European Journal of Heart Failure (2018)
doi:10.1002/ejhf.1170

HFA POSITION PAPER

Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

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Received 5 December 2017; revised 23 January 2018; accepted 2 February 2018

The coexistence of type 2 diabetes mellitus (T2DM) and heart failure (HF), either with reduced (HFrEF) or preserved ejection fraction (HFpEF), is frequent (30–40% of patients) and associated with a higher risk of HF hospitalization, all-cause and cardiovascular (CV) mortality. The most important causes of HF in T2DM are coronary artery disease, arterial hypertension and a direct detrimental effect of T2DM on the myocardium. T2DM is often unrecognized in HF patients, and vice versa, which emphasizes the importance of an active search for both

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disorders in the clinical practice. There are no specific limitations to HF treatment in T2DM. Subanalyses of trials addressing HF treatment in the general population have shown that all HF therapies are similarly effective regardless of T2DM. Concerning T2DM treatment in HF patients, most guidelines currently recommend metformin as the first-line choice. Sulphonylureas and insulin have been the traditional second- and third-line therapies although their safety in HF is equivocal. Neither glucagon-like peptide-1 (GLP-1) receptor agonists, nor dipeptidyl peptidase-4 (DPP4) inhibitors reduce the risk for HF hospitalization. Indeed, a DPP4 inhibitor, saxagliptin, has been associated with a higher risk of HF hospitalization. Thiazolidinediones (pioglitazone and rosiglitazone) are contraindicated in patients with (or at risk of) HF. In recent trials, sodium–glucose co-transporter-2 (SGLT2) inhibitors, empagliflozin and canagliflozin, have both shown a significant reduction in HF hospitalization in patients with established CV disease or at risk of CV disease. Several ongoing trials should provide an insight into the effectiveness of SGLT2 inhibitors in patients with HFrEF and HFpEF in the absence of T2DM.

Keywords Heart failure • Type 2 diabetes mellitus • Heart failure hospitalization • Heart failure treatment • Glucose-lowering agents

Introduction

The coexistence of heart failure (HF) and type 2 diabetes mellitus (T2DM) is common and has a strong impact on clinical management and prognosis. T2DM is associated with worse clinical status and increased all-cause and cardiovascular (CV) mortality in both patients with HF with reduced (HFrEF) and preserved ejection fraction (HFpEF), compared to HF patients without T2DM.[1] Conversely, HFrEF is an independent predictor of fatal and non-fatal clinical outcomes in patients with T2DM.[2,3] The major causes of HF in T2DM include coronary artery disease (CAD) and hypertension, but also, a possible direct detrimental effect of T2DM on the myocardium.[4] This position paper provides advice and education pertinent to the clinical management of patients with T2DM and HF. The document summarizes the epidemiology and current understanding of the mechanisms underlying the intersection between T2DM and HF. It further presents contemporary treatment options for patients with established T2DM and HF, and summarizes recent evidence of HF prevention with drugs used to treat T2DM.

Epidemiology

Prevalence of type 2 diabetes mellitus and heart failure in general populations

The prevalence of T2DM, which encompasses 90–95% of diabetic individuals, has globally increased from 4.7% in 1980 to 8.5% in 2014,[5] albeit diagnostic criteria have changed over that period.[6,7] Contemporary data suggest a stable overall HF prevalence of 11.8% (range 4.7–13.3%) in the general population.[8]

Prevalence of heart failure in patients with type 2 diabetes mellitus

In the Reykjavik study in the general population, the prevalence of HF in people with T2DM was 12%.[9] In this study, HF was more common in patients with T2DM aged >70 years (i.e. 16% and 22% of men and women, respectively). In the Kaiser Permanente population, patients with T2DM aged <75 years had an approximately three-fold higher prevalence of HF compared to those without T2DM.[10] In those aged 75–84 years, T2DM was associated with a doubling of risk for HF. In these relatively old studies, HF phenotype (i.e. HFrEF or HFpEF) or biomarker status was not reported. In clinical trials of T2DM patients, the prevalence of HF at baseline has varied between approximately 10% and 30% (*Table 1*).[11–24]

Table 1 Prevalence of heart failure in selected trials of type 2 antidiabetic drugs

Trial	Prevalence of HF at baseline
Glucose-lowering trials	
UKPDS 33[11]	NR (severe concurrent illness excluded)
ADVANCE[12,13]	NR
ACCORD[14]	4.3%
VADT[15]	NR
DPP4 inhibitor trials	
SAVOR-TIMI 53[16,17]	13%
TECOS[18]	18%
EXAMINE[19]	28%
SGLT2 inhibitor trials	
EMPA-REG OUTCOME[20]	10%
CANVAS[21]	14–15%
GLP-1 receptor agonist trials	
LEADER[22]	14%
ELIXA[23]	22%
EXSCEL[24]	16%

DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HF, heart failure; NR, not reported; SGLT2, sodium–glucose co-transporter type 2.

Prevalence of type 2 diabetes mellitus in patients with heart failure

In the general population, HF is associated with a higher prevalence of T2DM compared to patients without HF (*Table 2*),[9,25–29] but

Table 2 Prevalence of type 2 diabetes mellitus in patients with heart failure in the general population

Study	Year of publication	Age (years)	Prevalence of T2DM in HF	Prevalence of T2DM without HF
England[25]	2001	>45	24%	3%
Rotterdam[26]	2001	55–94	18%	10%
Italy[27]	1997	>65	30%	13%
Reykjavik[9]	2005	33–84	12%	3%
Copenhagen[28]	2005	Mean 69	25%	NA
USA, Olmsted County[29]	2006	Mean 77	20%	NA

HF, heart failure; NA, not available (cohort of HF patients only); T2DM, type 2 diabetes mellitus.

marked regional differences have been observed both in Europe and in rest of the world. In studies conducted in Iceland[9] and Italy,[27] T2DM prevalence was four and three times higher, respectively, whereas in Italy, T2DM prevalence was almost doubled in HF subjects (*Table 2*). Approximately 25% of patients with HF in England[25] and Denmark[28] also had T2DM. Despite younger age and less obesity, a significantly higher prevalence of T2DM (57%) was observed in a population-based cohort of Southeast Asian HF patients compared to Caucasian patients (24%).[30] The reasons for the wide regional variation in T2DM prevalence in HF patients warrant further international studies with shared study design and standardized data collection.

In clinical trials of chronic HF patients, the prevalence of T2DM was around 30%, irrespective of HF phenotype (i.e. HFrEF and HFpEF) (*Table 3*).[31–48] The highest prevalence of T2DM was seen in trials of acute HF (around 40%).

In registries of hospitalized HF patients in North America and Europe, the prevalence of T2DM is around 40–45%,[49–52] and a slight increase in the prevalence was reported in North America over time.[49,52]. In the Swedish HF Registry (68% from hospitals and 32% from primary care), T2DM was more prevalent in HF patients with CAD compared to those without (30% vs. 19%).[53]

Table 3 Prevalence of type 2 diabetes mellitus in selected trials of heart failure

Trial	Prevalence of T2DM
Trials of HFrEF	
PARADIGM-HF[31]	35%
SHIFT[32]	30%
EchoCRT[33]	41%
HF-ACTION[34]	32%
SENIORS[35]	26%
SOLVD[36]	15%
MERIT-HF[37]	25%
CHARM-Added[38]	29%
DIG-REF[39]	28%
Trials of HFpEF	
I-Preserve[40]	27%
PEP-CHF[41]	21%
DIG-PEF[42]	29%
CHARM-Preserved[43]	28%
TOPCAT[44]	33%
Trials of acute HF	
EVEREST[45]	39%
TRUE-AHF[46]	39%
ASCEND-HF[47]	42.6%
RELAX-AHF-2[48]	47%

HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2DM, type 2 diabetes mellitus.

Incidence of new type 2 diabetes mellitus in patients with heart failure

In patients with HF, data from observational and clinical trials demonstrate an increased risk for new-onset T2DM compared to patients without HF. In a Kaiser Permanente study, the incidence of T2DM was significantly higher in patients with than without HF (i.e. 13.6/1000 vs. 9.2/1000) over a 5-year follow-up.[10] In a Danish nationwide cohort study, 8% of HF patients developed T2DM over 3 years, and the severity of HF was associated with a stepwise increased risk of developing T2DM.[54] Similar incidence of T2DM was reported in clinical trials of HF patients, as demonstrated by the CHARM program, in which 7.8% of patients developed T2DM over 2.8 years.[55,56] In the EMPHASIS-HF trial including HFrEF patients, the incidence of T2DM was 3.7% over a median follow-up of 21 months.[57] Notably, HF treatment with angiotensin-converting enzyme (ACE) inhibitors was shown to lower the incidence of T2DM in HFrEF patients; in a substudy of the SOLVD trial, 6% of patients in the enalapril arm developed T2DM over a mean follow-up of 2.9 years as opposed to 22% in the placebo arm.[58] Registry data corroborate that the use of renin–angiotensin system inhibitors is associated with attenuated risk for T2DM in HF patients receiving loop diuretics.[54] Clinical trials also demonstrated that the severity of HF, as indicated by a higher New York Heart Association (NYHA) class, increases the likelihood of developing T2DM.[27,59]

Incidence of heart failure in patients with type 2 diabetes mellitus

Recently, a population-based study of 1.9 million patients with T2DM without overt CV disease, followed for 5.5 years, demonstrated that incident HF was observed more frequently (14.1%) than vascular events, including myocardial infarction (MI) or stroke.[60] T2DM is an independent risk factor for the development of HF.[10] In a retrospective cohort followed for up to 72 months, patients with T2DM were more likely to develop HF than patients without T2DM (incidence rate 30.9 vs. 12.4/1000 person-years, rate ratio 2.5).[61] In elderly patients with T2DM, the incidence of HF was two-fold higher compared to patients without T2DM (121 vs. 62 cases/1000 patient-years).[62] In the UKPDS 35 trial including newly diagnosed diabetic patients, HF incidence steeply increased with the severity of dysglycaemia ranging from 2.3 to 11.9/1000 person-years for patients with glycated haemoglobin (HbA_{1c}) <6% and HbA_{1c} >10%, respectively.[63] Similarly, in observational studies (NHANES[64] and ARIC[65]), the incidence of HF in patients with T2DM was higher than in those without T2DM, with the corresponding hazard ratios (HRs) of 1.85 and 3.54. Indeed, in the ARIC study, higher HbA_{1c} levels in T2DM patients were associated with significantly more incident HF cases than in patients with T2DM and lower HbA_{1c} levels.[65] The incidence of HF in T2DM patients compared to those without T2DM is even higher in patients with established CAD, in which each 1% increase in HbA_{1c} level was associated with a 36% increased risk for HF hospitalization.[66,67] Patients with pre-diabetes in the ARIC study also had more HF than those without pre-diabetes.[68]

Type 2 diabetes mellitus, clinical status and outcomes in patients with heart failure

Clinical presentation, quality of life and functional status of patients with type 2 diabetes mellitus and heart failure

Patients with T2DM and both HFrEF[1,34,69,70] and HFpEF[1] have worse NYHA functional class and more HF-related symptoms and signs than patients without T2DM, despite having similar ejection fraction.[69,70] In the SOLVD-Prevention trial of patients with asymptomatic left ventricular systolic dysfunction, patients with T2DM were more likely to progress to symptomatic HF than those without T2DM, although the increased risk appeared to be confined to patients with HF secondary to CAD.[71]

Most trials also demonstrated worse quality of life in patients with T2DM and concurrent HF (both HFrEF and HFpEF), as compared to patients without T2DM.[40,69] Patients with T2DM and HFrEF also have shorter 6-minute walk distances and decreased peak oxygen uptake in comparison to non-diabetics.[55,69,72]

Type 2 diabetes mellitus and mortality in patients with heart failure

In all population-based studies, T2DM was associated with increased all-cause mortality in HF patients, albeit substantial regional differences were reported across Europe, and no differentiation between HFrEF and HFpEF was performed (*Table 4*).[26,29,51,73–81] In Sweden, there was a moderately higher risk (HR 1.60)[53] and in the Netherlands a significantly higher risk of death (HR 3.19)[26] attributed to T2DM. Additionally, in the Rotterdam study, T2DM was associated with an excess risk for CV death (HR 3.25) that was similar to the risk of all-cause mortality.[26] Likewise, all studies of the effect of T2DM on mortality in HF outpatients have found a higher mortality risk attributable to T2DM (*Table 4*).

