Glucose dysregulation and repolarization variability markers are short-term mortality predictors in decompensated heart failure

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\textbf{Objective} As recently reported, elevated fasting glucose plasma level constitutes a risk factor for 30-day total mortality in acutely decompensated chronic heart failure (CHF). Aim of this study was to evaluate the 30-day mortality risk in decompensated CHF patients by fasting glucose plasma level and some repolarization ECG markers.

\textbf{Method} A total of 164 decompensated CHF patients (M/F: 94/71; mean age, 83 ± 10 years) were studied; Tend (Te), QT interval (QT) and 5 min of ECG recordings were obtained, studying mean, SD and normalized index of the abovementioned ECG intervals. These repolarization variables and fasting glucose were analyzed to assess the 30-day mortality risk among these patients.

\textbf{Results} Thirty-day mortality rate was 21%, deceased subjects showed a significant increase in N terminal-pro-brain natriuretic peptide (P < 0.001), higher sensitivity cardiac troponin, fasting glucose, creatinine clearance, QTSD, QTVen, Te mean, TeSD and TeVN than the survivors. Multivariable regression analysis reported that fasting glucose (hazard ratio, 1.59; 95% confidence interval, 1.09–2.10; P < 0.01), Te mean (hazard ratio, 1.03; 95% confidence interval, 1.01–1.05; P < 0.01) and QTSD (hazard ratio, 1.17; 95% confidence interval, 1.01–1.36; P < 0.05) were significantly related to higher mortality risk, whereas only fasting glucose (hazard ratio, 1.84; 95% confidence interval, 1.12–3.02; P < 0.05) and Te mean (hazard ratio, 1.07; 95% confidence interval, 1.02–1.11; P < 0.01) were associated to cardiovascular mortality.

\textbf{Conclusion} Data suggest that two simple, inexpensive, noninvasive markers, as fasting glucose and Te, were capable to stratify the short-term total and cardiovascular mortality risk in acutely decompensated CHF. \textit{Cardiovasc Endocrinol Metab} 11: 1–7 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

Keywords: acutely decompensated heart failure, diabetes, ECG markers, Tpeak–Tend

Introduction

As widely known, type 2 diabetes mellitus (T2DM) frequently causes macrovascular and microvascular pathological changes and, thereby, it increases the risks for the development of myocardial infarction, heart failure (HF), stroke, renal failure and reduced survival. Thus, T2DM often constitutes an important comorbidity in chronic HF (CHF). However, although almost 50 years ago, the Framingham study had already evidenced that the subjects with T2DM showed four- to eight-fold higher risk of CHF [1]; even today, it is a matter of debate whether the hyperglycemia, hyperinsulinemia and the other related metabolic disorders have a causal role in CHF or they are merely an epiphenomenon [2]. On the other hand, it is fairly intuitive that the CHF-related neurohormonal activation and proinflammatory state could trigger the glucose plasma level dysregulation and insulin resistance. In fact, as reported in a recent publication, elevated glycemic variability in acute HF admissions of patients with diabetes predicts short-term mortality. Patients with glucose coefficient of variation of more than 30.0% have an independent more than two-fold higher risk of 6-month death after an acute HF hospitalization [3]. Consequently, in acute decompensated CHF, during sympathetic over-activity, hyperglycemia should also be considered as a marker of decompensation and not only as a pathophysiological complication. Therefore, the aim of our study was to understand if the hyperglycemia and other cardiac damage biomarkers ([N terminal-pro-brain
natriuretic peptide (NT-proBNP), troponin, repolarization ECG repolarization variables, etc.) could be used to stratify the 30-day mortality risk in decompensated CHF subjects. In particular, we recently observed that an increase of Tpeak–Tend interval (Te), obtained during 5-min ECG recoding, was able to stratify the short-period mortality risk in this kind of patients [4–6]. Previously, in a meta-analysis based on patients with different cardiovascular risk profiles [7] and in a large longitudinal epidemiologic study [8], an increased risk of cardiovascular mortality, sudden arrhythmic death and total mortality associated with a Te increase were reported.

**Methods**

**Patients and protocol**

A total of 171 consecutive patients admitted to the Geriatric department were enrolled, from February 2019 to January 2021, due to decompensated CHF. We defined patients with decompensated or compensated CHF as in European Society of Cardiology guidelines, available at that time [9].

