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# Diabetes mellitus and heart failure – an overview of epidemiology and management

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## Abstract:

Heart failure and Diabetes mellitus are chronic complex medical conditions that are closely related and commonly co-exist. Treatment options have varied over the years, but newer treatment modalities have developed which have improved prognosis and longevity of patients with these conditions. Unfortunately, despite these advances, the evidence base remains insufficient, and larger randomised control trials need to be conducted. Here we discuss the available evidence and treatment and management of these inter-related conditions.

## Key words

Diabetes Mellitus, Heart failure, Left ventricular systolic dysfunction

## Introduction

HF has been a major health concern for a number of years, and is a leading cause for hospitalisation in patients over 65 years old.<sup>1</sup> DM is a chronic progressive disease, and is a well recognised risk factor for HF.<sup>2–5</sup> The Framingham Heart Study first demonstrated over 20 years ago an increased risk of congestive HF in patients with diabetes.<sup>6</sup> Over the years, they have been mostly treated as separate entities, but often a significant overlap exists.

In this article, we discuss the epidemiological characteristics, the associated mortality and morbidity and the management of these two inter-related conditions.

## Incidence

DM is an independent risk factor for development of HF.<sup>4</sup> Population studies such as the Cardiovascular Health Study have clearly shown DM as an independent risk factor for HF, with a HR of 1.74 (1.38–2.19).<sup>4</sup> The Framingham study showed the risk of HF was 2-fold higher in men and 5-fold higher in women with diabetes.<sup>6</sup> The association was even stronger in younger patients (ages  $\leq$  65 years), being 4-fold higher in male patients and 8-fold higher in female patients with diabetes than in subjects without diabetes. A large survey of patients in a Kaiser Permanente database showed that in subjects with diabetes HF approximately doubled from 33 cases per 1,000 for subjects aged 45–54 years to 68

cases per 1,000 for those aged 55–64 years; it then doubled again to 135 cases per 1,000 for subjects aged 65–74 years.<sup>7</sup> In a study of elderly nursing home residents initially free of HF, 39% of those with diabetes *vs.* 23% of those without diabetes had developed HF after 43 months of follow-up; RR, 1.3.<sup>8</sup>

Clinical trial data have also revealed similar associations between diabetes and HF. In the ALLHAT, Davis *et al.*<sup>9</sup> found that patients with diabetes had a nearly 2-fold risk for HF hospitalization or death after adjustment for other risk factors (RR, 1.95). The association with diabetes was independent from and equivalent in degree to that of coronary artery disease and greater than that for electrocardiographic left ventricular hypertrophy and renal dysfunction. The UKPDS demonstrated that the incidence of HF in patients with diabetes correlated with HbA<sub>1c</sub> levels.<sup>10</sup>

Interestingly, patients with HF are also at higher risk of developing diabetes. During a 3-year follow-up of HF patients without diabetes, 29% developed diabetes compared

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**Table 1.** Epidemiology of HF in patients with diabetes

- HF is twice as common in men with diabetes and five times as common in women with diabetes as in age-matched subjects without diabetes
- Overall prevalence of diabetes (both type 1 and 2) in HF is approximately 20–25%
- Patients with diabetes have a nearly 2-fold risk for HF hospitalization or death
- Prevalence of HF in elderly subjects with diabetes is 39%
- 1% rise in HbA<sub>1C</sub> is associated with a 12% increased risk of HF in elderly patients with diabetes
- Diabetes patients account for 25% of all patients enrolled in large HF trials

with 18% of matched control subjects; multivariate analysis also showed HF to be an independent risk factor for the development of diabetes. Subgroup analysis of clinical trials such as the SOLVD trial showed that 5.9% of patients developed diabetes over a mean of 2.9 years.<sup>11</sup>

## Prevalence

Over recent years, the prevalence of diabetes, in particular type 2 diabetes, has significantly increased, and this has in turn impacted on the incidence of associated complications, including HF. In 1995, the estimated prevalence of diabetes in adults worldwide was 4%. This has been projected to increase to 5.4% by 2025, which amounts to about 300 million adults.<sup>12</sup> Subgroup analysis of various randomised studies have shown that a significant proportion of HF patients suffer from diabetes.<sup>13–15</sup> Das *et al.*<sup>14</sup> conducted a retrospective study of the SOLVD trial population, and found that in patients with asymptomatic ischaemic cardiomyopathy, diabetes was a risk factor for the development of HF symptoms (HR, 1.56), HF hospitalization (RR, 2.16), or the composite of death or symptom development (HR, 1.50). In the SOLVD trial itself, 15% of the patients had diabetes in the Prevention arm, and 26% in the Treatment arm.<sup>11</sup>

Registry data usually provide a better estimate of prevalence, and the SOLVD registry classed 23% (1,425) of the total 6,076 patients with left ventricular systolic dysfunction as suffering from diabetes. Other registry data have also shown a similar prevalence, suggesting an overall prevalence of diabetes (both types 1 and 2) in HF of approximately 20–25%.

Key points regarding the epidemiology of HF in patients with diabetes have been summarised in table 1.

