Rosano G, Pecorelli S, Pani L, Network OMH-DB. Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database. *Eur Heart J* 2015; 36: 2454–2462.
9. Wang Y, Negishi T, Negishi K, Marwick TH. Prediction of heart failure in patients with type 2 diabetes mellitus—a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2015; 108: 55–66.
10. Sulaibani KJ, Panduranga P, Al-Zakwani I, Alsheikh-Ali A, Al-Habib K, Al-Suwaidi J, Al-Mahmeed W, Al-Faleh H, El-Asfar A, Al-Motarreb A, Ridda M, Bulbanat B, Al-Jarallah M, Bazargani N, Aasad N, Amin H. Rationale, design, methodology and hospital characteristics of the first Gulf acute heart failure registry (Gulf CARE). *Heart Views* 2014; 15: 6–12.
11. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M, Document R. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; 18: 891–975.

Availability of data and materials

There are no ethics restrictions preventing the sharing of the raw data.

Statement

The present submission (ESCHF-19-00101) does not have significant overlap with the previous ones (ESCHF-18-00056R3: Incidence and impact of cardio-renal anaemia syndrome on all-cause mortality in acute heart failure patients stratified by left ventricular ejection fraction in the Middle East and ESCHF-18-00214R2: “One-Year Outcome of Acute Heart Failure Patients with Reduced, Mid-Range and Preserved Ejection Fraction”), and the previous published submission has been adequately cited.
12. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Guidelines ESC Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008; 10: 933–989.

13. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smitseh OA, De Keulenaer G, Leite-Moraes AF, Borbely A, Edes I, Hanoldo ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert LD. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associates of the European Society of Cardiology. Eur Heart J 2007; 28: 2539–2550.

14. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, ESC Committee for practice guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 35: 1786–1847.

15. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Kasper EK, Levy WC, Mitchell JE, Peterson PN, Riegel B, Sam JH, Stevenson LW, Tuzcu EM, Wang Y, Zannad F. ACCF/AHA 2013 guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 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–e239.

16. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Gardner TJ, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B, American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005; 112: e154–e235.

17. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009; 32(7): 1377–1383.

18. Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. Diabetologia 2014; 57: 660–671.

19. Vaduganathan M, Fonarow GC. Epidemiology of hospitalized heart failure: differences and similarities between patients with reduced versus preserved ejection fraction. Heart Fail Clin 2013; 9: 271–276.

20. MacDonald MR, Jhund PS, Petrie MC, Lewsey JD, Hawkins NM, Bhagra S, Munoz N, Varyani F, Redpath A, Chalmers J, MacIntyre K, McMurray JJV. Discordant short- and long-term outcomes associated with diabetes in patients with heart failure: importance of age and sex. Circ Heart Fail 2008; 1: 234–224.

21. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JV. Glycemic control and heart failure among adult patients with diabetes. Circulation 2001; 103: 2668–2673.

22. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with vascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405–412.

23. Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. Diabetes Care 2001; 24: 1614–1619.

24. Wang Y, Negishi T, Negishi K, Marwick TH. Prediction of heart failure in patients with type 2 diabetes mellitus--systematic review and meta-analysis. Diabetologia Res Clin Pract 2015; 108: 55–66.

25. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genth U, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545–2559.

26. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ, Investigators CHARM. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Cardesinat in heart failure: assessment of reduction in morbidity and mortality (CHARM) program. Eur Heart J 2008; 29: 1377–1385.

27. Davis BR, Piller LB, Cutler JA, Furberg C, Dunn K, Franklin S, Goff D, Leenen F, Mohiuddin S, Papademetriou V, Proschan M, Ellsworth A, Golden J, Colón P, Crow R. Antihypertensive and lipid-lowering treatment to prevent heart attack trial collaborative research group. Role of diuretics in the prevention of heart failure: the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Circulation 2006; 113: 2201–2210.

28. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart study subjects. Circulation 1999; 88: 1079–1087.