When enrolled, all patients underwent to: clinical history, physical examination, standard ECG, transthoracic echocardiography, 5 min of II lead ECG (Miocardio Event, Rome, Italy) recording, a venous blood sample for NT-proBNP dosage, obtained by Alere Triage Analyser (Alere, San Diego, California, USA) and other routine serum variables, and, finally, an arterial blood sample for gas analysis. We used the Cockcroft-Gault formula to assess the creatinine clearance.

The patients provided written informed consent for the use of their records for research purpose, and the study was in accordance with good clinical practice and the principles of the Declaration of Helsinki of clinical research involving human patients. The study underwent Ethical Committee of Policlinico Umberto I approbation. Clinical trial was registered with the following ID: ClinicalTrials.gov number, NCT04127162.

**Offline data analysis**

We recorded 5 min of II lead ECG (Miocardio Event, Rome, Italy), and the signals were acquired, digitized at a sampling frequency of 500 Hz, and wirelessly transmitted to a cloud platform for the data storage via mobile phone [4–6]. Subsequently, all digitized signal recordings were downloaded by the cloud platform and automatically analyzed, and checked by a single physician blinded to subjects’ circumstances. Therefore, we measured the following intervals from the respective time series in ECG recordings: RR, QT and Te; QT was obtained by measuring the interval from the onset of the Q-wave to the T-wave end; Te was obtained from T peak to end of T-wave. To identify the repolarization intervals, we used a software originally proposed by Berger et al. [10] and validated in other subsequent studies [11–13].

We, therefore, calculated mean (QT mean and Te mean), variance and SD (QT SD and Te SD) values for each of these repolarization phase intervals, and finally, we calculated the variance normalized for mean of QT (QTVN) and Te (TeVN) [4,14,15].

\[
\text{QTVN} = \frac{\text{QT variance}}{\text{QT mean}}^2
\]

\[
\text{TeVI} = \frac{\text{Te variance}}{\text{Te mean}}^2
\]

Software for data analysis was designed and produced by our research group with the LabView program (National Instruments, Austin, Texas, USA).

**Statistical analysis**

All variables with normal distribution were expressed as means ± SD, whereas nonnormally distributed variables as median and interquartile range. Categorical variables were analyzed with the χ² test. Unpaired Student’s t-test was used to compare data for the normally distributed variables; on the contrary, Mann–Whitney test was used to compare nonnormally distributed variables (as evaluated by Kolmogorov–Smirnov test). Uni- and multivariable forward (A. Wald) Cox proportion-hazard regression analysis were used to determine the association between different repolarization continue variables (covariates) and total and cardiovascular 30-day mortality. We used the following covariates for the prognostic model: age, BMI, SBP, DBP; heart rate, left ventricular ejection fraction (LVEF), the arterial partial pressure of oxygen/fraction of inspired oxygen ratio (PaO₂/FIO₂ ratio), the alveolar-capillary oxygen partial pressure gradient (A-aDO₂), NT-proBNP, high sensitivity cardiac Troponin T (troponin), C-reactive protein, serum potassium, calcium and fasting glucose, creatinine clearance, glycated hemoglobin (HbA₁c), total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, QT mean, Te mean, QT SD, Te SD, QTVN and TeVN.

We used Kaplan–Maier to plot survival curve with three dichotomized variables individually or in combination: subjects with fasting glucose ≥7 mmol/l, subjects with HbA₁c ≥6.5% and, finally, subjects with Te ≥116 ms. This last cutoff was used according to previous studies [6,8]. Kaplan–Maier survival curves were compared with log-rank test. P-values of less than or equal to 0.05 were considered statistically significant. All data were evaluated by use of the database SPSS-PC+ (SPSS-PC+ Inc, Chicago, Illinois, USA).

**Results**

Starting from 170 eligible study subjects, six were not included, because the quality of ECG was suboptimal for repolarization analysis (absence or flat T-wave). Then, we conducted the study on a total of 164 acutely decompensated CHF patients (Table 1). During the 30-day follow-up, 26 patients died (overall mortality rate: 16%): 15 (9%) died for bronchopneumonia and respiratory failure, 9 (5%) for terminal HF; one (0.6%) for fatal myocardial
infarction and one (0.6%) for sudden cardiac death (sustained ventricular tachycardia and ventricular fibrillation) (overall cardiovascular mortality rate: 7%).

