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# Biomarkers for the prediction of heart failure and cardiovascular events in patients with type 2 diabetes: a position statement from the Heart Failure Association of the European Society of Cardiology

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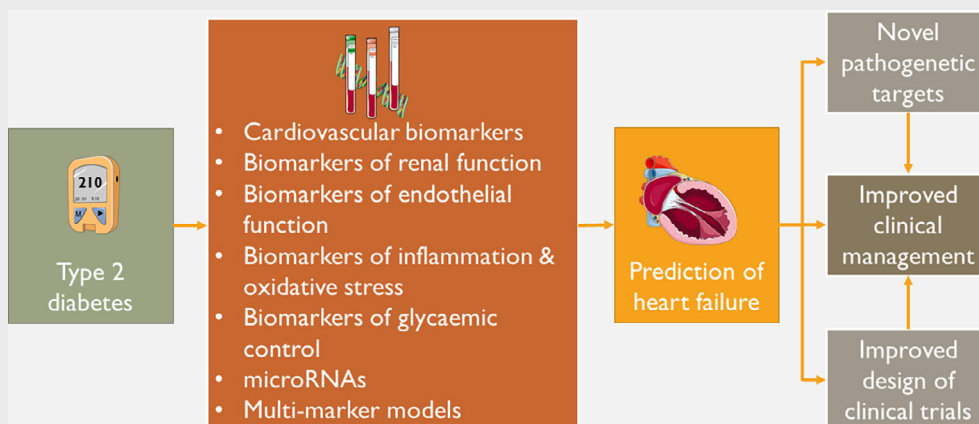
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Knowledge on risk predictors of incident heart failure (HF) in patients with type 2 diabetes (T2D) is crucial given the frequent coexistence of the two conditions and the fact that T2D doubles the risk of incident HF. In addition, HF is increasingly being recognized as an important endpoint in trials in T2D. On the other hand, the diagnostic and prognostic performance of established cardiovascular biomarkers may be modified by the presence of T2D. The present position paper, derived by an expert panel workshop organized by the Heart Failure Association of the European Society of Cardiology, summarizes the current knowledge and gaps in evidence regarding the use of a series of different biomarkers, reflecting various pathogenic pathways, for the prediction of incident HF and cardiovascular events in patients with T2D and in those with established HF and T2D.

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## Graphical Abstract



The identification of biomarkers for the accurate prediction of incident heart failure and cardiovascular events in patients with type 2 diabetes may enhance patient management and at the same time inform clinical trials and indicate novel pathogenetic and therapeutic targets that may further improve clinical practice.

## Keywords

Diabetes mellitus • Heart failure • Biomarkers • Cardiovascular risk • Cardiovascular prevention

## Introduction

Heart failure (HF) and type 2 diabetes (T2D) often coexist, while the presence of one increases the incidence and clinical event rates of the other.<sup>1,2</sup> This association partly reflects the common risk factors and pathogenetic mechanisms shared between the two conditions. According to the regulatory guidance issued by the US Food and Drug Administration in 2008, large outcome trials of glucose-lowering drugs needed to include cardiovascular (CV) death, non-fatal myocardial infarction and non-fatal stroke as safety endpoints<sup>3</sup>; HF was not initially included as a mandatory endpoint in these trials. Nevertheless, HF is increasingly becoming recognized as an important endpoint in glucose-lowering drug trials in patients with T2D, following the impressive outcomes of studies on sodium–glucose cotransporter 2 inhibitors (SGLT2i). These trials showed a consistent and substantial reduction of HF hospitalization in patients with T2D and either CV risk factors or established CV disease, a finding that has already led to the successful repurposing of some of these agents as HF drugs.<sup>4</sup> Evidence, however, on established and validated risk markers for incident HF in T2D, required to inform the design of clinical trials, is limited. The identification of biomarkers for the accurate prediction of incident HF and CV events in patients with T2D may thus inform clinical trials in T2D but also enhance patients' management and potentially indicate novel pathogenetic and therapeutic targets (*Graphical Abstract*). On the other hand, T2D is known to worsen prognosis in patients with acute or chronic HF, across the left ventricular ejection fraction spectrum, increasing

mortality and hospitalization rates.<sup>5–7</sup> The performance, however, of established biomarkers for the prediction of CV risk in patients with established HF may be modified by the coexistence of T2D.

The present position paper was the subject of an expert panel workshop, organized by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), with the aim to delineate the role of biomarkers for the prediction of incident HF and CV events in patients with T2D, as well as for the prediction of CV outcomes in patients with established HF and T2D. This document aims at (i) summarizing the existing evidence on biomarkers for the prediction of incident HF in T2D and of CV events in T2D with and without HF to inform clinical practice and the design of future trials; (ii) reporting the main findings of a relevant HFA survey; and (iii) identifying open issues to stimulate further research in the broader field of CV disease and T2D.

## Incidence of heart failure in diabetes

Large cohort studies and meta-analyses have shown that the presence of either T2D or HF doubles the incidence of the other. In a meta-analysis of 30 population-based studies, the pooled risk ratio (RR) for incident HF was 2.06 (95% confidence interval [CI] 1.73–2.46).<sup>8</sup> Similarly, in a more recent meta-analysis of 74 studies, the pooled RR for new-onset HF was 2.14 (1.96–2.34) and that concerned both HF with preserved ejection fraction (HFpEF; RR 2.22 [2.02–2.43]) and HF with reduced ejection fraction (HFrEF;

RR 2.73 [2.71–2.75].<sup>9</sup> In a cohort of 7953 individuals free of baseline HF and diabetes mellitus (DM), the incidence of HF over 11 years in participants who had first developed T2D was 8.5% versus 3.8% in those without T2D ( $p < 0.001$ ); the mean duration of HF onset after T2D was  $3.8 \pm 2.5$  years.<sup>10</sup> Conversely, the 11-year incidence of T2D in participants who had first developed HF was 11.8% versus 5.4% in those without HF ( $p < 0.001$ ), with a mean duration of T2D onset after HF of  $2.4 \pm 1.8$  years,<sup>10</sup> confirming the reciprocal relationship between the two conditions. Accordingly, in a nationwide cohort study of 104 522 HF patients, the annual incidence of new-onset diabetes following the first HF hospitalization was approximately 2%, rising to 3% after 5 years of follow-up.<sup>11</sup>