Concerning patients hospitalized for HF, data on the association between T2DM and in-hospital mortality are divergent. In the OPTIMIZE-HF, ADHERE and Get With the Guidelines-HF registries in the United States, T2DM was not associated with higher in-hospital mortality.[82–85] Conversely, in the ALARM registry (six European countries, Mexico and Australia), and in the European Society of Cardiology (ESC) HF Long-Term Registry, T2DM was independently associated with a higher risk of in-hospital mortality.[51,86] There is a suggestion from some cohorts[82,87] that short-term mortality in HF patients post-discharge may be similar or slightly lower in those with T2DM. However, with longer-term follow-up, an association between T2DM and worse outcomes in HF patients becomes evident. For example, in the EVEREST trial in which patients were followed for 9.9 months after a HF hospitalization, T2DM conferred a slightly higher mortality.[45] Also, in patients from Scotland, T2DM increased mid-to-long-term mortality following hospitalization for HF.[87] Likewise, in the ESC HF Long-Term Registry, the presence of T2DM was independently associated with increased 1-year all-cause mortality.[51,73]

Clinical trial results are somewhat conflicting regarding the risk of all-cause and CV mortality attributed to T2DM in HF patients, but most clinical trials reported an increased risk of death in patients with concurrent T2DM and HF (*Table 5*).[1,31–35,37,40,42,44,45,69,88–92] In HFrEF, five out of eight trials demonstrated an association between T2DM and increased all-cause mortality, with the reported HRs between 1.3 and 2.0 (mostly around 1.5) (*Table 5*). Also three HFrEF trials reported increased CV death, with HRs between 1.5 and 1.8.[1,31,33] Concerning HFpEF, all trials reported increased all-cause mortality (HRs 1.5 to 1.8) and two out of four trials also reported an increased risk of CV mortality in patients with T2DM compared to patients without T2DM, with HRs 1.6 to 1.9 (*Table 5*). In the CHARM trial, T2DM was an independent risk factor for both all-cause mortality and CV mortality even after adjustment for 32 covariates.[1] Additionally, in the same study, T2DM had a greater association with higher all-cause and CV mortality in patients with HFpEF than HFrEF.[1]

A recent meta-analysis of 31 registries and 12 clinical trials with 381 725 patients with acute and chronic HF, with a median follow-up of 3 years confirms that T2DM is independently associated with a higher risk of all-cause death (random-effects HR 1.28), CV death (HR 1.34), hospitalization (HR 1.35), and the combined endpoint of all-cause death or hospitalization (HR 1.41), and the observed long-term risk appears greater in patients with chronic than in those with acute HF.[93]

Table 4 Type 2 diabetes mellitus and mortality in heart failure in population studies, outpatient clinics and hospitalized patients

Country	Year of publication	Type of study	Total patients, *n*	Patients with T2DM, *n*	Adjusted all-cause mortality risk of T2DM*	Adjusted CV mortality risk of T2DM*
Population-based studies						
ESC-HFA HF Long-Term Registry[51]	2017	Population-based	9428	3440	1.28 (1.07–1.54)	1.28 (0.99–1.66)
ESC-HFA HF Long-Term Registry[73]	2017	Population-based	6926	3422	1.77 (1.28–2.45)	NA
Swedish HF Registry[74]	2014	Population and specialist outpatient-based	36 454	8809	1.60 (1.50-1.71)	NA
USA (Olmsted County)[29]	2006	Population-based	665	128	1.48 (1.20-1.82)	NA
Netherlands (Rotterdam)[26]	2001	Population-based	5540	557	3.19 (1.80–5.65)	3.25 (1.53–6.93) SCD: 3.65 (1.28–10.4)
Outpatient clinics						
UK[75]	2013	Cardiology clinics	1091	280	2.08 (1.61–2.69)	NA
USA[76,77]	2006	HF clinic	495	293	1.71 (1.16–2.51)	NA
Italy (BRING-UP Registry)[78]	2003	Outpatient-based	2843	621	1.44 (1.16–1.78)	NA
Hospitalized patients						
Spain (RICA Registry)[79]	2014	Hospitalization-based, multicentre	1082	490	1.54 (1.20–1.97)	NA
Spain (INCAex)[80]	2013	Hospitalization-based, single-centre	1659	NR	1.35 (1.11–1.66)	NA
USA (Medicare)[81]	1999	Hospitalization-based	170 239	NA	Black: 1.11 (1.06–1.16) White: 1.22 (1.24–1.25)	NA

CV, cardiovascular; HF, heart failure; NA, not available; NR, not reported; SCD, sudden cardiac death; T2DM, type 2 diabetes mellitus.
*Values are presented as hazard ratio (95% confidence interval).

Type 2 diabetes mellitus and causes of death in patients with heart failure

In the CHARM trial, patients with T2DM and both HFrEF and HFpEF were more likely to die of all subtypes of CV death [i.e. death due to HF, sudden cardiac death (SCD), death due to MI and death due to stroke].[1] The PARADIGM-HF study also reported that patients with T2DM and HFrEF were more likely to die of CV as well as all-cause mortality compared with patients without T2DM.[69] In the BEST trial, T2DM was an independent risk factor for death from pump failure.[94]

Aside from CV death, results from the Emerging Risk Factors Collaboration, including 820 900 people, demonstrate that T2DM is independently associated with increased risk of death from several cancers (i.e. liver, pancreas, ovary, colorectum, lung, bladder, and breast), renal and liver disease, pneumonia and other infectious diseases, mental and nervous system disorders, non-hepatic digestive diseases, external causes, and chronic obstructive pulmonary disease.[95] The study found that a 50-year-old with T2DM died, on average, 6 years earlier than an individual without T2DM, with about 40% of the difference in survival attributable to excess non-vascular deaths.[95]

Is the higher risk of type 2 diabetes mellitus only seen in heart failure secondary to coronary artery disease?

Whether or not the increased risk of mortality with T2DM in HF patients is seen in both those of ischaemic and non-ischaemic aetiology is uncertain. The majority of the available data suggests that T2DM is associated with higher risk of mortality in both patients of ischaemic and non-ischaemic aetiology (*Table 6*).[29,88,94,96–99] In a population-based Danish study, which followed patients for 6.8 years, patients with T2DM and HF had higher mortality whether or not they had CAD.[96] The higher risk appeared early and persisted throughout follow-up. In the CHARM trial, patients with both HFrEF and HFpEF had higher mortality attributed to T2DM whether or not they had CAD.[1] In the DIAMOND trial, T2DM was associated with a higher risk of mortality in both ischaemic and non-ischaemic HF.[100] These consistent findings conflict with two smaller population-based studies in the United States[29] and France[97] and one Spanish single-centre study[101] of patients hospitalized with HF, which suggested that diabetes was only associated with higher mortality in those with non-ischaemic aetiology. In three early clinical trials (SOLVD,[98] BEST,[94] and DIG[102]) the risk appeared to be confined to those with an ischaemic aetiology.

Table 5 Type 2 diabetes mellitus and all-cause mortality in clinical trials of heart failure

Clinical trial	Year of publication	Treatment	Total patients, *n*	Patients with T2DM, *n*	Adjusted all-cause mortality risk of T2DM*	Adjusted CV mortality risk of T2DM*
HFrEF trials						
PARADIGM-HF[31,69]	2016	Sacubitril/ valsartan	8399	2907	1.46 (1.26–1.70)	1.54 (1.30–1.83)
SHIFT[32]	2010	Ivabradine	6505	1979	1.10 (0.96–1.25)	1.05 (0.91–1.20) Mortality due to HF: 1.15 (0.88–1.49)
EchoCRT[33]	2013	CRT	809	328	2.08 (1.29–3.36)	1.79 (1.06, 3.03) Mortality due to HF: 2.45 (1.03–5.78)
HF-ACTION[34]	2016	Exercise	2331	748	0.97 (0.78–1.2)	NA
SENIORS[35]	2010	Nebivolol	2128	555	1.25 (0.99–1.58)	NA
SOLVD[88]	1996	Enalapril	4223	647	1.29 (1.1–1.5)	NA
MERIT-HF[37]	2005	Metoprolol	3991	985	1.08 (0.80–1.47)	NA
CHARM[1]	2008	Candesartan	4576	1306	1.55	1.54
HFpEF trials						
DIG-Preserved[42,89]	2010	Digoxin	987		1.48 (1.10–1.99)	NA
I-Preserve[40,90]	2017	Irbesartan	4128	1134	1.59 (1.33–1.91)	1.59 (1.28–1.96)
CHARM[1,91]	2008	Candesartan	3023	857	1.84	1.93
TOPCAT[44]	2017	Spironolactone	3385	1109	Without microvascular complications: 1.51 (1.14–1.99) With microvascular complications: 1.35 (1.04–1.75)	NA
Acute HF trials						
EVEREST[45,92]	2013	Tolvaptan	4133	1657	1.16 (1.00–1.34)	NA

CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, not available; T2DM, type 2 diabetes mellitus.
*Values are presented as hazard ratio (95% confidence interval).

Is the higher risk of mortality with type 2 diabetes mellitus and heart failure seen in both women and men?

An early report from the Framingham study reported that the mortality risk related to T2DM was confined to women and not to men.[103] In two population-based studies from Scotland and Sweden, the increased mortality risk of T2DM was seen in both women and men, but the effect was slightly greater in women.[87,96] Likewise, in the recent ESC HF Long-Term Registry and in the CHARM trial, T2DM was a risk factor for mortality in both men and women.[1,73]

Does glycated haemoglobin predict mortality in patients with heart failure and type 2 diabetes mellitus?

In the CHARM trial, high HbA_{1c} was associated with increased all-cause and CV mortality in patients with T2DM and both HFrEF and HFpEF.[104] A 1% increase in HbA_{1c} was associated with an increased HR of 1.1 for CV mortality.[104] In patients from a US study of HF clinics, a U-shaped relationship with regard to increased all-cause mortality was found.[71] Patients with either very low or very high HbA_{1c} were at greatest risk. A similar U-shaped curve was found in a single-centre study from Scotland.[105] In one single-centre observational study of 123 young patients with advanced HF and T2DM, patients with a HbA_{1c} of <7% had higher rates of all-cause mortality.[106] In the GISSI-HF study, including 6935 chronic HF patients, the presence of T2DM and higher HbA_{1c} levels was an independent predictor of all-cause mortality (HRs 1.43 and 1.21, respectively) and the composite outcome of mortality and CV hospitalization (HRs 1.21 and 1.14, respectively).[107]

In summary, high HbA_{1c} levels in T2DM and HF are consistently associated with higher mortality. Conversely, low HbA_{1c} levels can be associated with good outcomes (at least in a clinical trial cohort), but can be associated with worse outcomes (in population-based studies and those with very advanced HF).

Pre-diabetes and undiagnosed type 2 diabetes mellitus and risk of mortality in heart failure

In the PARADIGM-HF trial, patients with pre-diabetes were at increased risk of mortality.[69] Patients with undiagnosed T2DM were also at higher risk of mortality than subjects without T2DM, but the risk was not as high as in patients with previously known

Table 6 Type 2 diabetes mellitus and all-cause mortality in heart failure: ischaemic vs. non-ischaemic aetiology

Location/trial	Year of publication	Type of study/ treatment	Total patients, *n*	Patients with T2DM, *n*	Adjusted all-cause mortality risk of T2DM (ischaemic vs. non-ischaemic aetiology)*	Adjusted CV mortality risk of T2DM (ischaemic vs. non-ischaemic aetiology)
Population studies and HF clinics						
Denmark[96]	2010	Population-based cohort	2621	420	HF secondary to CAD: 1.45 (1.22–1.73) HF secondary to other aetiologies 1.50 (1.22–1.84)	NA
USA (Olmsted County)[29]	2006	Population-based cohort	665	128	HF secondary to CAD: 1.11 (0.81–1.51) HF secondary to other aetiologies: 1.79 (1.33–2.41)	NA
France[97]	2004	HF clinic	1246	274	HF secondary to CAD: 1.54 (1.13–2.09) HF secondary to other aetiologies: 0.65 (0.39–1.07)	NA
Clinical trials						
SOLVD[88,98]	1996	Enalapril	4223	647	HF secondary to CAD: 1.37 (1.21–1.55) HF secondary to other aetiologies: 0.98 (0.76–1.32)	NA
BEST[94]	2003	Bucindolol	2708	964	HF secondary to CAD: 1.33 (1.12–1.58) HF secondary to other aetiologies: 0.98 (0.74–1.30)	NA
DIG[99]	2004	Digoxin	4277	NA	HF secondary to CAD: 1.43 (1.26–1.63) HF secondary to other aetiologies: NR	NA

CAD; coronary artery disease; CV, cardiovascular; HF, heart failure; NA, not available; NR, not reported; T2DM, type 2 diabetes mellitus.
*Values are presented as hazard ratio (95% confidence interval).