Age (P < 0.05), NT-proBNP (P < 0.001), troponin (P < 0.01) and fasting glucose (P < 0.05) were significantly higher in the deceased patients (Table 1). Moreover, SBP (P < 0.01), DBP (P < 0.05), PaO2/FIO2 ratio (P < 0.05) and creatinine clearance (P < 0.01) were significantly lower in the same group of subjects (Table 1).

Survival decompensated CHF patients reported lower levels of repolarization variability markers in comparison to the deceased subjects [QT SD (P < 0.01); QT-VN (P < 0.05); Te SD (P < 0.01) and Te-VN (P < 0.001)] (Table 2).

### Table 1 General characteristics of the study subjects

| Patients’ characteristics | All (N = 164) | Deceased subjects (N = 26) | Survivors (N = 138) | P |
|--------------------------|--------------|---------------------------|---------------------|---|
| Age, years               | 83 ± 10      | 87 ± 10                   | 81 ± 9              | 0.011 |
| M/F, n                   | 90/74        | 13/13                     | 77/61               | 0.586 |
| BMI, kg/m²               | 28 ± 5       | 26.1 ± 6.8                | 26.0 ± 4.5          | 0.881 |
| SBP, mmHg                | 123 ± 19     | 116 ± 16                  | 127 ± 16            | 0.008 |
| DBP, mmHg                | 69 ± 6       | 65 ± 9                    | 70 ± 11             | 0.037 |
| Left ventricular ejection fraction, % | 42 ± 10      | 39 ± 11                   | 43 ± 14             | 0.054 |
| PaO2/FIO2, mmHg          | 328 ± 10     | 287 ± 14                  | 338 ± 87            | 0.042 |
| NT-proBNP, pg/ml         | 38 (93)      | 74 (208)                  | 36 (46)             | 0.071 |
| C-reactive protein (mg/dl) | 3.29 (8.43) | 4.93 (14.3)               | 3.14 (7.4)          | 0.307 |
| High sensitivity cardiac troponin (pg/ml) | 34 (101)     | 81 ± 101                  | 38 (37)             | 0.006 |
| Serum potassium (mmol/l) | 4.08 ± 0.59  | 4.16 ± 0.64               | 4.12 ± 0.56         | 0.727 |
| Serum calcium (mmol/l)   | 2.15 ± 0.23  | 2.18 ± 0.19               | 2.16 ± 0.26         | 0.738 |
| Creatinine clearance (ml/min) | 44 (35)     | 32 (27)                   | 45 (32)             | 0.005 |
| Fasting glucose (mg/dl)  | 6.8 ± 2.4    | 7.9 ± 2.6                 | 6.6 ± 2.3           | 0.019 |
| HbA1c (%)                | 6.1 ± 1.4    | 6.3 ± 1.4                 | 6.1 ± 1.4           | 0.497 |
| Total cholesterol (mmol/l) | 3.7 ± 1.3   | 3.5 ± 0.9                 | 3.8 ± 1.0           | 0.365 |
| HDL-cholesterol (mmol/l) | 1.1 ± 0.37   | 0.98 ± 0.22               | 1.13 ± 0.38         | 0.190 |
| LDL-cholesterol (mmol/l) | 2.16 ± 1.38  | 1.70 ± 0.58               | 2.23 ± 1.44         | 0.255 |
| Triglycerides (mmol/l)   | 1.82 ± 1.30  | 1.71 ± 0.89               | 1.83 ± 1.35         | 0.703 |
| Left ventricular ejection fraction | 42 ± 10   | 39 ± 8                    | 43 ± 11             | 0.054 |
| CHF with depressed systolic function, n (%) | 101 (62)     | 22 (85)                   | 79 (57)             | 0.008 |
| CHF with preserved systolic function, n (%) | 63 (48)     | 4 (15)                    | 59 (43)             | 0.008 |
| Hypertension, n (%)      | 129 (79)     | 19 (73)                   | 110 (80)            | 0.449 |