There seems to be a gradual increase in the risk of HF with increasing hyperglycaemia as expressed by blood glucose or glycated haemoglobin (HbA1c) levels. The risk of HF increases by 25% per each 20 mg/dl increase in blood glucose and by 8% per each 1% increase in HbA1c.<sup>8,12</sup> There is also evidence of an increased risk for HF in individuals with pre-diabetes.<sup>8,13</sup>

## Performance of biomarkers for predicting incident heart failure and cardiovascular events in patients with diabetes

### Cardiovascular biomarkers

In view of the above evidence, screening for HF would be particularly relevant in patients with T2D.<sup>14</sup> Natriuretic peptides and specifically B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are the established biomarkers for the diagnosis of HF.<sup>15</sup> The value of natriuretic peptides as screening tools for HF has been evaluated in patients with DM. In the STOP-HF trial on 1368 asymptomatic individuals with CV risk factors, BNP screening, measured by a point-of-care assay, was able to detect stage B pre-HF both in patients with and without DM, with similar diagnostic accuracy (area under the curve 0.75 [0.71–0.78] in T2D vs. 0.77 [0.72–0.82] in non-diabetics).<sup>16</sup> Patients with T2D required only a slightly lower BNP threshold for the same level of accuracy compared to those without DM. Thus, to achieve ~80% sensitivity with ~60% specificity, the cut-off for diabetics was 5 pg/ml lower than that in non-diabetics (20 pg/ml vs. 25 pg/ml).

Given the increased CV and HF risk of patients with diabetes, there is a need to evaluate the performance of established biomarkers of CV risk in these patients. In this context, in a secondary analysis of the EXAMINE trial, on 5380 patients with T2D recovering from an acute coronary syndrome, who were randomized to alogliptin or placebo, of whom 28% also had baseline HF, a number of biomarkers were evaluated as to their predictive value, including NT-proBNP, high-sensitivity troponin I, adiponectin, growth differentiation factor-15 (GDF-15), and galectin-3.<sup>17</sup> Among these biomarkers, NT-proBNP was the strongest predictor of the composite primary endpoint of CV death, HF hospitalization, subsequent NT-proBNP elevation or loop diuretics initiation during a median follow-up of 18 months. Similarly, in another study

of 3098 patients with DM, although several biomarkers, including NT-proBNP, high-sensitivity troponin T (hs-TnT), high-sensitivity C-reactive protein (hs-CRP) and interleukin-6, were associated with an increased risk for incident HF over 5 years after adjustment for major risk factors, only NT-proBNP allowed a meaningful improvement of HF prediction (greater improvement in discrimination and reclassification) when added to a model of conventional risk factors.<sup>18</sup> A one-standard deviation increase in NT-proBNP was associated with a three-fold higher risk of incident HF.

The predictive value of the more recently introduced marker of myocardial stress, mid-regional pro-A-type natriuretic peptide (MR-proANP) has also been evaluated in T2D. In a study on 806 patients with T2D, 18% of whom also had HFpEF and 2% HFrEF, a low plasma level of MR-proANP (<60 pmol/L) ruled out successfully HFrEF with a negative predictive value of 99.7%.<sup>19</sup> MR-proANP also predicted the incidence of CV events, including CV death or HF hospitalization, myocardial infarction, coronary revascularization, cardiac arrest, cerebrovascular disease and peripheral artery disease.<sup>20</sup> Patients with elevated MR-proANP ( $\geq 60$  pmol/L) and a history of HF had the highest incidence of CV events, compared to those with HF and low MR-proANP or those without HF, and thus MR-proANP had an additive value in predicting outcomes in patients with T2D.

More evidence on the prognostic value of cardiac biomarkers in patients with diabetes has been provided by CV outcome trials of antidiabetic agents in patients with T2D and a history or increased risk of CV disease. In the DECLARE-TIMI 58 trial on dapagliflozin or placebo, higher baseline levels of NT-proBNP and hs-TnT were associated with greater risk of CV death and hospitalization for HF, as well as greater absolute risk reduction with dapagliflozin.<sup>21</sup> In the SAVOR-TIMI 53 trial on saxagliptin or placebo, the risk of hospitalization for HF associated with saxagliptin was even greater in patients with higher NT-proBNP levels.<sup>22</sup>

### Renal biomarkers

Renal dysfunction and chronic kidney disease represent key complications of T2D and a common comorbidity in T2D and HF. In an analysis of the previously mentioned EXAMINE trial of 5380 patients with T2D and a recent acute coronary syndrome, a series of renal biomarkers including serum cystatin C, urine neutrophil gelatinase-associated lipocalin (NGAL), urine kidney injury molecule-1 protein (KIM-1) and urinary protein excretion, were all significantly associated with the composite endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke over 18 months, independently of baseline estimated glomerular filtration rate (eGFR). However, only cystatin C remained significantly associated with CV events in the multivariate analysis, including the composite endpoint, all-cause death and HF hospitalization.<sup>23</sup> In contrast, in a small study on 119 patients with T2D without evidence of CV disease, NGAL was independently associated with CV death or incident CV disease (coronary heart disease, stroke, or peripheral artery disease) over a period of 9 years,<sup>24</sup> while in another trial on 91 elderly patients with DM, urinary KIM-1/creatinine ratio was independently associated with CV

death, but this was not the case for urinary NGAL/creatinine ratio or urinary cystatin C/creatinine ratio.<sup>25</sup>