29. Das SR, Drazner MH, Yancy CW, Stevenson LW, Gersh BJ, Dries DL. Effects of diabetes mellitus and ischemic heart disease on the progression from asymptomatic left ventricular dysfunction to symptomatic heart failure: a retrospective analysis from the studies on left ventricular dysfunction (SOLVD) prevention trial. Am J Heart 2004; 148: 883–888.

30. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974; 34: 200–206.

31. Al-Jarallah M, Rajan R, Al-Zakwani I, Dashiti R, Bulbanat B, Sulaiman K, Alsheikh-Ali AA, Panduranga P, Al-Habib KF, Al Suwaidi J, Al-Mahmeed W, AlFaleh H, Elasfar A, Al-Matarbab A, Ridha M, Bazargani N, Aasaad N, Amin H. Incidence and impact of cardiorenal anaemia syndrome on all-cause mortality in acute heart failure patients stratified by left ventricular ejection fraction in the Middle East. ESC Heart Fail 2018; 6: 103–110.

32. Rajan R, Al Jarallah M. New prognostic risk calculator for heart failure. Oman Med J 2018; 33: 266–267.

33. Form AM, Leibson CL, Bursi F, Redfield MM, Weston SA, Jacobsen SJ, Rodeheffer RJ, Roger VL. Diabetes in heart failure: prevalence and impact on outcome in the population. Am J Med 2006; 119: 591–599.

34. Bhupal RS, Bansal N, Fischbacher CM, Brown H, Capewell S, Scottish Health and Ethnicity Linkage Study. Ethnic
variations in heart failure: Scottish Health and Ethnicity Linkage Study (SHELS). Heart 2012; 98: 468–473.
35. Dries DL, Exner D, Gersh B, Cooper HA, Carson PE, Domanski MJ. Racial differences in the outcome of left ventricular dysfunction. N Engl J Med 1999; 340: 609–616.
36. Bertoni AG, Goff DC, D’Agostino RB, Liu K, Hundley WG, Lima JA, Polak JF, Saad MF, Szklo M, Tracy RP, Siscovick DS. Diabetic cardiomyopathy and subclinical cardiovascular disease: the multi-ethnic study of atherosclerosis (MESA). Diabetes Care 2006; 29: 588–594.
37. Panduranga P, Al-Zakwani I, Sulaiman K, Al-Habib K, Alsheikh-Ali A, Al-Suwaidi J, Al-Mahmeed W, Al-Faleh H, Elasfar A, Ridha M, Bulbanat B, Al-Jarallah M, Asaad N, Bazargani N, Al-Motarreb A, Amin H. Comparison of Indian subcontinent and Middle East acute heart failure patients: results from the Gulf acute heart failure registry. Indian Heart J 2016; 68: 36–44.
38. Eeitch D, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA, Tjosvold L, Vanderloo SE, McAlister FA. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. Circ Heart Fail 2013; 6: 395–402.
39. Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron CB, Stanifer JW, Mock CK, Wang X, Tang S, Nagi A, Kosinski AS, Williams JW Jr. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med 2017; 166: 191–200.
40. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RH, Murray J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019; 139: 2528–2536.
41. Fitchett D, Butler J, van de Borne P, Zinman B, Lachin JM, Wanner C, Woerle HJ, Hantel S, George JT, Johansen OE, Inzucchi SE, EMPA-REG OUTCOME® trial investigators. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. Eur Heart J 2017; 38: 363–370.
42. Li L, Li S, Deng K, Liu J, Vandvik PO, Zhao P, Zhang L, Shen J, Bala MM, Sohani ZN, Wong E, Busse JW, Ebrahim S, Malaga G, Rios LP, Wang Y, Chen Q, Guyatt GH, Sun X. Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies. BMJ 2016; 352: i610.
43. Kaplinsky E. After having changed the treatment of heart failure with reduced ejection fraction: what are the latest evidences with sacubitril valsartan? J Geriatr Cardiol 2019; 16: 151–155.