| Hypercholesterolemia, n (%) | 77 (47)     | 13 (50)                   | 64 (46)             | 0.734 |
| Diabetes, n (%)          | 65 (40)      | 9 (35)                    | 56 (41)             | 0.688 |
| Renal insufficiency, n (%) | 79 (48)     | 13 (50)                   | 66 (48)             | 0.839 |
| Known myocardial ischemia history, n (%) | 58 (36)     | 11 (42)                   | 47 (34)             | 0.420 |
| Valve diseases           | 37 (23)      | 6 (23)                    | 31 (23)             | 0.945 |
| Premature supraventricular complexes, n (%) | 18 (11)     | 3 (12)                    | 15 (11)             | 0.920 |
| Premature ventricular complexes, n (%) | 33 (20)     | 9 (35)                    | 24 (17)             | 0.944 |
| Permanent atrial fibrillation, n (%) | 51 (31)     | 8 (31)                    | 43 (31)             | 0.969 |
| Left bundle branch block, n (%) | 35 (21)     | 4 (15)                    | 31 (23)             | 0.419 |
| Right bundle branch block, n (%) | 28 (17)    | 8 (31)                    | 20 (15)             | 0.043 |
| Pacemaker-ICD, n (%)     | 36 (22)      | 4 (15)                    | 32 (23)             | 0.378 |
| β-blockers, n (%)        | 105 (65)     | 16 (62)                   | 90 (65)             | 0.719 |
| Furosemide, n (%)        | 124 (76)     | 22 (85)                   | 102 (74)            | 0.244 |
| ACE/Sartans              | 69 (42)      | 5 (19)                    | 64 (46)             | 0.010 |
| Aldosterone antagonists, n (%) | 20 (12)    | 2 (8)                     | 18 (13)             | 0.444 |
| Potassium, n (%)         | 8 (5)        | 0 (0)                     | 8 (6)               | 0.208 |
| Nitrites, n (%)          | 24 (15)      | 3 (12)                    | 21 (15)             | 0.626 |
| Ibradivine, n (%)        | 5 (3)        | 1 (4)                     | 4 (3)               | 0.797 |
| Digoxin, n (%)           | 7 (4)        | 0 (0)                     | 7 (5)               | 0.241 |
| Statins, n (%)           | 49 (30)      | 5 (19)                    | 44 (32)             | 0.196 |
| Antiplatelet drugs, n (%) | 67 (41)     | 9 (35)                    | 58 (42)             | 0.481 |
| Oral anti-coagulants, n (%) | 41 (25)    | 6 (23)                    | 35 (25)             | 0.805 |
| Diltiazem or verapamil, n (%) | 6 (4)       | 0 (0)                     | 6 (4)               | 0.279 |
| Dihydropyridine calcium channel blockers, n (%) | 23 (14)     | 3 (12)                    | 20 (16)             | 0.691 |
| Propafenone, n (%)       | 2 (1)        | 0 (0)                     | 2 (1)               | 0.537 |
| Amiodarone, n (%)        | 16 (10)      | 3 (12)                    | 13 (9)              | 0.738 |
| Ranolazine, n (%)        | 6 (4)        | 0 (0)                     | 6 (4)               | 0.279 |
| Valsartan/sacubitril, n (%) | 2 (1)       | 0 (0)                     | 2 (1)               | 0.537 |
| Insulin, n (%)           | 22 (14)      | 4 (16)                    | 18 (14)             | 0.801 |
| Metformin, n (%)         | 11 (7)       | 0 (0)                     | 11 (8)              | 0.136 |
| Other anti-diabetic drugs, n (%) | 3 (2)       | 0 (0)                     | 3 (2)               | 0.448 |