## Biomarkers of endothelial function

Endothelial dysfunction is a key mechanism of CV involvement in T2D and a common denominator in the pathophysiology of T2D and HF, especially HFpEF, resulting from shared risk factors and CV and non-CV comorbidities.<sup>26</sup> In addition, markers of endothelial dysfunction have been shown to predict future development of HF in the general population.<sup>27</sup> In a study on 119 patients with T2D without known CV disease, functional markers of endothelial function, such as increased pulse wave velocity (>10 m/s) and decreased flow-mediated dilatation ( $\leq 2.2\%$ ) were independently associated with CV events including CV death, coronary heart disease, stroke or peripheral artery disease over 9 years.<sup>24</sup> In terms of circulating biomarkers of endothelial function, another study on 128 patients with T2D showed that vascular cell adhesion molecule-1 and vascular endothelial growth factor (VEGF) were independently associated with CV risk as estimated by the Framingham risk score and the UKPDS calculators.<sup>28</sup> Soluble E-selectin and factor XIIa were further independently associated with the 10-year risk of coronary heart disease or any CV disease, including HF, in another analysis on 86 patients with T2D.<sup>29</sup>

## Biomarkers of inflammation and oxidative stress

Inflammation and oxidative stress are believed to play a key role in the pathogenesis of HF and CV involvement in patients with diabetes. In a multicentre study on 936 patients with DM, a series of biomarkers of inflammation (interleukin-6, chemokine ligand 3, pentraxin-3, and hs-CRP) along with indices of endothelial dysfunction (hepatocyte growth factor and VEGF-A) were associated with incident CV events of atherosclerotic origin, without including HF and only in patients with coexistent CV disease and not in those without.<sup>30</sup>

Regarding oxidative stress, in a prospective cohort study consecutively on 1468 patients with T2D, a series of oxidative biomarkers failed to predict incident CV events including CV death, non-fatal myocardial infarction or non-fatal stroke over a median period of 64 months or provide incremental prognostic value on top of a conventional risk prediction model.<sup>31</sup> The tested biomarkers included advanced oxidation protein products, oxidative haemolysis inhibition assay, ischaemia-modified albumin, total reductive capacity of plasma, fluorescent advanced glycation end-products and carbonyls.

## Biomarkers of glycaemic control

Poor glycaemic control with elevated levels of HbA1c has been associated with increased risk for HF, although studies targeting tight glycaemic control have generally failed to improve CV outcomes in patients with T2D.<sup>32,33</sup> Notwithstanding, these latter trials did not use the more recent drugs that are now used, while the number of hypoglycaemic events was quite high, which may have

had an impact on outcomes, as discussed below.<sup>34</sup> In the ARIC study on 11 057 participants without T2D or HF at baseline, higher HbA1c was an independent predictor of incident HF, with a baseline HbA1c level of 6.0–6.4% being associated with a 40% higher risk of HF compared to a HbA1c of 5.0–5.4%.<sup>35</sup> Similar results were obtained in the same study when evaluating 1827 participants with T2D but without HF at baseline; HbA1c was also an independent predictor of incident HF, with 20% higher risk of HF per 1% increase in HbA1c.<sup>36</sup> Similarly, in a retrospective study of 4723 patients with T2D and HF, a HbA1c  $\geq 9.0\%$  was associated with a 13% higher risk of all cause death and a 33% higher risk of HF hospitalization compared to HbA1c of 8.0–8.9%.<sup>37</sup>

Glycaemic markers in the range of pre-diabetes may carry an increased risk for future development of HF, even without progression to diabetes. In a study on 336 709 individuals without CV disease or type 1 diabetes in the UK Biobank, followed over a median period of 11 years, individuals with pre-diabetes developed at least one of the incident outcomes including atherosclerotic CV disease, HF or chronic kidney disease, with only 12% of these patients having developed T2D prior to the diagnosis of CV or renal disease.<sup>13</sup> The adjusted hazard ratios for HF were 1.07 (1.01–1.14) for patients with baseline pre-diabetes and 1.25 (1.14–1.37) for those with baseline diabetes. The risk for HF increased significantly with a baseline HbA1c of 7.0% and higher. Increased levels of HbA1c have also been associated with an increased risk of HF hospitalization and CV death in patients with T2D and a recent acute coronary syndrome in the ELIXA trial, independently of left ventricular ejection fraction.<sup>38</sup>

Variability of glycaemic control has further been associated with CV outcomes in patients with diabetes, and greater variability both in the short and in the long term is associated with a higher risk of adverse outcomes including CV events. In a prospective study of 8439 patients with HF, long-term HbA1c variability, expressed as the standard deviation of serial measurements, was associated both with incident CV disease, including HF, and chronic kidney disease over a follow-up of 7 years, independently of mean HbA1c or other confounders.<sup>39</sup> In another prospective study of 902 patients with T2D and HF, HbA1c was measured at least three times over a period of 18 months and patients were subsequently followed for 42 months.<sup>40</sup> During follow-up, 60% of patients experienced all-cause death or HF hospitalization. HbA1c variability, expressed as either the standard deviation of serial measurements or as the coefficient of variation, was an independent predictor of the composite endpoint, regardless of HF phenotype (HFpEF, HF with mildly reduced ejection fraction [HFmrEF] or HFpEF), in multivariate models that also included BNP. Severe hypoglycaemia has also been associated with an increased risk of incident HF in the ACCORD trial.<sup>34</sup> Accordingly, a U-shaped relationship between HbA1c levels and both HF hospitalization and non-HF CV events in patients with T2D and established atherosclerotic disease in the TECOS trial, with a nadir around a HbA1c of 7%.<sup>41</sup>

Besides biomarkers of glycaemia, surrogates of poor glycaemic control, have further been associated with an increased risk of incident HF. Albuminuria has been independently associated with left ventricular systolic and diastolic dysfunction, and diabetic retinopathy with a two-fold higher adjusted risk of incident HF.<sup>42,43</sup>

## Novel and alternative biomarkers

A more recently introduced biomarker of myocardial stress that has been evaluated in patients with T2D is mid-regional pro-adrenomedullin (MR-proADM), a surrogate of adrenomedullin, a peptide inducing vasodilatation and natriuresis. The prognostic value of MR-proADM was compared with that of NT-proBNP in 1438 patients with T2D.<sup>44</sup> Both biomarkers were significantly associated with incident HF hospitalization in multivariate analysis. However, MR-proADM had an additive prognostic value on top of clinical risk factors but not when added to a model containing NT-proBNP. Thus, MR-proADM did not seem to contribute supplementary information for HF prediction beyond NT-proBNP.