T2DM. In CHARM, pre-diabetes and undiagnosed T2DM were both associated with greater rates of HF hospitalization, CV and all-cause mortality than those without T2DM.[108] However, not all studies have reported an increased mortality risk with pre-diabetes. In a study of 970 non-diabetic patients with HF, an increased 1-year mortality risk was found only in patients with HbA_{1c} >6.7% and reduced left ventricular ejection fraction (≤45%), but not in those with HFpEF.[109] Also, in the GISSI-HF study of unselected HF patients, pre-diabetes was not an independent predictor of increased mortality.[107] The reasons behind these discrepancies might be attributed to differences in patient characteristics and warrant further assessment.

Type 2 diabetes mellitus and risk for heart failure hospitalization

Several clinical trials documented that patients with T2DM and HFrEF were more likely than patients without T2DM to be hospitalized for HF.[1,37,69,70,94] In the CHARM trial, rates of hospitalization for HF in patients with T2DM were greater for those with HFpEF than HFrEF and patients with HFpEF and T2DM were almost 2.5 times more likely to be hospitalized for HF than those without T2DM.[1] In I-Preserve, patients with T2DM and HFpEF were also more likely to be hospitalized with HF.[40]

Readmission after a hospitalization for heart failure

Registry data indicate that patients with T2DM had more all-cause rehospitalizations than those without T2DM.[79,82,110] In a population-based study in Scotland, T2DM was a predictor of readmission for HF (with the increased risk greatest in younger women).[87] In the ESC HF Long-Term Registry, T2DM was independently associated with rehospitalization for HF.[51] Likewise, in the EVEREST trial, T2DM was associated with greater rates of HF rehospitalization (HR 1.19).[45]

In addition, as demonstrate by the OPTIMIZE-HF and Get With The Guidelines-HF registries in the United States, patients with HF and T2DM experience slightly longer hospitalizations than patients without T2DM.[82–84]

Type 2 diabetes mellitus, myocardial infarction and stroke in patients with heart failure

The only trial to investigate the association between T2DM and risk of MI and stroke in HF patients was the CHARM trial demonstrating that the presence of T2DM increased the risk for MI and stroke irrespective of HF phenotype (i.e. HFrEF or HFpEF).[1]

Risk for HF hospitalization in patients with type 2 diabetes mellitus without a previous history of heart failure

In the ARIC registry, representing a cohort of 14 079 people in the community without known HF, T2DM was the most powerful risk factor for incident HF hospitalization.[110] In a large meta-analysis of patients with T2DM but without HF, predictors of incident HF included insulin use, HbA_{1c} and fasting glucose.[111]

Mortality in type 2 diabetes mellitus patients with heart failure

In the CV outcomes trials of new therapies for T2DM, the development of HF is associated with markedly higher mortality (especially in RECORD[112] and SAVOR-TIMI 53[16]). Patients with T2DM who developed HF had a 10 to 12 times greater mortality than those who did not develop HF.[3,113] In addition, they are also at a 2.45-fold greater risk of CV death compared with patients with T2DM but without HF.[114]

Unrecognized heart failure in patients with type 2 diabetes mellitus and unrecognized type 2 diabetes mellitus in patients with heart failure

Observational evidence indicates that a significant proportion of patients aged ≥60 years (27.7%) may have unrecognized HF (22.9% and 4.8%, HFpEF and HFrEF, respectively) based on the ESC diagnostic criteria.[115,116] On the other hand, pre-diabetes and undiagnosed T2DM are common in patients with HF. In the PARADIGM-HF trial, 13% of patients with HFrEF had undiagnosed T2DM and 25% had pre-diabetes.[69] Likewise, 11% of 'non-T2DM' patients with HFrEF in the RESOLVD trial had undiagnosed T2DM.[117] In the CHARM study, undiagnosed T2DM was common in both HFrEF and HFpEF.[108] In the ESC HF Long-Term Registry, even higher proportion of HF patients (19.1%) had undiagnosed T2DM.[73]

Considering prognostic implications of concurrent T2DM and HF, these findings stress the importance of developing screening strategies for unrecognized HF among T2DM patients and vice versa. Since evidence of strategies for HF screening is sparse,[116] in T2DM patients, screening for HF might be currently based on clinical characteristics (i.e. age, history of CAD, exercise-related shortness of breath, body mass index, laterally displaced apex beat) that have been shown to reliably identify elderly subjects at risk of HF that may require further assessment (e.g. echocardiography).[118] Such a strategy may be used to prevent complications and possibly improve outcomes, particularly in subjects with HFrEF.[119] Conversely, since undiagnosed T2DM is common among patients with HF, it is prudent to screen patients without known T2DM in accordance with current recommendations using the 8 h fasting plasma glucose, 2 h glucose tolerance test or HbA_{1c} levels (equally appropriate).[120]

Pathophysiological aspects of myocardial dysfunction in type 2 diabetes mellitus

The most common co-existing conditions that cause HF in patients with T2DM are CAD and hypertension. It has also been hypothesized that T2DM-related processes can cause HF by directly affecting the structure and function of the heart.[4] The major drivers of myocardial dysfunction in T2DM are insulin resistance/hyperinsulinaemia and impaired glucose tolerance, which may be effective years or even decades before overt T2DM develops.[121] Their detrimental effect is associated with numerous metabolic abnormalities such as advanced glycosylation end products (AGEs) deposition, lipotoxicity and microvascular rarefication.[4] Harmful interrelations between these pathophysiologic mechanisms may exert a potentiating effect, leading to several maladaptive responses and resulting in myocyte alteration.[4] Insulin resistance leads to increased free fatty acid release and is linked with HF-related neuroendocrine dysregulation.[122] It is also an important aetiological factor in the development of left ventricular hypertrophy,[123] as confirmed in the Framingham study, where left ventricular mass was significantly higher in female patients with T2DM compared to patients without T2DM.[124] Hyperglycaemia also exerts extensive influences on CV changes in T2DM, and can directly cause cardiomyocyte contractile dysfunction, mitochondrial network fragmentation and an increase in protein kinase C activity.[125–127] Also, it causes activation of reactive oxygen species and the deposition of AGEs in both endothelial and smooth muscle cells, which predisposes to concentric left ventricular remodelling and raises left ventricular diastolic stiffness.[125,126] High myocardial free fatty acid uptake results in the accumulation of triglyceride in the myocardium (i.e. lipotoxicity). Cardiac steatosis, confirmed by proton magnetic resonance spectroscopy, is the clinical equivalent of high myocardial triglyceride content and may present as left ventricular diastolic dysfunction.[128]

Diabetic cardiomyopathy

In 1954, Lundbaek was the first to propose the existence of a specific diabetic heart muscle disease without involvement of CAD or hypertension.[129] Two decades later, Rubler *et al.*[130] described diabetic-related post-mortem findings in four patients with T2DM, glomerulosclerosis and HFrEF with normal epicardial coronary arteries. There is no definition of diabetic cardiomyopathy, which makes studies of epidemiology, pathophysiology, natural history and associated clinical outcomes challenging. The most commonly accepted definition refers to a myocardial dysfunction which occurs in the absence of all other CV disease.[120,131]

Phenotypes of type 2 diabetes mellitus-related cardiomyopathy

Left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in type 2 diabetes mellitus

Left ventricular diastolic dysfunction can be detected in 75% of T2DM patients and develops early in T2DM course, as confirmed by demographic characteristics of these patients, including younger age, normal blood pressure and optimal T2DM control.[132,133] Furthermore, the degree of glucose dysregulation correlates with left ventricular diastolic dysfunction severity,[134] and with increased risk of incident HF and CV mortality in T2DM.[135–137] Almost half of HF patients with T2DM have HFpEF, which is more frequent in older, hypertensive and female patients with T2DM and is difficult to diagnose because the symptoms are often mild, appear upon physical activity, and could be frequently misdiagnosed as chronic obstructive pulmonary disease.[89]

HFpEF is usually associated with mild T2DM complications in the early stages of T2DM, whilst HFrEF is associated with more severe T2DM complications.[138] This suggests that severity and duration of hyperglycaemia are important for the development of left ventricular dysfunction.

Heart failure with reduced ejection fraction in type 2 diabetes mellitus

The major cause of HFrEF in T2DM is CAD. T2DM is associated with a two-fold higher risk of CAD and ischaemic stroke, and a two- to four-fold higher CAD- and stroke-related mortality.[139–141] CAD in T2DM is usually diffuse, multi-vessel and may lead to silent MI.

Treatment of heart failure in patients with type 2 diabetes mellitus

There are no specific constraints to HF treatment in T2DM patients as recommended by the 2016 ESC guidelines for the management of HF.[116] In clinical trials, all pharmacological and device therapies for HF were similarly effective whether or not patients had T2DM. Thus far, there were no clinical trials of HF treatment that included only patients with T2DM, and available evidence is derived from subanalyses of mixed populations. However, several HF drugs may exert metabolic effects that should be taken into account in T2DM patients.

Pharmacological therapy

Angiotensin-converting enzyme inhibitors

The ESC/EASD guidelines on diabetes, pre-diabetes, and CV diseases recommend angiotensin-converting enzyme (ACE)-inhibitors in patients with HFrEF and T2DM, as they have been shown to improve symptoms and reduce morbidity and mortality.[116] The effectiveness of ACE-inhibitors in patients with both T2DM and HF, or post-MI left ventricular systolic dysfunction was examined in a large meta-analysis of seven randomized clinical trials (RCTs).[142] For the endpoint of all-cause mortality, ACE-inhibitors had a similar treatment benefit in subjects with and without T2DM (HR 0.84 and 0.85, respectively).

The only large ACE-inhibitor trial in HFrEF to provide detailed information on patients with T2DM was the ATLAS, which compared low-dose (2.5–5.0 mg daily) to high-dose (32.5–35.0 mg daily) lisinopril.[143,144] The greater relative benefit for the composite primary endpoint (all-cause mortality or HF hospitalization) of high-dose lisinopril was similar in patients with and without T2DM. However, because patients with T2DM were at greater risk, the absolute benefit of high-dose lisinopril was larger in patients with T2DM.[144] The occurrence of adverse effects with high-dose lisinopril was similar in those with and without T2DM with respect to hypotension/dizziness (35% vs. 32%), renal dysfunction/hyperkalaemia (29% vs. 22%) and cough (12% vs. 10%).[144]

Angiotensin receptor blockers

In the CHARM trial, a significant reduction in CV death, HF hospitalization and all-cause mortality was achieved with candesartan in patients with HF and HFrEF, irrespectively of T2DM.[1] Also, in the Val-HeFT, valsartan treatment led to a significant relative risk reduction in the co-primary composite endpoint (death or HF morbidity—mainly HF hospitalization) regardless of T2DM.[145] A subsequent trial (HEAAL[146]) showed that 150 mg daily of losartan was superior to 50 mg daily in reducing the risk of death or HF hospitalization, supporting the similar findings of the ATLAS trial with the ACE-inhibitor lisinopril. The treatment effect was again not different in the subgroup of patients with T2DM compared to those without T2DM (HR 0.96; interaction P=0.35).

There is little information about the tolerability of angiotensin receptor blockers (ARBs) in T2DM. In the overall CHARM program, patients with T2DM had double the risk of developing hyperkalaemia on candesartan compared to those without T2DM.[147]

T2DM confers a higher risk of diabetic nephropathy and chronic kidney disease.[148] Specifically, diabetic nephropathy is characterized by increased renal sodium retention[149,150] and a higher risk of hyperkalaemia.[151] This caveat deserves consideration when ACE-inhibitors or ARBs are administered to diabetic patients, as these drugs may interfere with renal potassium excretion. Hence, monitoring of serum electrolytes and creatinine is recommended when starting or escalating the dose of ACE-inhibitors or ARBs.