Data are expressed as mean ± SD, or median (interquartile range), or number of patients (%).

ACE, angiotensin converting enzyme; CHF, chronic heart failure.

Bold indicates statistical significance P < 0.05.
Univariable Cox regression analysis reported a significant relationship between that 30-day total mortality and age (hazard ratio, 1.07; 95% confidence interval, 1.01–1.12; P < 0.05), SBP (hazard ratio, 0.97; 95% confidence interval, 0.95–0.99; P < 0.01), DBP (hazard ratio, 0.96; 95% confidence interval, 0.92–1.00; P < 0.05), PaO2/FIO2 ratio (hazard ratio, 1.00; 95% confidence interval; 0.99–1.00; P < 0.05), A-aDO2 (hazard ratio, 1.00; 95% confidence interval, 1.00–1.00; P < 0.05), NT-proBNP (hazard ratio, 1.00; 95% confidence interval, 1.00–1.00; P < 0.01), troponin (hazard ratio, 1.00; 95% confidence interval, 1.00–1.00; P < 0.05), fasting glucose (hazard ratio, 1.58; 95% confidence interval, 1.19–2.10; P < 0.05), QTSD (hazard ratio, 1.17; 95% confidence interval, 1.01–1.36; P < 0.05), Te mean (hazard ratio, 1.03; 95% confidence interval, 1.01–1.05; P < 0.01) and TeSD (hazard ratio, 1.12; 95% confidence interval, 1.01–1.024; P < 0.05). Multivariable regression analysis confirmed a positive significant association between 30-day mortality and fasting glucose (P < 0.01), QTSD (P < 0.05) and Te mean (P < 0.01) (Fig. 1). In addition, the univariable Cox regression analysis showed the following variables significantly associated with cardiovascular mortality: SBP (hazard ratio, 0.94; 95% confidence interval, 0.91–0.98; P < 0.01), DBP (hazard ratio, 0.92; 95% confidence interval, 0.86–0.99; P < 0.05), LVEF (hazard ratio, 0.93; 95% confidence interval, 0.88–0.98; P < 0.05), NT-proBNP (hazard ratio, 1.00; 95% confidence interval, 1.00–1.00; P < 0.01), troponin (hazard ratio, 1.00; 95% confidence interval, 1.00–1.00; P < 0.01), potassium (hazard ratio, 2.71; 95% confidence interval, 1.01–7.24; P < 0.05) fasting glucose (hazard ratio, 1.58; 95% confidence interval, 1.19–2.10; P < 0.05), QTSD (hazard ratio, 1.84; 95% confidence interval, 1.12–3.02; P < 0.05), Te mean (hazard ratio, 1.07; 95% confidence interval, 1.02–1.11; P < 0.01) and TeSD (hazard ratio, 1.16; 95% confidence interval, 1.01–1.34; P < 0.05). Multivariable regression analysis confirmed a positive significant association between 30-day mortality and fasting glucose (P < 0.05) and Te mean (P < 0.01) (Fig. 1).

### Table 2 Short-period repolarization temporal dispersion variables in study patients

| ECG characteristics | All N = 164 | Deceased subjects N = 26 | Survivors N = 138 | P |
|---------------------|-------------|--------------------------|------------------|---|
| QT mean, ms         | 447 ± 76    | 458 ± 84                 | 445 ± 74         | 0.434 |
| QTSD, ms²           | 6.6 (5.4)   | 8.6 (3.9)                | 5.9 (5.2)        | 0.006 |
| QTVN                | 0.24 (0.32) | 0.33 (0.26)              | 0.26 (0.33)      | 0.015 |
| Te mean, ms         | 107 ± 26    | 119 ± 33                 | 104 ± 24         | 0.009 |
| Te², ms²            | 7.2 (4.2)   | 8.7 (2.9)                | 6.8 (4.3)        | 0.009 |
| TeVN                | 4.2 (5.6)   | 6.4 (7.3)                | 4.1 (7.3)        | 0.210 |

Data are expressed as mean ± SD, or median (interquartile range), or number of patients (%).

QT, QT interval; QTVN, variance normalized for mean of QT; Te, Tend. Bold indicates statistical significance P < 0.05.

Fig. 1

**Multivariable Analysis**

| Variable     | Hazard Ratio (95% CI) | P Value |
|--------------|-----------------------|---------|
| Te mean      | 1.03 (1.01–1.05)      | 0.002   |
| QTSD         | 1.17 (1.01–1.36)      | 0.042   |
| Fasting Glucose | 1.58 (1.19–2.10)      | 0.006   |

Hazard ratio for Te mean, QTSD, and fasting glucose in respect to total and cardiovascular mortality in multivariable analysis. QT, QT interval; Te, Tend.
The Kaplan–Maier survival curves indicated that the subjects with fasting glucose ≥7 mmol/l \( (P < 0.05) \) or Te ≥ 116 ms \( (P < 0.05) \) reported a significantly higher total or cardiovascular mortality in comparison to the subjects, respectively, with fasting glucose level < 7 mmol/l or Te < 116 ms (Fig. 2a and b). The double combination with Te ≥ 116 ms and fasting glucose ≥ 7 mmol/l \( (P < 0.01) \) or Te ≥ 116 ms and HBA1c ≥ 6.5% \( (P < 0.05) \) individuated subjects with higher risk for total or cardiovascular mortality (Fig. 3a and b).