A study on 169 patients with T2D evaluated the prognostic value of a series of alternative biomarkers including asymmetric dimethylarginine, a marker of endothelial dysfunction, endothelin-1, an inflammatory marker and placental growth factor, another vascular index, along with NT-proBNP.<sup>45</sup> Among these biomarkers, only NT-proBNP was significantly correlated with the risk of coronary artery or cerebrovascular disease and the CV risk predicted by calculators such as the ADVANCE, the UKPDS 2.0 and the Framingham risk score.

The role of microRNAs (miRNAs) that are small, non-coding RNA holding key roles in several processes affecting cell survival, differentiation, proliferation and function, have further been proposed as potential markers of CV risk in T2D.<sup>46</sup> A series of different miRNAs has been associated with the microvascular complications of the disease, namely retinopathy, nephropathy and neuropathy. Specific circulating miRNAs have further been related with microvascular manifestations including coronary and peripheral artery disease. Among the implicated miRNAs, overexpression of miR-21 has been associated with HF in patients with T2D and inhibition of miR-21 is known to block cardiac and other forms of fibrosis.<sup>47,48</sup> In addition, the overexpression of miR-1 and miR-133a has been associated with myocardial steatosis, a hallmark of diabetic cardiomyopathy, and therefore may serve as potential markers for the early diagnosis of diabetic cardiomyopathy.<sup>49</sup> In pre-clinical studies, inhibition of miR-132 has been shown to reduce blood glucose and improve metabolic status.<sup>50</sup> Clinical translation to patients with chronic HF is currently under investigation and miR-132 inhibition provided beneficial cardiac effects in a phase 1b study.<sup>51</sup>

## Multi-marker models

In an analysis of 6799 participants with diabetes or pre-diabetes without baseline CV disease from three cohort studies (ARIC, DHS and MESA), investigators constructed a biomarker score with 1 point attributed for each of the following: NT-proBNP  $\geq 125$  pg/ml, hs-TnT  $\geq 6$  ng/L, hs-CRP  $\geq 3$  mg/L and left ventricular hypertrophy by electrocardiography.<sup>52</sup> This biomarker score successfully predicted the risk of incident HF, with a graded increase in 5-year risk with increasing score and the highest risk noted with scores of  $\geq 3$ . Another study on 1290 patients with T2D from two cohorts (SMART and EPIC-NL) evaluated a series of 23 biomarkers addressing different pathogenetic pathways in an

effort to improve CV risk prediction in T2D provided by traditional risk factors.<sup>53</sup> Among them, only NT-proBNP, osteopontin and matrix metalloproteinase-3 were the only biomarkers significantly associated with CV events, including HF, and were used to build a multi-marker model that improved significantly the predictive performance of traditional risk factors in both cohorts, although with a limited number of patients being reclassified to a different risk level.

Other multi-marker models incorporate widely available clinical parameters with or without the addition of laboratory measurements. The WATCH-DM risk score, incorporating a list of readily available clinical parameters, predicts accurately the 5-year risk of incident HF in a community-based population with dysglycaemia;<sup>54</sup> the addition of natriuretic peptides to the score parameters improved HF risk prediction more greatly in individuals with low or intermediate risk than in those with high risk.<sup>54</sup>

In another study on 581 patients with T2D, a screening tool incorporating simple clinical parameters concerning demographics, history, symptoms and signs, had a good discriminative value for detecting or excluding HF (C-statistic 0.82 [95% CI 0.79–0.86], negative predictive value 88%).<sup>55</sup> The addition of electrocardiogram or natriuretic peptides improved further its discriminatory value. Similarly, the TIMI risk score for HF in diabetes, derived from the SAVOR-TIMI 53 trial and validated using the DECLARE-TIMI 58 trial, combines clinical and laboratory parameters including previous history of HF, atrial fibrillation or coronary artery disease, an eGFR and albumin-to-creatinine ratio to predict the risk of hospitalization for HF.<sup>56</sup>

## Cardiovascular risk prediction and duration of diabetes

Given the evolving pathophysiology of CV injury in patients with DM, the prognostic value of biomarkers of CV risk may change dynamically in the course of the disease. For this reason, a prospective study on 746 patients with T2D, followed for 60 months, assessed the prognostic value of several biomarkers in relation to the duration of diabetes.<sup>57</sup> Indeed, the biomarkers that predicted significantly the primary endpoint of death or unplanned CV hospitalization, including HF hospitalization, changed according to the duration of T2D; hs-TnT and GDF-15 were predictive in patients with T2D lasting less than 7 years, NT-proBNP in those with T2D duration of 7–12 years, NT-proBNP and urinary albumin to creatinine ratio for duration of 12–22 years and only NT-proBNP for duration of more than 22 years.

## Performance of biomarkers for predicting cardiovascular events in patients with established heart failure and diabetes