Beta-blockers

Subgroup analyses of large HF trials show that beta-blockers reduce mortality and hospitalization and improve symptoms in moderate to severe HF, irrespectively of T2DM.[37,152,153] Beta-blockers recommended in HF and T2DM include metoprolol succinate (MERIT-HF),[37] bisoprolol (CIBIS II)[152] and carvedilol (COPERNICUS and COMET).[154,155] The MERIT-HF trial reported similar efficacy and safety of metoprolol succinate in patients with and without T2DM.[37] Adverse events were more often observed in T2DM patients, but were less likely to occur if those patients were treated with metoprolol succinate than with placebo. In a meta-analysis of six trials, beta-blocker therapy reduced all-cause mortality in patients with T2DM (HR 0.84) similarly to those without T2DM (HR 0.72).[156] An analysis of three trials (CIBIS II, MERIT-HF and COPERNICUS) reported a relative risk reduction for mortality of 0.77 in patients with T2DM and 0.65 in patients without T2DM.[142] A third meta-analysis that focused on seven trials using carvedilol, including a post-MI trial, revealed a similar, significant reduction in the risk for mortality with carvedilol in patients with and without T2DM (28% and 37%, respectively, interaction P=0.25).[157]

Hypoglycaemia is a concern in patients with T2DM treated with insulin or sulfonylureas. Theoretically, beta-blockers could alter awareness of hypoglycaemia by decreasing palpitations and tremor and prolong recovery from hypoglycaemia by blocking β_2 receptors, which partly control glucose production in the liver. However, among patients with T2DM in MERIT-HF only three (0.6%) in the placebo group and four (0.8%) in the metoprolol succinate group had an adverse event related to hypoglycaemia (in each case in patients taking insulin).[37]

In summary, beta-blockers in patients with T2DM and HF lead to significant improvements in morbidity and mortality that are consistent with results in patients without T2DM. These treatment benefits of beta-blockers in diabetic patients far outweigh the theoretical risks related to hypoglycaemia and minor changes in HbA_{1c} and serum lipids. These benefits strongly support beta-blocker treatment in patients with concurrent T2DM and HF.

Mineralocorticoid receptor antagonists

The mortality benefit of spironolactone in the RALES trial and eplerenone in the EMPHASIS-HF trial was consistent in T2DM and non-T2DM patients with HFrEF.[158,159] Importantly, eplerenone seems to have no effect on new-onset T2DM in patients with HF, suggesting a neutral metabolic profile.[160] Caution is necessary when these medications are used in patients with impaired renal function and in those with serum potassium levels of $\geq$5.0 mmol/L. Monitoring of kidney function and potassium is mandatory since nephropathy is frequent in T2DM. Addition of an ARB (or renin inhibitor) to a combination of ACE-inhibitor and mineralocorticoid receptor antagonists is prohibited because of the increased risk of renal dysfunction and hyperkalaemia and the lack of additional benefit.[161]

Sacubitril/valsartan

In the PARADIGM-HF trial, sacubitril/valsartan was superior to the ACE-inhibitor enalapril in reducing the risks of death and HF hospitalization (primary endpoint) in patients with HFrEF.[31] A T2DM subgroup analysis has shown that the effect of sacubitril/valsartan compared with enalapril for the primary endpoint was similar in patients with and without T2DM (HR 0.83 and 0.77; respectively, interaction P=0.40).[69] In the post hoc analysis, treatment with sacubitril/valsartan was associated with a greater HbA_{1c} reduction and a lower rate of initiation of insulin or other drugs for T2DM compared to enalapril.[162]

Nitrates and hydralazine

The A-HeFT trial examined the efficacy for the reduction in all-cause mortality, hospitalization and quality of life of a fixed dose combination of isosorbide dinitrate and hydralazine hydrochloride in African Americans with HF.[163] A very large proportion (41%) of patients in the study had T2DM. The treatment effect on mortality was similar in patients with and without T2DM (HRs 0.56 and 0.59, respectively).

Ivabradine

In a large trial involving 6558 patients with HF (30% with T2DM), ivabradine demonstrated a significant reduction in the composite endpoint of CV death or HF hospitalization, with no difference between T2DM and non-T2DM patients (HRs 0.81 and 0.83, respectively).[164]

Diuretics

Diuretics are usually required to treat the symptoms and signs of fluid overload in patients with HF. There are no clinical trials examining their efficacy in patients with both T2DM and HF. Theoretically thiazide diuretics can lead to increased insulin resistance and subsequent worsening of glycaemic control.

Devices and surgery

Implantable cardioverter-defibrillators

In addition to a higher risk of death due to worsening HF, patients with T2DM and HF are at increased risk of malignant ventricular arrhythmias and SCD. In the CHARM trial, patients with T2DM experienced a significantly higher rate of SCD compared to patients without T2DM (40 vs. 25.9 events/1000 patient-years of follow-up), and the increased risk of SCD was observed irrespective of HF phenotype (i.e. HFrEF and HFpEF).[1] Observational data also demonstrate an increased risk of SCD in the presence of T2DM in HF of both ischaemic and non-ischaemic aetiology.[75] Device therapies, implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy with ICD (CRT-D) offer a possibility to reduce overall mortality with effective prevention of SCD, and data from clinical trials support this notion in patients with and without T2DM.

The SCD-HeFT trial included patients with both non-ischaemic and ischaemic HFrEF who were randomized to placebo, amiodarone, or an ICD.[165] The study included approximately 30% of patients with T2DM in every treatment arm. ICD treatment led to a significant relative risk reduction in death and in subgroup analysis, there were no interactions with T2DM. The HRs for the primary endpoint of all-cause mortality in the ICD group were 0.95 for patients with T2DM and 0.67 for those without T2DM and in the amiodarone group 1.2 for patients with T2DM, and 1.0 for those without T2DM. In the DANISH trial, patients with non-ischaemic cardiomyopathies were randomized to ICD and optimal medical therapy or optimal medical therapy alone.[166] Approximately 19% of patients had T2DM. In pre-specified subgroup analysis, there was no significant difference in treatment effect in patients with and without T2DM (HRs 0.92 and 0.85, respectively, interaction P=0.60).

Cardiac resynchronization therapy

The effectiveness of CRT to reduce the risk of all-cause death and HF hospitalization was evaluated in two clinical trials (COMPANION[167] and CARE-HF[168]) that randomized patients with moderate to severely symptomatic HF (NYHA class III or IV) to either optimal medical therapy or optimal medical therapy plus CRT. Additionally, two trials (MADIT-CRT[169] and RAFT[170]), randomized patients with mild to moderate HF symptoms to optimal medical therapy plus ICD, or optimal medical therapy plus CRT-D, for the primary endpoint (death or HF hospitalization). In relation to T2DM status, both COMPANION (41% of T2DM patients), and CARE-HF (29% of T2DM patients) demonstrated similar effectiveness of CRT for the reduction in mortality and HF hospitalization.[171,172]

In MADIT-CRT, CRT-D treatment, compared with optimal medical therapy plus ICD, led to a similar reduction in the risk of all-cause death or HF hospitalization in patients with and without T2DM (adjusted HRs 0.56 and 0.67, respectively).[169,173] Also, subgroup analysis of the RAFT trial showed that the benefit of CRT-D was similar in patients with and without T2DM.[170] Patients with T2DM did not experience a higher rate of complications related to device implantation, including infection.[170] There were similar CRT-related improvements in left ventricular volumes and ejection fraction in those with and without T2DM.

Coronary artery bypass grafting

Coronary artery disease is the leading cause of premature mortality in patients with T2DM, which stresses the importance of an early detection (e.g. stress echocardiography, coronary angiography) based on the estimated CV risk, and a timely treatment of CAD.[174,175]

The STICH trial addressed the broader role of surgical revascularization in patients with HFrEF and less severe CAD.[176] Patients suitable for surgery were randomized to coronary artery bypass graft (CABG) plus medical therapy or medical therapy alone. In the subanalysis of the STICH trial, there was no significant difference between patients with (40%) and without T2DM with respect to the primary outcome of all-cause mortality.[177] This trial therefore extends the indication for CABG to 'STICH-like' patients with two- or three-vessel CAD, including a left anterior descending stenosis, who are otherwise suitable for surgery. The benefits are similar whether or not a patient has T2DM.

Cardiac transplantation

Cardiac transplantation in T2DM with macrovascular complications and end-stage HF may impose several challenging issues, including renal dysfunction, peripheral vascular disease, increased risk of infection and the need for prednisolone-based immunosuppression. T2DM was an independent risk factor for reduced 10-year survival in a large registry of 22 385 transplant patients.[178] However, with modern immunosuppression regimens allowing more rapid tapering of steroid doses and steroid-free immunosuppression, cardiac transplantation in T2DM (in the absence of major T2DM complications) should be considered on a case-by-case basis.

Exercise prescription

Recently, a single large trial (HF-ACTION[34]) investigated the effects of exercise training in patients with mild to moderately severe HF symptoms. In an adjusted analysis, exercise training led to an 11% (P=0.03) reduction in the primary composite outcome of all-cause mortality or all-cause hospitalization. The trial enrolled 32% of patients with T2DM and there was no interaction between T2DM status and the effect of exercise on clinical outcomes.

Type 2 antidiabetic drugs and the risk of heart failure

Drugs that increase heart failure hospitalizations

Over the last 15 years there has been concern that some of T2DM drugs might increase the risk for HF (*Table 7*).[16,17,179–182] Drugs that are now known to increase the risk for HF are thiazolidinediones (TZDs) and a dipeptidyl peptidase-4 (DPP4) inhibitor, saxagliptin.[16,17] In the RECORD[112] and the PROactive trials,[183] patients randomized to TZDs, rosiglitazone and pioglitazone, respectively, had more HF events than those on placebo. In the SAVOR-TIMI 53 trial (saxagliptin vs. placebo), saxagliptin significantly increased the risk for HF hospitalizations (HR 1.27, P=0.007).[16] Patients at greatest risk were those with a history of HF, an estimated glomerular filtration rate (eGFR) ≤60 mL/min, or elevated baseline levels of N-terminal pro B-type natriuretic peptide (NT-proBNP).[16] In both RECORD and SAVOR-TIMI trials, patients who developed HF had a high rate of subsequent death. On that basis, pioglitazone, rosiglitazone and saxagliptin are contraindicated in patients with HF or at risk of HF.

Not all DPP4 inhibitors are associated with higher rates of HF (*Table 8*).[16–24,184–186] In the EXAMINE trial of alogliptin vs. placebo in patients who had had an acute coronary syndrome, there was not a statistically significant increase in the risk of HF hospitalizations in patients randomized to alogliptin.[19,184] Likewise, sitagliptin in the TECOS trial had no signal of excess rates of HF.[18,185] Two ongoing trials, CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes; NCT01243424), and CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients with Type 2 Diabetes Mellitus; NCT01897532), will allow further clarification on the role DPP4 inhibitors in patients with T2DM and HF.

Table 7 Summary of evidence for type 2 antidiabetic drugs in patients with prevalent heart failure

Class of drug	Evidence
SGLT2 inhibitors (e.g. empagliflozin, canagliflozin)	No RCTs in HF. Large RCTs in patients with HF with an without T2DM are underway
Metformin	No RCTs in HF. In observational studies in HF, metformin is associated with lower mortality rates than sulphonylureas or insulin.[179] Benefit/risk ratio unknown.
GLP-1 receptor antagonists (e.g. liraglutide, albiglutide)	No large RCTs. Liraglutide - two small RCTs reported no effect on (i) LV function,[180] (ii) hierarchical composite of death/HF hospitalization/BNP change.[181] Benefit/risk ratio unknown.
Sulphonylureas	No RCTs in HF. Data equivocal. Some observational data suggest an increased mortality risk with sulphonylureas compared with metformin.[179,182]
Insulin	No RCTs in HF. In observational studies in HF, insulin was associated with higher mortality rates than metformin.[179] Benefit/risk ratio unknown.
DPP4 inhibitors	No RCTs in HF (saxagliptin contraindicated in HF[16,17]). Benefit/risk ratio unknown.