**Discussion**

In the present study, we observed an increase of 30-day mortality risk in decompensated CHF patients with higher fasting glucose plasma levels and prolonged Te duration. In particular, the association of these two variables resulted in the best predictive factors capable to identify these critical patients with higher risk of total and cardiovascular mortality. In fact, although age, creatinine clearance, blood pressure and NT-proBNP (Table 1) were significantly different in 30-day deceased CHF subjects, these variables were not able to indicate an increase of total or cardiovascular mortality risk in multivariable regression analysis. For these reasons, we believe that elevated fasting glucose level and an increase of Te mean could be also considered a simple noninvasive marker of short-period mortality in acutely decompensated patients. In previous studies, both fasting glucose [16] and Te mean [4-6] were significantly associated with short-period mortality in this kind of CHF subjects; the novelty of the present study was the evidence that these two studied variables mutually increased their predictive power. Whereas we do not know if these two variables are merely mortality risk markers or if they even have a causal role, however, the link between these two variables should be sought in the combination of frequent diabetes complications and pathophysiological CHF derangement. In fact, it is possible to hypothesize that the abnormal Te duration could be caused by a combination of myocardial diabetic [17] and CHF pathophysiological alterations (autonomic nervous system imbalance). In particular, as a consequence of T2DM, micro- and macroangiopathies, autonomic neuropathy, myocardial hypertrophy and fibrosis are observable, and on the other hand...
hand, the typical CHF induced dysregulation as the neurohormonal activation and proinflammatory state [18]. Finally, elevated glucose blood levels could be considered a dynamic marker of the sympathetic hyperactivity [18] and higher levels of sympathetic activity are associated with a higher mortality risk [19].

However, it is well known that diabetes induces an increase of cardiomyocyte action potential duration and QT interval in surface ECG [20,21]. In particular, about 20 years ago, in National Heart and Nutritional Examination Survey III, it was reported an increase of subjects with acquired long QT in T2DM patients [22] and, subsequently, it was published that, in NANES III study, the cardiovascular and total mortality rate were higher in acquired long QT than in normal subjects [22]. Finally, it was reported that in T1DM and T2DM the channels mediating sodium, potassium and calcium currents were altered [23]. All these diabetes-related changes and myocardial CHF substrate contributed together to prolong and disperse the repolarization and its short-period markers (Table 2).

Although the electrophysiologic basis of Te remains controversial [24], some authors believe that the Te is a noninvasive marker of transmural repolarization dispersion [25]. In particular, the II ECG lead recordings, the same used in our study, could represent a marker of apicobasal and interventricular repolarization myocardial dispersion rather than transmural [24]. However, whatever the genesis of this parameter could be, Te remains a powerful predictive marker of total and cardiovascular mortality [4–8] and not a mere marker of sudden cardiac death.

Another important element to consider is that HbA1c was not significantly different between the studied groups,
giving to the acute fasting glucose imbalance a stronger significance, suggesting that the modifications that occur in acutely decompensated patients are more important as mortality predictors than the T2DM itself.

Therefore, the 5-min single-lead ECG recording, evaluating the markers of left ventricular repolarization, which results altered in diabetic population, added an extra independent prediction to the outcome of this category of patients suffering from HF. This element is of particular interest considering that the evaluation of these ECG parameters can take place remotely and can be consulted by any operator connected with a simple device (e.g., smartphone), providing the proofs of the clinical severity and the possibility to remotely correct the therapy.

In conclusion, our data seem to indicate that two simple, routine, noninvasive, inexpensive, easily repeatable parameters, as fasting glucose and Tc mean, are able to improve the stratification for death risk in acute decompensate CHF patients.

Limitations
An actual limitation of the study is the absence of patients treated with SGLT2 inhibitors. The sample was, in fact, studied before the recent indications provided by the European Society of Cardiology guidelines on the use in class I evidence A of these drugs in subjects with HF and diabetes [26]. Further enrollment will help fill this gap. Moreover, an interventional study could definitively assess the power and utility of these evidences.

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Part of the same database analyzed in this paper has been already studied in two previous published papers, from different point of view [5,6]. ClinicalTrials.gov number, NCT04127162.

Conflicts of interest
There are no conflicts of interest.

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