### Chronic heart failure and diabetes

Evidence from the SwedeHF registry showed that NT-proBNP levels were generally higher in HF patients with T2D compared to those without T2D, particularly in patients with HF<sub>rEF</sub>

and HFmrEF.<sup>6</sup> A few studies have evaluated the performance of CV biomarkers in patients with HFrEF or HFpEF and coexisting T2D. In a study of 1069 ambulatory patients with HF, mostly HFrEF (mean ejection fraction  $34 \pm 13\%$ ), in whom 36% also had T2D, a series of biomarkers were analysed, including NT-proBNP, hs-TnT, galectin-3, hs-CRP, cystatin C, ST2, soluble transferrin receptor (sTfR) and neprilysin.<sup>58</sup> Although the levels of most of these biomarkers were higher in patients with T2D, after adjustment for age, sex, body mass index and eGFR, only NT-proBNP, hs-TnT and sTfR levels remained significantly higher in patients with T2D. All biomarkers were associated with an increased risk of all-cause and CV death in patients with and without T2D. However, in the multivariable analysis, only hs-TnT and ST2 were independently associated with all-cause and CV death in patients with both HF and T2D. In a secondary analysis of the PARADIGM-HF trial on 1907 patients with HFrEF, 40% of whom also had diabetes, TnT but not NT-proBNP was higher in patients with T2D than in those without.<sup>59</sup> TnT remained independently predictive of worse outcomes in multivariate analysis including NT-proBNP and the two biomarkers had an additive value for predicting adverse prognosis in these patients. In multivariable analyses, among patients with diabetes, those having a TnT level  $\geq 18$  ng/L and a NT-proBNP  $>1342$  pg/ml had a 4.5-fold higher risk of CV death or HF hospitalization than those with lower TnT and NT-proBNP values. The risk associated with the above values was 4.2-fold higher among patients without diabetes.<sup>59</sup>

In the TOPCAT trial, patients with HFpEF and diabetes had lower eGFR and higher levels of hs-CRP, pro-collagen type III amino-terminal peptide, tissue inhibitor of metalloproteinase-1 (TIMP-1), and galectin-3 than those with HFpEF but without diabetes.<sup>60</sup> In addition, these patients also exhibited larger longitudinal increases in the levels of hs-TnT over a 12-month period than those without DM. Elevated pro-collagen type III amino-terminal peptide and galectin-3 levels were associated with an increased risk of the primary composite endpoint of CV death, aborted cardiac arrest or HF hospitalization in patients with diabetes, but not in those without. Patients with T2D also showed a significantly greater reduction in hs-TnT and TIMP-1 under treatment with spironolactone than those without diabetes.

In a study of 366 patients with HF, the presence of T2D did not have an impact on the concentrations or the predictive value of MR-proADM.<sup>61</sup> The biomarker did not differ in patients with and without T2D and was associated with all-cause death and the composite of death or hospitalization irrespectively of the presence of T2D.

Finally, in a study of 195 patients with chronic HF and 116 controls, plasma levels of soluble E-selectin and von Willebrand factor were elevated in HF patients with T2D but not in those without T2D.<sup>62</sup> Increased levels of E-selectin were associated with ischaemic events in patients with T2D but not in those without. Whether the levels or the predictive value of other biomarkers of endothelial dysfunction are also impaired by the coexistence of T2D is not known.

## Acute heart failure and diabetes

Patients with acute HF and T2D may have a diverse biomarker profile than those with acute HF without diabetes. In a network analysis of 48 circulating biomarkers measured within 24 h of acute HF admission in 2033 patients in the context of the PROTECT trial, patients with acute HF and T2D differed from those with acute HF without T2D in biomarkers of cardiomyocyte stretch (BNP), renal function (NGAL, KIM-1), inflammation (tumour necrosis factor alpha receptor 1, periosteal) and angiogenesis (VEGF receptor 1, angiogenin).<sup>63</sup> In a study on 328 patients with acute HF, in contrast, BNP concentration, both on admission and at discharge, was similarly elevated in patients with T2D and pair-matched patients without T2D.<sup>64</sup> Despite any difference in biomarker profile among acute HF patients with and without diabetes, natriuretic peptides seemed to retain their performance in the presence of diabetes. In a study on 145 patients with both HF and diabetes, seen in the outpatient HF clinic after an acute episode of HF decompensation, BNP was independently associated with CV events at 6-month follow-up.<sup>65</sup> A value of 200 pg/ml had 88% sensitivity and 71% specificity, while a value of 500 pg/ml had 46% sensitivity and 89% specificity to predict CV events at 6 months.

## Heart Failure Association survey on heart failure biomarkers in diabetes

In association with the workshop which led to the development of this position paper, the HFA developed and presented a questionnaire to its members. The questions asked are as detailed in online supplementary *Appendix S1*. The survey explored the characteristics and performance of biomarkers for HF prediction and monitoring and in particular within a T2D population. There was a lack of knowledge of any biomarker specifically being of value in predicting new-onset HF within a T2D population. If a biomarker in the future could be proven to be reliable for the prediction of new-onset HF and/or HF hospitalizations within a T2D population, this was found to be of considerable interest to the survey respondents. If T2D patients shown to be at risk for HF by biomarkers are subsequently proven to benefit from effective HF preventive therapies such as SGLT2i, this was rated as of considerable interest.

## Conclusions, future needs and open issues

Overall, there is a limited number of studies on the performance of biomarkers for the prediction of HF in patients with T2D. More studies have investigated the role of biomarkers for the prognostication of general CV risk, but without referring particularly to HF. In addition, several studies provide data only for patients with diabetes and not comparative evidence versus non-diabetic patients. According to the available evidence, among cardiac biomarkers, it seems that natriuretic peptides maintain their diagnostic and

prognostic value for HF and CV events in patients with T2D, and they seem to outperform other candidate biomarkers for risk prediction in these patients. The established thresholds of natriuretic peptides seem to be rather adequate also for T2D patients, but the issue of cut-offs for these and other biomarkers warrants further investigation. More recently introduced biomarkers of myocardial stress, including MR-proANP and MR-proADM, also seem to perform well for HF prediction in T2D but their additive value on top of conventional natriuretic peptides remains questionable, particularly for MR-proADM, and further research in this regard is needed. Regarding biomarkers of glycaemia, HbA1c level and its longitudinal variability seem to predict incident HF and CV risk in patients with T2D or even pre-diabetes, perhaps with additive value on top of natriuretic peptides, an issue that requires further investigation. Whether the predictive value of Hb1Ac alters when a given patient progresses from pre-diabetes to uncomplicated or complicated diabetes is not known, but the duration of diabetes may modify the performance of biomarkers such as natriuretic peptides. Evidence on biomarkers of endothelial or renal function remains rather limited and inconclusive, while studies on markers of inflammation or oxidative stress have focused only on purely atherosclerotic CV events without reference to HF and have hitherto failed to provide proof of successful risk prediction. Among novel biomarkers, miRNAs are emerging as potential early diagnostic and predictive markers but also therapeutic targets and among other CV manifestation of T2D, they may help in the delineation and early identification of diabetic cardiomyopathy. Given the complex pathophysiology linking HF and T2D, a multi-marker approach that captures more than a single mechanism or pathway seems an attractive option and initial evidence is promising but requires further confirmation. It should also be taken into consideration that the value of biomarkers to predict HF events or CV risk in general may dynamically change over time, with NT-proBNP being probably more accurate for patients with long-lasting T2D according to a single study,<sup>57</sup> although these findings need to be further confirmed.