BNP, B-type natriuretic peptide; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HF, heart failure; LV, left ventricular; RCT, randomized clinical trial; SGLT2, sodium–glucose co-transporter type 2; T2DM, type 2 diabetes mellitus.

Drugs that might increase the risk for heart failure

Over many years there has been suspicion that insulin, which causes sodium and water retention, may increase the risk for the development of HF. In large observational studies, insulin is associated with higher mortality rates than metformin.[2] There have been similar concerns with sulphonylureas which, as insulin secretagogues, have also been associated with higher death rates than metformin.[2] These studies, although large, are non-randomized and therefore inconclusive. In the only RCT of insulin vs. placebo [ORIGIN, 12 537 people with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM (i.e. not in patients with HF)], insulin was not associated with higher rates of HF hospitalization than placebo.[187] Remarkably, despite the use of insulin and sulphonylureas for decades, there are no other placebo-controlled randomized trials.

Currently, sulphonylureas and insulin could be used in T2DM patients with HF (usually as a second- or third-line treatment), although their safety in HF is still inconclusive.

Antidiabetic drugs that might be safe in heart failure

It has been proposed that metformin might be safe and efficacious in patients with T2DM and HF. This was based on large observational studies where metformin was associated with lower mortality and HF hospitalization rates than other T2DM drugs (primarily insulin and sulphonylureas).[2] There are no RCTs of metformin in patients with T2DM and HF. Whether or not metformin is efficacious or safe is inconclusive. Previous concerns that metformin may cause metabolic acidosis are no longer justified.[2] Accordingly, metformin could be recommended as first-line treatment for patients with T2DM and HF who have preserved or moderately reduced renal function (i.e. eGFR >30 mL/min).

Glucagon-like peptide 1 (GLP-1) receptor agonists have been the subject of many large placebo-controlled trials in patients with T2DM and CV disease or at high risk of CV disease (*Table 8*).[22–24,186] In these trials, GLP-1 receptor agonists had a neutral effect on the risk for HF hospitalization. Similarly, no signal for a higher risk for HF hospitalization was seen with acarbose (vs. placebo) in patients with insulin resistance and CAD.[188] Bromocriptine has not been studied with respect to its effect on HF outcomes.

Prevention of heart failure by type 2 antidiabetic drugs

A significant breakthrough in contemporary cardiology was the finding that some T2DM drugs are associated with a lower risk of HF hospitalization in patients with CV disease or at high risk of CV disease (*Table 8*). Two large RCTs that assessed CV safety of the sodium–glucose co-transporter type 2 (SGLT2) inhibitors, empagliflozin and canagliflozin, have shown a significant reduction in HF hospitalization with both drugs.[20,189] The primary outcome in both trials was the three-point major adverse CV event (i.e. CV death, non-fatal MI or non-fatal stroke) and HF hospitalization was a secondary outcome. In the EMPA-REG OUTCOME trial (n=7020), including patients with T2DM, established CV disease and eGFR >30 mL/min/1.73 m^2, there was a major reduction in HF hospitalization (HR 0.65) with empagliflozin compared with placebo.[20] The observed beneficial effect of empagliflozin became evident early (i.e. 2–3 months of treatment) and was observed across a range of pre-specified subgroups, including patients with (10%) and without investigator-reported HF at baseline, that had a similar reduction in HF hospitalizations with empagliflozin compared with placebo. No echocardiograms or natriuretic peptide measurements are available from this trial, so the detail of the beneficial effect on HF hospitalization is not available. Patients hospitalized for HF during the study had a high mortality, which was lower in patients receiving empagliflozin than placebo (13.5% vs. 24.2%).[20] In the CANVAS trial, patients with T2DM (n=10 143) either with established CV disease or at high risk of CV disease, randomized to

Table 8 Heart failure outcomes in published large cardiovascular outcome trials in patients with type 2 diabetes mellitus

Study	Antidiabetic drug	Comparator	Results
DPP4 inhibitors			
SAVOR-TIMI 53[16,17]	Saxagliptin	Placebo	Increase in HF hospitalization
EXAMINE[19,184]	Alogliptin	Placebo	No statistically significant increase in HF hospitalization
TECOS[18,185]	Sitagliptin	Placebo	No effect on HF hospitalization
GLP-1 receptor agonists			
ELIXA[23]	Lixisenatide	Placebo	No effect on HF hospitalization
LEADER[22]	Liraglutide	Placebo	No effect on HF hospitalization
SUSTAIN-6[186]	Semaglutide	Placebo	No effect on HF hospitalization
EXSCEL[24]	Exenatide	Placebo	No effect on HF hospitalization
SGLT2 inhibitors			
EMPA-REG OUTCOME[20]	Empagliflozin	Placebo	Reduced HF hospitalization
CANVAS[21]	Canagliflozin	Placebo	Reduced HF hospitalization

DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HF, heart failure, SGLT2, sodium–glucose co-transporter type 2.

canagliflozin or placebo had a significantly lower risk of HF hospitalization (HR 0.67).[21,189] Empagliflozin in EMPA-REG OUTCOME, but not canagliflozin in CANVAS, reduced all-cause and CV mortality as well as HF hospitalization. In the EMPA-REG OUTCOME trial, the only major adverse event was an increased risk of genital tract infections, which were treatable, and infrequently recurred.[20] In the CANVAS trial, treatment with canagliflozin was associated with a significantly higher risk of lower-limb amputations (6.3 vs. 3.4 per 1000 patient-years; HR 1.97) and possibly a higher risk of fractures compared with placebo.[21] Large RCTs of other new T2DM drugs have not shown a reduction in incident HF (*Table 8*).

Treatment of heart failure with type 2 antidiabetic drugs

Randomized clinical trials with SGLT2 inhibitors

While two drugs (i.e. empagliflozin and canagliflozin) have a favourable effect on HF hospitalization, no T2DM drug has yet been investigated as a treatment for HF. In 2017, three large RCTs with SGLT2 inhibitors (i.e. empagliflozin and dapagliflozin) have started, which will enrol HF patients either with or without T2DM (i.e. T2DM is not a mandatory inclusion criteria). Two trials will assess safety and efficacy of empagliflozin vs. placebo on top of guideline-based medical therapy for the reduction in primary outcome (CV death or HF hospitalization) both in patients with HFrEF (EMPEROR-Reduced, NCT03057977) and HFpEF (EMPEROR-Preserved, NCT03057951) (*Table 9*). Among secondary outcomes, the two trials will assess all-cause mortality, and renal effects of empagliflozin vs. placebo in patients with HF. The third trial (Dapa-HF, NCT03036124) will assess safety and efficacy of dapagliflozin vs. placebo for the reduction in CV death or HF hospitalization (or urgent HF visit) in patients with HFrEF. Secondary outcomes will include all-cause mortality and effects on renal function. The results of these trials will shed more light on potential beneficial CV and renal effects of SGLT2 inhibitors in HF patients, including those without T2DM.

In addition, a number of ongoing smaller RCTs are assessing the effect of SGLT2 inhibitors on CV outcomes, including various aspects of HF in patients with and without T2DM, as summarized in *Table 9*.

Randomized clinical trials with GLP-1 receptor agonists

In the LIVE trial, in patients with stable HFrEF, with and without T2DM, there were no significant changes in left ventricular ejection fraction between patients randomized on liraglutide or placebo.[180] However, there was a significant increase in heart rate ($P<0.0001$) and more serious cardiac adverse events with liraglutide ($P=0.04$). In a placebo-controlled FIGHT trial, of patients with HFrEF, with and without T2DM (41%), liraglutide was not associated with an improvement in the composite primary endpoint of death, rehospitalization and NT-proBNP change.[181] Pre-specified subgroup analyses in patients with T2DM did not reveal any significant between-group differences. A small randomized, placebo-controlled trial of albiglutide in HFrEF showed no effect on left ventricular function and 6-minute walk distance.[190] These observations have raised some concern regarding the safety of liraglutide in HFrEF patients that warrants further research.

Conclusions

Type 2 diabetes mellitus and HF are both common and frequently co-exist. The causes of HF in T2DM are numerous, but CAD and hypertension are likely the most important contributors to concurrent T2DM and HF, whereas a direct effect of T2DM on the myocardium (e.g. 'diabetic cardiomyopathy') might also play a role. Evidence from recent large-scale clinical trials and registries

Table 9 Selected ongoing randomized clinical trials of SGLT2 inhibitors in patients with prevalent heart failure

Clinical trial	Brief description of the trial
Empagliflozin	
EMPEROR-Reduced (NCT03057977)	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction • Study population: HFrEF, with and without T2DM. • Estimated enrolment: *n*=2850. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: CV death or HF hospitalization (time frame: up to 38 months).
EMPEROR-Preserved (NCT03057951)	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction • Study population: HFpEF, with and without T2DM. • Estimated enrolment: *n*=4126. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: CV death or HF hospitalization (time frame: up to 38 months).
Empire HF (NCT03198585)	Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction • Study population: HFrEF, with and without T2DM. • Estimated enrolment: *n*=189. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: change in plasma concentrations of NT-proBNP (time frame: 90 days) as a measure of treatment impact on HF.
EMMY (NCT03087773)	Impact of Empagliflozin on Cardiac Function and Biomarkers of Heart Failure in Patients With Acute Myocardial Infarction • Study population: patients with acute MI with and without T2DM. • Estimated enrolment: *n*=476. • Treatment: empagliflozin vs. placebo. • Primary outcome: change in plasma concentrations of NT-proBNP (time frame: 26 weeks) as a measure of treatment impact on HF.
RECEDE-CHF (NCT03226457)	SGLT2 Inhibition in Combination With Diuretics in Heart Failure • Study population: HFrEF with T2DM. • Estimated enrolment: *n*=34. • Treatment: empagliflozin vs. placebo. • Primary outcome: the effect on the change in urine output from baseline (time frame: 6 weeks).
Canagliflozin	
(NCT02920918)	Treatment of Diabetes in Patients With Systolic Heart Failure • Study population: HFrEF with T2DM. • Estimated enrolment: *n*=88. • Treatment: canagliflozin vs. sitagliptin. • Primary outcome: change in aerobic exercise capacity and ventilator efficiency (time frame: baseline and 12 weeks).
Dapagliflozin	
Dapa-HF (NCT03036124)	Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure • Study population: HFrEF with and without T2DM • Estimated enrolment: *n*=4500. • Treatment: dapagliflozin vs. placebo. • Primary outcome: CV death or hospitalization for HF, or an urgent HF visit (time frame: from randomization up to approximately 3 years).
DEFINE-HF (NCT02653482)	Dapagliflozin Effect on Symptoms and Biomarkers in Diabetic Patients With Heart Failure • Study population: HFrEF with T2DM. • Estimated enrolment: *n*=250. • Treatment: dapagliflozin vs. placebo. • Primary outcome: change in plasma concentrations of NT-proBNP (time frame: 12 weeks) as a measure of treatment impact on HF.

Table 9 Continued

Clinical trial	Brief description of the trial
PRESERVED-HF (NCT03030235)	Dapagliflozin Effect on Symptoms and Biomarkers in patients HFpEF • Study population: HFpEF with T2DM or pre-diabetes. • Estimated enrolment: *n*=320. • Treatment: dapagliflozin vs. placebo. • Primary outcome: change in plasma concentrations of NT-proBNP (time frame: baseline to week 6 and 12) as a measure of treatment impact on HF.
REFORM (NCT02397421)	Safety and Effectiveness of SGLT2 Inhibitors in Patients With Heart Failure and Diabetes • Study population: HFrEF with T2DM. • Estimated enrolment: *n*=56. • Treatment: dapagliflozin vs. placebo. • Primary outcome: changes in LV systolic and diastolic volumes in patients as determined by cardiac magnetic resonance imaging.

CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; MI, myocardial infarction; NT-proBNP, N-terminal pro B-type natriuretic peptide; SGLT2, sodium–glucose co-transporter type 2; T2DM, type 2 diabetes mellitus.

indicates a significantly higher risk of adverse outcomes in patients with HF and T2DM, including a higher risk for hospitalization and rehospitalization for HF, as well as increased all-cause and CV mortality, independent of HF aetiology or phenotype (i.e. HFrEF and HFpEF). HF treatment with medications and devices (e.g. ICD, CRT-D) is similarly effective in patients with and without T2DM. There has been uncertainty about the safety of older T2DM drugs such as insulin and sulphonlyureas in patients with T2DM and HF but there are no RCTs to allow firm conclusions. In patients with T2DM without HF, some drugs have been shown to increase the risk of HF hospitalizations (i.e. rosiglitazone, pioglitazone and saxagliptin) and, consequently, these medications are contraindicated in patients T2DM with prior HF or at risk of HF. Large clinical trials investigating CV safety of newer antidiabetic drugs in patients with CV disease or at high CV risk have demonstrated that GLP-1 receptor agonists and a DPP4 inhibitor, sitagliptin, have a neutral effect on the risk of HF hospitalisations. In addition, SGLT2 inhibitors, empagliflozin and canagliflozin demonstrated a significant reduction in the risk of HF hospitalizations in patients with T2DM. SGLT2 inhibitors are currently being investigated as a potential addition to the optimal medical treatment of HF, not only in patients with, but also in those without T2DM.

Conflict of interest: none declared.

References

1. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S; Pfeffer MA, McMurray JJ; CHARM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008;**29**:1377–1385.
2. MacDonald MR, Petrie MC, Hawkins NM, Petrie JR, Fisher M, McKelvie R, Aquilar D, Krum H, McMurray JJ. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. *Eur Heart J* 2008;**29**:1224–1240.
3. Vaur L, Gueret P, Lievre M, Chabaud S, Passa P; DIABHYCAR Study Group. Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 DIABetes, Hypertension, CArdiovascular Events and Ramipril) study. *Diabetes Care* 2003;**26**:855–860.
4. Seferovic PM, Paulus WJ. Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. *Eur Heart J* 2015;**36**:1718–1727, 1727a–1727c.
5. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT_2R_2 score. *Chest* 2013;**144**:1555–1563.
6. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;**20**:1183–1197.
7. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009;**32**:1327–1334.
8. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016;**18**:242–252.
9. Thrainsdottir IS, Aspelund T, Thorgeirsson G, Gudnason V, Hardarson T, Malmberg K, Sigurdsson G, Rydén L. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. *Diabetes Care* 2005;**28**:612–616.
10. 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.
11. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;**352**:837–853.
12. Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;**370**:829–840.
13. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;**358**:2560–2572.
14. Castagno D, Baird-Gunning J, Jhund PS, Biondi-Zoccai G, MacDonald MR, Petrie MC, Gaita F, McMurray JJ. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis. *Am Heart J 2011;162*:**938–48**.e2.
15. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;**360**:129–139.

16. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 2015;132:**e198**.
17. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;**369**:1317–1326.
18. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;**373**:232–242.
19. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;**369**:1327–1335.
20. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
21. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–657.
22. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**:311–322.
23. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;**373**:2247–2257.
24. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;**377**:1228–1239.
25. Davies M, Hobbs F, Davis R, Kenkre J, Roalfe AK, Hare R, Wosomu D, Lancashire RJ. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet* 2001;**358**:439–444.
26. Mosterd A, Cost B, Hoes AW, de Bruijne MC, Deckers JW, Hofman A, Grobbee DE. The prognosis of heart failure in the general population: the Rotterdam Study. *Eur Heart J* 2001;**22**:1318–1327.
27. Amato L, Paolisso G, Cacciatore F, Ferrara N, Ferrara P, Canonico S, Varricchio M, Rengo F. Congestive heart failure predicts the development of non-insulin-dependent diabetes mellitus in the elderly. The Osservatorio Geriatrico Regione Campania Group. *Diabetes Metab* 1997;**23**:213–218.
28. Kistorp C, Galatius S, Gustafsson F, Faber J, Corell P, Hildebrandt P. Prevalence and characteristics of diabetic patients in a chronic heart failure population. *Int J Cardiol* 2005;**100**:281–287.
29. From 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.
30. Bank IE, Gijsberts CM, Teng TK, Benson L, Sim D, Yeo PS, Ong HY, Jaufeerally F, Leong GK, Ling LH, Richards AM, de Kleijn DP, Dahlström U, Lund LH, Lam CS. Prevalence and clinical significance of diabetes in asian versus white patients with heart failure. *JACC Heart Fail* 2017;**5**:14–24.
31. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
32. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
33. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J 3rd, Gras D, Krum H, Sogaard P, Holzmeister J; EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;**369**:1395–1405.
34. Banks AZ, Mentz RJ, Stebbins A, Mikus CR, Schulte PJ, Fleg JL, Cooper LS, Leifer ES, Badenhop DT, Keteyian SJ, Piña IL, Kitzman DW, Fiuzat M, Whellan DJ, Kraus WE, O'Connor CM. Response to exercise training and outcomes in patients with heart failure and diabetes mellitus: insights from the HF-ACTION trial. *J Card Fail* 2016;**22**:485–491.
35. de Boer RA, Doehner W, van der Horst IC, Anker SD, Babalis D, Roughton M, Coats AJ, Flather MD, van Veldhuisen DJ; SENIORS Investigators. Influence of diabetes mellitus and hyperglycemia on prognosis in patients ≥70 years old with heart failure and effects of nebivolol (data from the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure [SENIORS]). *Am J Cardiol* 2010;**106**:78–86.e1.
36. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN; SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
37. Deedwania PC, Giles TD, Klibaner M, Ghali JK, Herlitz J, Hildebrandt P, Kjekshus J, Spinar J, Vitovec J, Stanbrook H, Wikstrand J; MERIT-HF Study Group. Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. *Am Heart J* 2005;**149**:159–167.
38. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;**362**:767–771.
39. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525–533.
40. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D, Win S, Køber L, McKelvie RS, Zile MR, Anand IS, Komajda M, Gottdiener JS, Carson PE, McMurray JJ. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). *Circulation* 2017;**135**:724–735.
41. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–2345.
42. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF Jr, Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary Digitalis Investigation Group trial. *Circulation* 2006;**114**:397–403.
43. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;**362**:759–766.
44. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383–1392.
45. Sarma S, Mentz RJ, Kwasny MJ, Fought AJ, Huffman M, Subacius H, Nodari S, Konstam M, Swedberg K, Maggioni AP, Zannad F, Bonow RO, Gheorghiade M; EVEREST investigators. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. *Eur J Heart Fail* 2013;**15**:194–202.
46. Packer M, O'Connor C, McMurray JJV, Wittes J, Abraham WT, Anker SD, Dickstein K, Filippatos G, Holcomb R, Krum H, Maggioni AP, Mebazaa A, Peacock WF, Petrie MC, Ponikowski P, Ruschitzka F, van Veldhuisen DJ, Kowarski LS, Schactman M, Holzmeister J; TRUE-AHF Investigators. Effect of ularitide on cardiovascular mortality in acute heart failure. *N Engl J Med* 2017;**376**:1956–1964.
47. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJ, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF Jr, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalán R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Méndez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011;**365**:32–43.
48. Teerlink JR, Voors AA, Ponikowski P, Pang PS, Greenberg BH, Filippatos G, Felker GM, Davison BA, Cotter G, Gimpelewicz C, Boer-Martins L, Wernsing M, Hua TA, Severin T, Metra M. Serelaxin in addition to standard therapy in acute heart failure: rationale and design of the RELAX-AHF-2 study. *Eur J Heart Fail* 2017;**19**:800–809.

49. Echouffo-Tcheugui JB, Xu H, DeVore AD, Schulte PJ, Butler J, Yancy CW, Bhatt DL, Hernandez AF, Heidenreich PA, Fonarow GC. Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: findings from Get With The Guidelines-Heart Failure registry. *Am Heart J* 2016;**182**:9–20.
50. Sud M, Yu B, Wijeysundera HC, Austin PC, Ko DT, Braga J, Cram P, Spertus JA, Domanski M, Lee DS. Associations between short or long length of stay and 30-day readmission and mortality in hospitalized patients with heart failure. *JACC Heart Fail* 2017;**5**:578–588.
51. Targher G, Dauriz M, Laroche C, Temporelli PL, Hassanein M, Seferovic PM, Drozdz J, Ferrari R, Anker S, Coats A, Filippatos G, Crespo-Leiro MG, Mebazaa A, Piepoli MF, Maggioni AP, Tavazzi L; 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.
52. Win TT, Davis HT, Laskey WK. Mortality among patients hospitalized with heart failure and diabetes mellitus: results from the National Inpatient Sample 2000 to 2010. *Circ Heart Fail* 2016;**9**:e003023.
53. Johansson I, Dahlstrom U, Edner M, Nasman P, Ryden L, Norhammar A. Risk factors, treatment and prognosis in men and women with heart failure with and without diabetes. *Heart* 2015;**101**:1139–1148.
54. Demant MN, Gislason GH, Kober L, Vaag A, Torp-Pedersen C, Andersson C. Association of heart failure severity with risk of diabetes: a Danish nationwide cohort study. *Diabetologia* 2014;**57**:1595–1600.
55. Ingle L, Reddy P, Clark AL, Cleland JG. Diabetes lowers six-minute walk test performance in heart failure. *J Am Coll Cardiol* 2006;**47**:1909–1910.
56. Preiss D, Zetterstrand S, McMurray JJ, Ostergren J, Michelson EL, Granger CB, Yusuf S, Swedberg K, Pfeffer MA, Gerstein HC, Sattar N; Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Investigators. Predictors of development of diabetes in patients with chronic heart failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Diabetes Care* 2009;**32**:915–920.
57. Preiss D, van Veldhuisen DJ, Sattar N, Krum H, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, Zannad F, McMurray JJ. Eplerenone and new-onset diabetes in patients with mild heart failure: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Eur J Heart Fail* 2012;**14**:909–915.
58. Vermes E, Ducharme A, Bourassa MG, Lessard M, White M, Tardif JC; Studies Of Left Ventricular Dysfunction. Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the Studies Of Left Ventricular Dysfunction (SOLVD). *Circulation* 2003;**107**:1291–1296.
59. Tenenbaum A, Motro M, Fisman EZ, Leor J, Freimark D, Boyko V, Mandelzweig L, Adler Y, Sherer Y, Behar S. Functional class in patients with heart failure is associated with the development of diabetes. *Am J Med* 2003;**114**:271–275.
60. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A, Hemingway H. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet Diabetes Endocrinol* 2015;**3**:105–113.
61. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;**27**:1879–1884.
62. Aronow WS, Ahn C. Incidence of heart failure in 2,737 older persons with and without diabetes mellitus. *Chest* 1999;**115**:867–868.
63. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;**321**:405–412.
64. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med* 2001;**161**:996–1002.
65. Pazin-Filho A, Kottgen A, Bertoni AG, Russell SD, Selvin E, Rosamond WD, Coresh J. HbA 1c as a risk factor for heart failure in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia* 2008;**51**:2197–2204.
66. Bibbins-Domingo K, Lin F, Vittinghoff E, Barrett-Connor E, Hulley SB, Grady D, Shlipak MG. Predictors of heart failure among women with coronary disease. *Circulation* 2004;**110**:1424–1430.
67. van Melle JP, Bot M, de Jonge P, de Boer RA, van Veldhuisen DJ, Whooley MA. Diabetes, glycemic control, and new-onset heart failure in patients with stable coronary artery disease: data from the Heart and Soul Study. *Diabetes Care* 2010;**33**:2084–2089.
68. Matsushita K, Blecker S, Pazin-Filho A, Bertoni A, Chang PP, Coresh J, Selvin E. The association of hemoglobin a1c with incident heart failure among people without diabetes: the Atherosclerosis Risk in Communities Study. *Diabetes* 2010;**59**:2020–2026.
69. Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, Martinez F, Starling RC, Desai AS, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, McMurray JJ, Packer M; PARADIGM-HF Investigators and Committees. Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. *Circ Heart Fail* 2016;**9**:e002560.
70. Suskin N, McKelvie RS, Burns RJ, Latini R, Pericak D, Probstfield J, Rouleau JL, Sigouin C, Solymoss CB, Tsuyuki R, White M, Yusuf S. Glucose and insulin abnormalities relate to functional capacity in patients with congestive heart failure. *Eur Heart J* 2000;**21**:1368–1375.
71. 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 of Left Ventricular Dysfunction (SOLVD) Prevention trial. *Am Heart J* 2004;**148**:883–888.
72. Egstrup M, Kistorp CN, Schou M, Hofsten DE, Moller JE, Tuxen CD, Gustafsson I. Abnormal glucose metabolism is associated with reduced left ventricular contractile reserve and exercise intolerance in patients with chronic heart failure. *Eur Heart J Cardiovasc Imaging* 2013;**14**:349–357.
73. Dauriz M, Targher G, Laroche C, Temporelli PL, Ferrari R, Anker S, Coats A, Filippatos G, Crespo-Leiro M, Mebazaa A, Piepoli MF, Maggioni AP, Tavazzi L; ESC-HFA Heart Failure Long-Term Registry. Association between diabetes and 1-year adverse clinical outcomes in a multinational cohort of ambulatory patients with chronic heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. *Diabetes Care* 2017;**40**:671–678.
74. Johansson I, Edner M, Dahlstrom U, Nasman P, Ryden L, Norhammar A. Is the prognosis in patients with diabetes and heart failure a matter of unsatisfactory management? An observational study from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2014;**16**:409–418.
75. Cubbon RM, Adams B, Rajwani A, Mercer BN, Patel PA, Gherardi G, Gale CP, Batin PD, Ajjan R, Kearney L, Wheatcroft SB, Sapsford RJ, Witte KK, Kearney MT. Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology. *Diabetes Vasc Dis Res* 2013;**10**:330–336.
76. Kamalesh M, Cleophas TJ. Heart failure due to systolic dysfunction and mortality in diabetes: pooled analysis of 39,505 subjects. *J Card Fail* 2009;**15**:305–309.
77. Kamalesh M, Subramanian U, Sawada S, Eckert G, Temkit M, Tierney W. Decreased survival in diabetic patients with heart failure due to systolic dysfunction. *Eur J Heart Fail* 2006;**8**:404–408.
78. Bobbio M, Ferrua S, Opasich C, Porcu M, Lucci D, Scherillo M, Tavazzi L, Maggioni AP; BRING-UP Investigators. Survival and hospitalization in heart failure patients with or without diabetes treated with beta-blockers. *J Card Fail* 2003;**9**:192–202.
79. Carrasco-Sanchez FJ, Gomez-Huelgas R, Formiga F, Conde-Martel A, Trullas JC, Bettencourt P, Arévalo-Lorido JC, Pérez-Barquero MM; RICA investigators. Association between type-2 diabetes mellitus and post-discharge outcomes in heart failure patients: findings from the RICA registry. *Diabetes Res Clin Pract* 2014;**104**:410–419.
80. Fernandez-Berges D, Consuegra-Sanchez L, Felix-Redondo FJ, Robles NR, Galan Montejano M, Lozano-Mera L. Clinical characteristics and mortality of heart failure. INCAex study. *Rev Clin Esp (Barc)* 2013;**213**:16–24.
81. Croft JB, Giles WH, Pollard RA, Keenan NL, Casper ML, Anda RF. Heart failure survival among older adults in the United States: a poor prognosis for an emerging epidemic in the Medicare population. *Arch Intern Med* 1999;**159**:505–510.
82. Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, Stough WG, Gheorghiade M, O'Connor CM, Sun JL, Yancy CW, Young JB, Fonarow GC. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2007;**154**:277.e1–8.
83. Kapoor JR, Fonarow GC, Zhao X, Kapoor R, Hernandez AF, Heidenreich PA. Diabetes, quality of care, and in-hospital outcomes in patients hospitalized with heart failure. *Am Heart J 2011;162*:**480–6**.e3.
84. O'Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, Greenberg BH, Yancy CW, Young JB, Fonarow GC. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2008;**156**:662–673.
85. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC; ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006;**47**:76–84.