In patients with established HF, the coexistence of T2D may modify the diagnostic and prognostic performance of biomarkers and hitherto evidence in this issue also remains limited. In chronic HF with T2D, cardiac troponins seem to be useful markers for the prediction of CV risk and their potential additive value on top of natriuretic peptides needs to be studied further. In HFpEF with T2D, biomarkers of fibrosis such as pro-collagen type III amino-terminal peptide, galectin-3 and TIMP-1 may have an important role for the prediction of CV risk and of the response to antifibrotic therapies. Endothelial dysfunction is a common denominator in HF and T2D and biomarkers of endothelial dysfunction may have a role in these patients that need to be investigated. Finally, in acute HF with T2D small studies seem to confirm the value of natriuretic peptides in this setting, but more evidence is required.

The complex and multifactorial pathophysiology of CV involvement in T2D may often lead to conflicting evidence, as shown by studies reported herein. Therefore, more focus should be placed on larger, prospective and more extensively adjusted studies and

even more importantly on the confirmation of the hitherto findings by ongoing research.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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## References

- Seferović PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;**20**:853–72.
- Maack C, Lehrke M, Backs J, Heinzl FR, Hulot JS, Marx N, et al. Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. *Eur Heart J*. 2018;**39**:4243–54.
- Butler J, Packer M, Greene SJ, Fuzat M, Anker SD, Anstrom KJ, et al. Heart failure end points in cardiovascular outcome trials of sodium glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus: a critical evaluation of clinical and regulatory issues. *Circulation*. 2019;**140**:2108–18.
- Farmakis D, Butler J, Filippatos G. Sodium-glucose co-transporter 2 inhibitors: 'a tale of two sisters', diabetes and heart failure. *Eur J Heart Fail*. 2020;**22**:1259–62.
- Targher G, Dauriz M, Laroche C, Temporelli PL, Hassanein M, Seferovic PM, et al.; ESC-HFA HF Long-Term Registry Investigators. In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;**19**:54–65.
- Johansson I, Dahlström U, Edner M, Näsman P, Rydén L, Norhammar A. Type 2 diabetes and heart failure: characteristics and prognosis in preserved, mid-range and reduced ventricular function. *Diab Vasc Dis Res*. 2018;**15**:494–503.
- Varela-Roman A, Grigorian Shmagian L, Barge Caballero E, Mazon Ramos P, Rigueiro Veloso P, Gonzalez-Juanatey JR. Influence of diabetes on the survival of patients hospitalized with heart failure: a 12-year study. *Eur J Heart Fail*. 2005;**7**:859–64.
- Aune D, Schlesinger S, Neuenschwander M, Feng T, Janszky I, Norat T, et al. Diabetes mellitus, blood glucose and the risk of heart failure: a systematic review and meta-analysis of prospective studies. *Nutr Metab Cardiovasc Dis*. 2018;**28**:1081–91.
- Kodama S, Fujihara K, Horikawa C, Sato T, Iwanaga M, Yamada T, et al. Diabetes mellitus and risk of new-onset and recurrent heart failure: a systematic review and meta-analysis. *ESC Heart Fail*. 2020;**7**:2146–74.
- Suthahar N, Meijers WC, Brouwers FP, Heerspink HJL, Gansevoort RT, van der Harst P, et al. Heart failure and inflammation-related biomarkers as predictors of new-onset diabetes in the general population. *Int J Cardiol*. 2018;**250**:188–94.
- Zareini B, Rørth R, Holt A, Mogensen UM, Selmer C, Gislason G, et al. Heart failure and the prognostic impact and incidence of new-onset of diabetes mellitus: a nationwide cohort study. *Cardiovasc Diabetol*. 2019;**18**:79.
- Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;**321**:405–12.
- Honigberg MC, Zekavat SM, Pirruccello JP, Natarajan P, Vaduganathan M. Cardiovascular and kidney outcomes across the glyemic spectrum: insights from the UK Biobank. *J Am Coll Cardiol*. 2021;**78**:453–64.
- Lund LH, Hage C, Savarese G. Implementation science and potential for screening in heart failure. *Eur Heart J*. 2022;**43**:413–5.
- Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, et al.; Heart Failure Association of the European Society of Cardiology. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail*. 2019;**21**:715–31.
- Watson C, James S, O'Connell E, Gallagher J, O'Reilly J, Tallon E, et al. Influence of diabetes on natriuretic peptide thresholds in screening for Stage B heart failure. *Biomarkers*. 2016;**21**:538–43.
- Sharma A, Vaduganathan M, Ferreira JP, Liu Y, Bakris GL, Cannon CP, et al. Clinical and biomarker predictors of expanded heart failure outcomes in patients with type 2 diabetes mellitus after a recent acute coronary syndrome: insights from the EXAMINE trial. *J Am Heart Assoc*. 2020;**9**:e012797.
- Ohkuma T, Jun M, Woodward M, Zoungas S, Cooper ME, Grobbee DE, et al.; ADVANCE Collaborative Group. Cardiac stress and inflammatory markers as predictors of heart failure in patients with type 2 diabetes: the ADVANCE trial. *Diabetes Care*. 2017;**40**:1203–9.