86. Parissis JT, Rafouli-Stergiou P, Mebazaa A, Ikonomidis I, Bistola V, Nikolaou M, Meas T, Delgado J, Vilas-Boas F, Paraskevaidis I, Anastasiou-Nana M, Follath F. Acute heart failure in patients with diabetes mellitus: clinical characteristics and predictors of in-hospital mortality. *Int J Cardiol* 2012;**157**:108–113.
87. MacDonald MR, Jhund PS, Petrie MC, Lewsey JD, Hawkins NM, Bhagra S, Munoz N, Varyani F, Redpath A, Chalmers J, MacIntyre K, McMurray JJ. Discordant short- and long-term outcomes associated with diabetes in patients with heart failure: importance of age and sex: a population study of 5.1 million people in Scotland. *Circ Heart Fail* 2008;**1**:234–241.
88. Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, Stewart D, Pinkett T, Ghali JK, Wilson AC. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *Am J Cardiol* 1996;**77**:1017–1020.
89. Aguilar D, Deswal A, Ramasubbu K, Mann DL, Bozkurt B. Comparison of patients with heart failure and preserved left ventricular ejection fraction among those with versus without diabetes mellitus. *Am J Cardiol* 2010;**105**:373–377.
90. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;**359**:2456–2467.
91. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;**362**:777–781.
92. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007;**297**:1319–1331.
93. Dauriz M, Mantovani A, Bonapace S, Verlato G, Zoppini G, Bonora E, Targher G. Prognostic impact of diabetes on long-term survival outcomes in patients with heart failure: a meta-analysis. *Diabetes Care* 2017;**40**:1597–1605.
94. Domanski M, Krause-Steinrauf H, Deedwania P, Follmann D, Ghali JK, Gilbert E, Haffner S, Katz R, Lindenfeld J, Lowes BD, Martin W, McGrew F, Bristow MR; BEST Investigators. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. *J Am Coll Cardiol* 2003;**42**:914–922.
95. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njølstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;**364**:829–841.
96. Andersson C, Weeke P, Pecini R, Kjaergaard J, Hassager C, Kober L, Torp-Pedersen C. Long-term impact of diabetes in patients hospitalized with ischemic and non-ischemic heart failure. *Scand Cardiovasc J* 2010;**44**:37–44.
97. De Groote P, Lamblin N, Mouquet F, Plichon D, McFadden E, Van Belle E, Bauters C. Impact of diabetes mellitus on long-term survival in patients with congestive heart failure. *Eur Heart J* 2004;**25**:656–662.
98. Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ. Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. *J Am Coll Cardiol* 2001;**38**:421–428.
99. Brophy JM, Dagenais GR, McSherry F, Williford W, Yusuf S. A multivariate model for predicting mortality in patients with heart failure and systolic dysfunction. *Am J Med* 2004;**116**:300–304.
100. Gustafsson I, Brendorp B, Seibaek M, Burchardt H, Hildebrandt P, Kober L, Torp-Pedersen C; Danish Investigatord of Arrhythmia and Mortality on Dofetilde Study Group. Influence of diabetes and diabetes-gender interaction on the risk of death in patients hospitalized with congestive heart failure. *J Am Coll Cardiol* 2004;**43**:771–777.
101. Varela-Roman A, Grigorian Shamagian 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**:859–864.
102. Abdul-Rahim AH, MacIsaac RL, Jhund PS, Petrie MC, Lees KR, McMurray JJ; VICCTA-Heart Failure Collaborators. Efficacy and safety of digoxin in patients with heart failure and reduced ejection fraction according to diabetes status: an analysis of the Digitalis Investigation Group (DIG) trial. *Int J Cardiol* 2016;**209**:310–316.
103. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;**34**:29–34.
104. Gerstein HC, Swedberg K, Carlsson J, McMurray JJ, Michelson EL, Olofsson B, Yusuf S; CHARM Program Investigators. The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Arch Intern Med* 2008;**168**:1699–1704.
105. Elder DH, Singh JS, Levin D, Donnelly LA, Choy AM, 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.
106. Eshaghian S, Horwich TB, Fonarow GC. An unexpected inverse relationship between HbA1c levels and mortality in patients with diabetes and advanced systolic heart failure. *Am Heart J* 2006;**151**:91.
107. Dauriz M, Targher G, Temporelli PL, Lucci D, Gonzini L, Nicolosi GL, Marchioli R, Tognoni G, Latini R, Cosmi F, Tavazzi L, Maggioni AP; GISSI-HF Investigators. Prognostic impact of diabetes and prediabetes on survival outcomes in patients with chronic heart failure: a post-hoc analysis of the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure) Trial. *J Am Heart Assoc* 2017;**6**:e005156.
108. Kristensen SL, Jhund PS, Lee MM, Kober L, Solomon SD, Granger CB, Yusuf S, Pfeffer MA, Swedberg K, McMurray JJ; CHARM Investigators and Committees. Prevalence of prediabetes and undiagnosed diabetes in patients with HFpEF and HFrEF and associated clinical outcomes. *Cardiovasc Drugs Ther* 2017;**31**:545–549.
109. Goode KM, John J, Rigby AS, Kilpatrick ES, Atkin SL, Bragadeesh T, Clark AL, Cleland JG. Elevated glycated haemoglobin is a strong predictor of mortality in patients with left ventricular systolic dysfunction who are not receiving treatment for diabetes mellitus. *Heart* 2009;**95**:917–923.
110. Avery CL, Loehr LR, Baggett C, Chang PP, Kucharska-Newton AM, Matsushita K, Rosamond WD, Heiss G. The population burden of heart failure attributable to modifiable risk factors: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Coll Cardiol* 2012;**60**:1640–1646.
111. 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.
112. Komajda M, McMurray JJ, Beck-Nielsen H, Gomis R, Hanefeld M, Pocock SJ, Curtis PS, Jones NP, Home PD. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. *Eur Heart J* 2010;**31**:824–831.
113. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* 2004;**27**:699–703.
114. Cavender MA, Steg PG, Smith SC Jr, Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL; REACH Registry Investigators. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation* 2015;**132**:923–931.
115. Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH, Rutten GE, Hoes AW. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia* 2012;**55**:2154–2162.
116. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-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. 2016 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.
117. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, Tsuyuki RT, White M, Rouleau J, Latini R, Maggioni A, Young J, Pogue J. Comparison of candesartan, enalapril, and their combination in congestive heart failure: Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation* 1999;**100**:1056–1064.
118. Kievit RF, Gohar A, Hoes AW, Bots ML, van Riet EE, van Mourik Y, Bertens LC, Boonman-de Winter LJ, den Ruijter HM, Rutten FH; Queen Of Hearts And RECONNECT Consortium. Efficient selective screening for heart failure in elderly men and women from the community: a diagnostic individual participant data meta-analysis. *Eur J Prev Cardiol* 2018 Jan 1. https://doi.org/10.1177/2047487317749897. [Epub ahead of print]
119. van Giessen A, Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH, Hoes AW, Koffijberg H. Cost-effectiveness of screening strategies to detect heart failure in patients with type 2 diabetes. *Cardiovasc Diabetol* 2016;**15**:48.
120. Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular

diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;**34**:3035–3087.