- Jensen J, Schou M, Kistorp C, Faber J, Hansen TW, Jensen MT, et al. Prevalence of heart failure and the diagnostic value of MR-proANP in outpatients with type 2 diabetes. *Diabetes Obes Metab*. 2019;**21**:736–40.
- Jensen J, Schou M, Kistorp C, Faber J, Hansen TW, Jensen MT, et al. MR-proANP and incident cardiovascular disease in patients with type 2 diabetes with and without heart failure with preserved ejection fraction. *Cardiovasc Diabetol*. 2020;**19**:180.
- Zelniker TA, Morrow DA, Mosenzon O, Goodrich EL, Jarolim P, Murphy SA, et al. Relationship between baseline cardiac biomarkers and cardiovascular death or hospitalization for heart failure with and without sodium-glucose co-transporter 2 inhibitor therapy in DECLARE-TIMI 58. *Eur J Heart Fail*. 2021;**23**:1026–36.
- Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation*. 2014;**130**:1579–88.
- Vaduganathan M, White WB, Charytan DM, Morrow DA, Liu Y, Zannad F, et al.; EXAMINE Investigators. Relation of serum and urine renal biomarkers to cardiovascular risk in patients with type 2 diabetes mellitus and recent acute coronary syndromes (from the EXAMINE trial). *Am J Cardiol*. 2019;**123**:382–91.
- Naka KK, Papathanassiou K, Bechlioulis A, Pappas K, Tigas S, Makriyannis D, et al. Association of vascular indices with novel circulating biomarkers as prognostic factors for cardiovascular complications in patients with type 2 diabetes mellitus. *Clin Biochem*. 2018;**53**:31–7.
- Tonkonogi A, Carlsson AC, Helmersson-Karlqvist J, Larsson A, Årnlöv J. Associations between urinary kidney injury biomarkers and cardiovascular mortality risk in elderly men with diabetes. *Ups J Med Sci*. 2016;**121**:174–8.
- Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan RS, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J*. 2018;**39**:3439–50.
- Årnlöv J, Sang Y, Ballew SH, Vaidya D, Michos ED, Jacobs DR, et al. Endothelial dysfunction and the risk of heart failure in a community-based study: the Multi-Ethnic Study of Atherosclerosis. *ESC Heart Fail*. 2020;**7**:4231–40.
- Néri AK, da S Junior GB, Meneses GC, Mc Martins A, De F Daher E, da C Lino DO, et al. Cardiovascular risk assessment and association with novel biomarkers in patients with type 2 diabetes mellitus. *Biomark Med*. 2021;**15**:561–76.
- Natarajan A, Marshall SM, Kesteven PJ, McComb JM, Rutter MK. Impact of biomarkers for endothelial dysfunction and procoagulant state on 10-year cardiovascular risk in type 2 diabetes. *Diabet Med*. 2011;**28**:1201–5.
- Shore AC, Colhoun HM, Natali A, Palombo C, Khan F, Östling G, et al.; SUMMIT Consortium. Use of vascular assessments and novel biomarkers to predict cardiovascular events in type 2 diabetes: the SUMMIT VIP study. *Diabetes Care*. 2018;**41**:2212–9.
- Cournot M, Burillo E, Saulnier PJ, Planesse C, Gand E, Rehman M, et al. Circulating concentrations of redox biomarkers do not improve the prediction of adverse cardiovascular events in patients with type 2 diabetes mellitus. *J Am Heart Assoc*. 2018;**7**:e007397.
- Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;**360**:129–39.
- Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**:2545–59.
- Echouffo-Tcheugui JB, Kaze AD, Fonarow GC, Dagogo-Jack S. Severe hypoglycemia and incident heart failure among adults with type 2 diabetes. *J Clin Endocrinol Metab*. 2022;**107**:e955–62.
- Matsushita K, Blecker S, Pazin-Filho A, Bertoni A, Chang PP, Coresh J, et al. The association of hemoglobin a1c with incident heart failure among people without diabetes: the Atherosclerosis Risk in Communities study. *Diabetes*. 2010;**59**:2020–6.
- Pazin-Filho A, Kottgen A, Bertoni AG, Russell SD, Selvin E, Rosamond WD, et al. HbA 1c as a risk factor for heart failure in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia*. 2008;**51**:2197–204.
- Blecker S, Park H, Katz SD. Association of HbA1c with hospitalization and mortality among patients with heart failure and diabetes. *BMC Cardiovasc Disord*. 2016;**16**:99.
- Shin SH, Claggett B, Pfeffer MA, Skali H, Liu J, Aguilar D, et al.; ELIXA Investigators. Hyperglycaemia, ejection fraction and the risk of heart failure or cardiovascular death in patients with type 2 diabetes and a recent acute coronary syndrome. *Eur J Heart Fail*. 2020;**22**:1133–43.
- Luk AOY, Ma RCW, Lau ESH, Yang X, Lau WWY, Yu LWL, et al. Risk association of HbA1c variability with chronic kidney disease and cardiovascular disease in type 2 diabetes: prospective analysis of the Hong Kong Diabetes Registry. *Diabetes Metab Res Rev*. 2013;**29**:384–90.
- Gu J, Pan JA, Fan YQ, Zhang HL, Zhang JF, Wang CQ. Prognostic impact of HbA1c variability on long-term outcomes in patients with heart failure and type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2018;**17**:96.
- McAlister FA, Zheng Y, Westerhout CM, Buse JB, Standl E, McGuire DK, et al.; TECOS Study Group. Association between glycated haemoglobin levels and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease: a secondary analysis of the TECOS randomized clinical trial. *Eur J Heart Fail*. 2020;**22**:2026–34.

42. Liu JE, Robbins DC, Palmieri V, Bella JN, Roman MJ, Fabsitz R, et al. Association of albuminuria with systolic and diastolic left ventricular dysfunction in type 2 diabetes: the Strong Heart Study. *J Am Coll Cardiol.* 2003;**41**:2022–8.
43. Cheung N, Wang JJ, Rogers SL, Brancati F, Klein R, Sharrett AR, et al.; ARIC (Atherosclerosis Risk in Communities) Study Investigators. Diabetic retinopathy and risk of heart failure. *J Am Coll Cardiol.* 2008;**51**:1573–8.
44. Fraty M, Velho G, Gand E, Fumeron F, Ragot S, Sosner P, et al.; SURDIAGENE Study Group. Prognostic value of plasma MR-proADM vs NT-proBNP for heart failure in people with type 2 diabetes: the SURDIAGENE prospective study. *Diabetologia.* 2018;**61**:2643–53.
45. Markova A, Boyanov M, Bakalov D, Kundurdjiev A, Tsakova A. Cardiovascular biomarkers and calculated cardiovascular risk in orally treated type 2 diabetes patients: is there a link? *Horm Metab Res.* 2021;**53**:41–8.
46. Bielska A, Niemira M, Kretowski A. Recent highlights of research on miRNAs as early potential biomarkers for cardiovascular complications of type 2 diabetes mellitus. *Int J Mol Sci.* 2021;**22**:3153.
47. Al-Hayali MA, Sozer V, Durmus S, Erdenen F, Altunoglu E, Gelisgen R, et al. Clinical value of circulating microribonucleic acids miR-1 and miR-21 in evaluating the diagnosis of acute heart failure in asymptomatic type 2 diabetic patients. *Biomolecules.* 2019;**9**:193.
48. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, et al. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. *Nature.* 2008;**456**:980–4.
49. de Gonzalo-Calvo D, van der Meer RW, Rijzewijk LJ, Smit JWA, Revuelta-Lopez E, Nasarre L, et al. Serum microRNA-1 and microRNA-133a levels reflect myocardial steatosis in uncomplicated type 2 diabetes. *Sci Rep.* 2017;**7**:47.
50. Bijkerk R, Esguerra JLS, Ellenbroek JH, Au YW, Hanegraaf MAJ, de Koning EJ, et al. In vivo silencing of microRNA-132 reduces blood glucose and improves insulin secretion. *Nucleic Acid Ther.* 2019;**29**:67–72.
51. Täubel J, Hauke W, Rump S, Viereck J, Batkai S, Poetzsch J, et al. Novel antisense therapy targeting microRNA-132 in patients with heart failure: results of a first-in-human Phase 1b randomized, double-blind, placebo-controlled study. *Eur Heart J.* 2021;**42**:178–88.
52. Pandey A, Vaduganathan M, Patel KV, Ayers C, Ballantyne CM, Kosiborod MN, et al. Biomarker-based risk prediction of incident heart failure in pre-diabetes and diabetes. *JACC Heart Fail.* 2021;**9**:215–23.
53. van der Leeuw J, Beulens JWJ, van Dieren S, Schalkwijk CG, Glatz JFC, Hofker MH, et al. Novel biomarkers to improve the prediction of cardiovascular event risk in type 2 diabetes mellitus. *J Am Heart Assoc.* 2016;**5**:e003048.
54. Segar MW, Khan MS, Patel KV, Vaduganathan M, Kannan V, Willett D, et al. Incorporation of natriuretic peptides with clinical risk scores to predict heart failure among individuals with dysglycaemia. *Eur J Heart Fail.* 2022;**24**:169–80.
55. Boonman-de Winter LJM, Rutten FH, Cramer MJ, Landman MJ, Zuithoff NPA, Liem AH, et al. Efficiently screening heart failure in patients with type 2 diabetes. *Eur J Heart Fail.* 2015;**17**:187–95.
56. TIMI Study Group. TIMI Risk Score for HF in Diabetes. <https://timi.org/timi-risk-score-for-hf-in-diabetes/> (21 June 2022).
57. Resl M, Vila G, Heinzl M, Luger A, Neuhold S, Prager R, et al. Changes in the prognostic values of modern cardiovascular biomarkers in relation to duration of diabetes mellitus. *J Diabetes Complications.* 2021;**35**:107990.
58. Alonso N, Lupón J, Barallat J, de Antonio M, Domingo M, Zamora E, et al. Impact of diabetes on the predictive value of heart failure biomarkers. *Cardiovasc Diabetol.* 2016;**15**:151.
59. Rørth R, Jhund PS, Kristensen SL, Desai AS, Køber L, Rouleau JL, et al. The prognostic value of troponin T and N-terminal pro B-type natriuretic peptide, alone and in combination, in heart failure patients with and without diabetes. *Eur J Heart Fail.* 2019;**21**:40–9.
60. de Marco C, Claggett BL, de Denus S, Zile MR, Huynh T, Desai AS, et al. Impact of diabetes on serum biomarkers in heart failure with preserved ejection fraction: insights from the TOPCAT trial. *ESC Heart Fail.* 2021;**8**:1130–8.
61. Holmager P, Schou M, Egstrup M, Gustafsson I, Goetze JP, Gustafsson F, et al. The influence of diabetes mellitus on midregional proadrenomedullin concentrations and prognostic value in heart failure outpatients. *J Card Fail.* 2015;**21**:250–7.
62. Kistorp C, Chong AY, Gustafsson F, Galatius S, Raymond I, Faber J, et al. Biomarkers of endothelial dysfunction are elevated and related to prognosis in chronic heart failure patients with diabetes but not in those without diabetes. *Eur J Heart Fail.* 2008;**10**:380–7.
63. Sharma A, Demissei BG, Tromp J, Hillege HL, Cleland JG, O'Connor CM, et al. A network analysis to compare biomarker profiles in patients with and without diabetes mellitus in acute heart failure. *Eur J Heart Fail.* 2017;**19**:1310–20.
64. Cunha FM, Pereira J, Marques P, Moreira H, Rodrigues P, Pinto MJ, et al. Natriuretic peptide system activation in acute heart failure patients with diabetes. *J Diabetes Res.* 2017;**2017**:1426705.
65. Aspromonte N, Feola M, Milli M, Scardovi AB, Coletta C, Carbonieri E, et al. Prognostic role of B-type natriuretic peptide in patients with diabetes and acute decompensated heart failure. *Diabet Med.* 2007;**24**:124–30.