121. Poornima IG, Parikh P, Shannon RP. Diabetic cardiomyopathy: the search for a unifying hypothesis. *Circ Res* 2006;**98**:596–605.
122. Doehner W, Frenneaux M, Anker SD. Metabolic impairment in heart failure: the myocardial and systemic perspective. *J Am Coll Cardiol* 2014;**64**:1388–1400.
123. Paternostro G, Pagano D, Gnecchi-Ruscone T, Bonser RS, Camici PG. Insulin resistance in patients with cardiac hypertrophy. *Cardiovasc Res* 1999;**42**:246–253.
124. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PW, Vasan RS. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation* 2003;**107**:448–454.
125. van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, Ijsselmuiden AJ, Schalkwijk CG, Bronzwaer JG, Diamant M, Borbély A, van der Velden J, Stienen GJ, Laarman GJ, Niessen HW, Paulus WJ. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation* 2008;**117**:43–51.
126. Falcao-Pires I, Hamdani N, Borbely A, Gavina C, Schalkwijk CG, van der Velden J, van Heerebeek L, Stienen GJ, Niessen HW, Leite-Moreira AF, Paulus WJ. Diabetes mellitus worsens diastolic left ventricular dysfunction in aortic stenosis through altered myocardial structure and cardiomyocyte stiffness. *Circulation* 2011;**124**:1151–1159.
127. Zhang M, Kho AL, Anilkumar N, Chibber R, Pagano PJ, Shah AM, Cave AC. Glycated proteins stimulate reactive oxygen species production in cardiac myocytes: involvement of Nox2 (gp91phox)-containing NADPH oxidase. *Circulation* 2006;**113**:1235–1243.
128. Rijzewijk LJ, van der Meer RW, Smit JW, Diamant M, Bax JJ, Hammer S, Romijn JA, de Roos A, Lamb HJ. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. *J Am Coll Cardiol* 2008;**52**:1793–1799.
129. Lundbaek K. Diabetic angiopathy: a specific vascular disease. *Lancet* 1954;**266**:377–379.
130. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 1972;**30**:595–602.
131. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. *Circulation* 2007;**115**:3213–3123.
132. Boyer JK, Thanigaraj S, Schechtman KB, Perez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. *Am J Cardiol* 2004;**93**:870–875.
133. Liu JE, Palmieri V, Roman MJ, Bella JN, Fabsitz R, Howard BV, Welty TK, Lee ET, Devereux RB. The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. *J Am Coll Cardiol* 2001;**37**:1943–1949.
134. Stahrenberg R, Edelmann F, Mende M, Kockskamper A, Dungen HD, Scherer M, Kochen MM, Binder L, Herrmann-Lingen C, Schönbrunn L, Gelbrich G, Hasenfuss G, Pieske B, Wachter R. Association of glucose metabolism with diastolic function along the diabetic continuum. *Diabetologia* 2010;**53**:1331–1340.
135. Blomstrand P, Engvall M, Festin K, Lindstrom T, Lanne T, Maret E, Nyström FH, Maret-Ouda J, Östgren CJ, Engvall J. Left ventricular diastolic function, assessed by echocardiography and tissue Doppler imaging, is a strong predictor of cardiovascular events, superior to global left ventricular longitudinal strain, in patients with type 2 diabetes. *Eur Heart J Cardiovasc Imaging* 2015;**16**:1000–1007.
136. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol* 2010;**55**:300–305.
137. Mogelvang R, Sogaard P, Pedersen SA, Olsen NT, Marott JL, Schnohr P, Goetze JP, Jensen JS. Cardiac dysfunction assessed by echocardiographic tissue Doppler imaging is an independent predictor of mortality in the general population. *Circulation* 2009;**119**:2679–2685.
138. Poulsen MK, Henriksen JE, Dahl J, Johansen A, Gerke O, Vach W, Haghfelt T, Hoilund-Carlsen PF, Beck-Nielsen H, Moller JE. Left ventricular diastolic function in type 2 diabetes mellitus: prevalence and association with myocardial and vascular disease. *Circ Cardiovasc Imaging* 2010;**3**:24–31.
139. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971–1993. *Diabetes Care* 1998;**21**:1138–1145.
140. Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care* 1979;**2**:120–126.
141. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care* 2000;**23**:962–968.
142. Shekelle PG, Rich MW, Morton SC, Atkinson CS, Tu W, Maglione M, Rhodes S, Barrett M, Fonarow GC, Greenberg B, Heidenreich PA, Knabel T, Konstam MA, Steimle A, Warner Stevenson L. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. *J Am Coll Cardiol* 2003;**41**:1529–1538.
143. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Rydén L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999;**100**:2312–2318.
144. Rydén L, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Packer M, Polle-Wilson PA. Efficacy and safety of high-dose lisinopril in chronic heart failure patients at high cardiovascular risk, including those with diabetes mellitus. Results from the ATLAS trial. *Eur Heart J* 2000;**21**:1967–1978.
145. Maggioni AP, Anand I, Gottlieb SO, Latini R, Tognoni G, Cohn JN; Val-HeFT Investigators (Valsartan Heart Failure Trial). Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 2002;**40**:1414–1421.
146. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GA, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA; HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009;**374**:1840–1848.
147. Desai AS, Swedberg K, McMurray JJ, Granger CB, Yusuf S, Young JB, Dunlap ME, Solomon SD, Hainer JW, Olofsson B, Michelson EL, Pfeffer MA; CHARM Program Investigators. Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM Program. *J Am Coll Cardiol* 2007;**50**:1959–1966.
148. Collins AJ, Foley RN, Herzog C, Chavers BM, Gilbertson D, Ishani A, Kasiske BL, Liu J, Mau LW, McBean M, Murray A, St Peter W, Guo H, Li Q, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers PW, Agodoa L. Excerpts from the US Renal Data System 2009 Annual Data Report. *Am J Kidney Dis* 2010;**55**(1 Suppl 1):S1–420, A6–7.
149. de Chatel R, Weidmann P, Flammer J, Ziegler WH, Beretta-Piccoli C, Vetter W, Reubi FC. Sodium, renin, aldosterone, catecholamines, and blood pressure in diabetes mellitus. *Kidney Int* 1977;**12**:412–421.
150. Anderson S, Jung FF, Ingelfinger JR. Renal renin-angiotensin system in diabetes: functional, immunohistochemical, and molecular biological correlations. *Am J Physiol* 1993;**265**(4 Pt 2):F477–486.
151. DeFronzo RA. Hyperkalemia and hyporeninemic hypoaldosteronism. *Kidney Int* 1980;**17**:118–134.
152. Erdmann E, Lechat P, Verkenne P, Wiemann H. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. *Eur J Heart Fail* 2001;**3**:469–479.
153. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *Circulation* 2002;**106**:2194–2199.
154. Torp-Pedersen C, Metra M, Charlesworth A, Spark P, Lukas MA, Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Remme WJ, Scherhag A; COMET Investigators. Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 2007;**93**:968–973.
155. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;**344**:1651–1658.
156. Haas SJ, Vos T, Gilbert RE, Krum H. Are beta-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. *Am Heart J* 2003;**146**:848–853.
157. Bell DS, Lukas MA, Holdbrook FK, Fowler MB. The effect of carvedilol on mortality risk in heart failure patients with diabetes: results of a meta-analysis. *Curr Med Res Opin* 2006;**22**:287–296.
158. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717.

159. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
160. Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, Tschoepe D, Doehner W, Greene SJ, Senni M, Gheorghiade M, Fonarow GC. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. *JACC Heart Fail* 2015;**3**:136–145.
161. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, Pitt B, Solomon SD; Randomized Aldactone Evaluation Study (RALES) Investigators. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. *Circ Heart Fail* 2014;**7**:573–579.
162. Seferovic JP, Claggett B, Seidelmann SB, Seely EW, Packer M, Zile MR, Rouleau JL, Swedberg K, Lefkowitz M, Shi VC, Desai AS, McMurray JJ, Solomon SD. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. *Lancet Diabetes Endocrinol* 2017;**5**:333–340.
163. Taylor AL, Ziesche S, Yancy CW, Carson P, Ferdinand K, Taylor M, Adams K, Olukotun AY, Ofili E, Tam SW, Sabolinski ML, Worcel M, Cohn JN; African-American Heart Failure Trial Investigators. Early and sustained benefit on event-free survival and heart failure hospitalization from fixed-dose combination of isosorbide dinitrate/hydralazine: consistency across subgroups in the African-American Heart Failure Trial. *Circulation* 2007;**115**:1747–1753.
164. Komajda M, Tavazzi L, Francq BG, Bohm M, Borer JS, Ford I, Swedberg K; SHIFT Investigators. Efficacy and safety of ivabradine in patients with chronic systolic heart failure and diabetes: an analysis from the SHIFT trial. *Eur J Heart Fail* 2015;**17**:1294–1301.
165. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237.
166. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230.
167. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
168. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
169. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–1338.
170. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–2395.
171. Ghali JK, Boehmer J, Feldman AM, Saxon LA, Demarco T, Carson P, Yong P, Galle EG, Leigh J, Ecklund FL, Bristow MR. Influence of diabetes on cardiac resynchronization therapy with or without defibrillator in patients with advanced heart failure. *J Card Fail* 2007;**13**:769–773.
172. Hoppe UC, Freemantle N, Cleland JG, Marijianowski M, Erdmann E. Effect of cardiac resynchronization on morbidity and mortality of diabetic patients with severe heart failure. *Diabetes Care* 2007;**30**:722–724.
173. Martin DT, McNitt S, Nesto RW, Rutter MK, Moss AJ. Cardiac resynchronization therapy reduces the risk of cardiac events in patients with diabetes enrolled in the multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy (MADIT-CRT). *Circ Heart Fail* 2011;**4**:332–338.
174. Howard BV, Best LG, Galloway JM, Howard WJ, Jones K, Lee ET, Ratner RE, Resnick HE, Devereux RB. Coronary heart disease risk equivalence in diabetes depends on concomitant risk factors. *Diabetes Care* 2006;**29**:391–397.
175. Juutilainen A, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. *Diabetes Care* 2005;**28**:2901–2907.
176. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, Oh JK, She L, Moore VL, Desvigne-Nickens P, Sopko G, Rouleau JL; STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med* 2016;**374**: 1511–1520.
177. MacDonald MR, She L, Doenst T, Binkley PF, Rouleau JL, Tan RS, Lee KL, Miller AB, Sopko G, Szalewska D, Waclawiw MA, Dabrowski R, Castelvecchio S, Adlbrecht C, Michler RE, Oh JK, Velazquez EJ, Petrie MC. Clinical characteristics and outcomes of patients with and without diabetes in the Surgical Treatment for Ischemic Heart Failure (STICH) trial. *Eur J Heart Fail* 2015;**17**:725–734.
178. Kilic A, Weiss ES, George TJ, Arnaoutakis GJ, Yuh DD, Shah AS, Conte JV. What predicts long-term survival after heart transplantation? An analysis of 9,400 ten-year survivors. *Ann Thorac Surg* 2012;**93**:699–704.
179. MacDonald MR, Eurich DT, Majumdar SR, Lewsey JD, Bhagra S, Jhund PS, Petrie MC, McMurray JJ, Petrie JR, McAlister FA. Treatment of type 2 diabetes and outcomes in patients with heart failure: a nested case-control study from the U.K. General Practice Research Database. *Diabetes Care* 2010;**33**:1213–1218.
180. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hanselmann A, Nilsson B, Møller JE, Hjort J, Rasmussen J, Boesgaard TW, Schou M, Videbaek L, Gustafsson I, Flyvbjerg A, Wiggers H, Tarnow L. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE) – a multicentre, double-blind, randomised, placebo-controlled trial. *Eur J Heart Fail* 2017;**19**:69–77.
181. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, Mann DL, Whellan DJ, Kiernan MS, Felker GM, McNulty SE, Anstrom KJ, Shah MR, Braunwald E, Cappola TP; NHLBI Heart Failure Clinical Research Network. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2016;**316**:500–508.
182. Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, Hughes RI, Khunti K, Wilkins MR, Majeed A, Elliott P. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ* 2009;**339**:b4731.
183. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet* 2007;**370**:1129–1136.
184. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet* 2015;**385**:2067–2076.
185. McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, Bethel MA, Cornel JH, Lopes RD, Halvorsen S, Ambrosio G, Buse JB, Josse RG, Lachin JM, Pencina MJ, Garg J, Lokhnygina Y, Holman RR, Peterson ED; Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) Study Group. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: secondary analysis of a randomized clinical trial. *JAMA Cardiol* 2016;**1**:126–135.
186. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;**375**:1834–1844.
187. Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, Maggioni AP, Pogue J, Probstfield J, Ramachandran A, Riddle MC, Rydén LE, Yusuf S. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;**367**: 319–328.
188. Holman RR, Coleman RL, Chan JCN, Chiasson JL, Feng H, Ge J, Gerstein HC, Gray R, Huo Y, Lang Z, McMurray JJ, Rydén L, Schröder S, Sun Y, Theodorakis MJ, Tendera M, Tucker L, Tuomilehto J, Wei Y, Yang W, Wang D, Hu D, Pan C; ACE Study Group. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017;**5**:877–886.
189. Mahaffey KW, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Fabbrini E, Sun T, Li Q, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018;**137**:323–334.
190. Lepore JJ, Olson E, Demopoulos L, Haws T, Fang Z, Barbour AM, Fossler M, Davila-Roman VG, Russell SD, Gropler RJ. Effects of the novel long-acting GLP-1 agonist, albiglutide, on cardiac function, cardiac metabolism, and exercise capacity in patients with chronic heart failure and reduced ejection fraction. *JACC Heart Fail* 2016;**4**:559–566.