## Diabetes and HF – Mortality and Morbidity

Patients with diabetes that develop HF have a markedly increased mortality. HF in type 2 diabetes is generally associated with a high death rate (45% vs. 24% of those with

diabetes and no HF over 5 years).<sup>16</sup> In population-based studies such as the Framingham Heart Study, mortality in diabetes patients 1 year after diagnosis of HF was 34%.<sup>17</sup> In the DIABHYCAR study the incidence for hospitalisation due to HF was noted to be 10/1,000 person-years.<sup>18</sup>

## Management of HF in Patients with Diabetes

### Risk reduction

It is a well known fact that a number of patients with diabetes and HF have associated cardiac risk factors such as hypercholesterolaemia, hypertension and obesity. Adequate control of these via dietary measures and exercise could prevent coronary artery disease, and subsequently reduce the incidence of subsequent HF. Trials have also shown that weight reduction and increased exercise reduces the risk of diabetes in HF patients<sup>19</sup>.

As mentioned above in table 1, the risk of HF increases by 12% for every 1% rise in HbA<sub>1C</sub>. However, it is not clearly known whether improving glycaemic control necessarily reduces the risk of HF, and certainly this was not demonstrated in the UKPDS.<sup>19</sup>

### Medical treatment – options

**Reduction of neuro-hormonal activation.** The ACC and the AHA<sup>20</sup> emphasise the importance of neuro-hormonal blockade as the foundation of treatment of HF. Several clinical trials conducted over the years have indicated the benefit of reduction of neuro-hormonal activation in improving the prognosis of patients with chronic HF.

**ACE inhibitors.** Placebo controlled clinical trials enrolling >7,000 patients with LVSD due to a wide range of causes and with varied symptom severity have demonstrated the effectiveness of ACE inhibitors in prolonging life and reducing the risk for hospitalization.<sup>20</sup> These benefits have been attributed to the reduction in the production of angiotensin II through antagonism of ACE as well as to inhibition of kininase-II, which results in the accumulation of bradykinin (leads to cough in some patients).

In a meta-analysis of five clinical trials of patients with LVSD or HF with an average of 35 months of follow-up, therapy with ACE inhibitors was associated with a reduction in the risk for death (ARR, 3.8%). Only 18% of the patients had diabetes; however, no subgroup analysis was performed<sup>21</sup>. In a meta-analysis of six placebo-controlled clinical trials in patients with LVSD, Shekelle *et al.* found that the RR of death in ACE inhibitor-treated, compared with placebo-treated, patients was 0.85 (0.78–0.92) in non-diabetes patients compared with 0.84 (0.70–1.00) in diabetes patients<sup>22</sup> (see table 2). In a community-based observational study of older patients hospitalised with HF, the prescription of ACE inhibitors at hospital discharge was

**Table 2.** A summary of ACE inhibitor use and RR analysis between subjects with and without diabetes in various HF trials

Name of study	Non-DM	DM	RR non-DM	RR, DM	RRR (95% CI)
CONSENSUS <sup>24</sup>	197	56	0.64 (0.46–0.88)	1.06 (0.65–1.74)	1.67 (0.93–3.01)
SAVE <sup>25</sup>	1,739	492	0.82 (0.68–0.99)	0.89 (0.68–1.16)	1.09 (0.79–1.50)
SOLVD <sup>26</sup>	1,906	663	0.84 (0.74–0.95)	1.01 (0.85–1.21)	1.21 (0.97–1.50)
TRACE <sup>27</sup>	1,512	273	0.85 (0.74–0.97)	0.73 (0.57–0.94)	0.87 (0.65–1.15)

**Table 3.** Mortality benefits of beta-blockers in the MERIT-HF trial

Hospitalisations	Patients with diabetes			Patients without diabetes		
	Placebo (n=106)	Metoprolol CR/XL (n=93)	P	Placebo (n=290)	Metoprolol CR/XL (n=306)	P
<b>Cardiovascular causes</b>						
No. of patients with any hospitalisation n (%)	49 (46)	30 (32)	0.03	96 (33)	69 (23)	0.007
Total no. of hospitalisations n (%)	101 (95)	47 (50)	0.026	168 (58)	136 (44)	0.009
<b>Worsening HF</b>						
No. of patients with any hospitalisation n (%)	40 (38)	20 (22)	0.0024	63 (22)	40 (14)	0.0053
Total no. of hospitalisations n (%)	75 (71)	27 (29)	0.002	112 (39)	78 (26)	0.005

associated with lower RRs for death at 1 year in patients with and without diabetes.<sup>23</sup>

ACE inhibitors should therefore be considered in all patients with diabetes and LVSD, regardless of cause or symptom severity, in the absence of treatment contraindications. With proper monitoring, ACE inhibitors can be used safely in patients with advanced renal failure,<sup>28</sup> and there is evidence from observational studies of the benefits of ACE inhibitors in patients with HF and severe renal dysfunction.<sup>23</sup>

**Beta-blockers.** In the past, there have been concerns that beta-blockers may be deleterious in patients with diabetes by blunting the adrenergic response to hypoglycaemia. A review of HF treatment conducted in Australia showed that diabetes patients with HF are less likely to be discharged from hospital on beta-blockers compared with patients without diabetes.<sup>29</sup> Data from the COPERNICUS trial, comparing the beta-blocker carvedilol with placebo in patients with LVSD and severe symptomatic HF, showed that the mortality benefit of therapy was significant in the subgroup of patients with diabetes and identical to that of patients without diabetes.<sup>30</sup> In the US Carvedilol Heart Failure study, carvedilol resulted in a 65% reduction in mortality.<sup>31</sup> Analyses of trial data from the CIBIS-II study and MERIT-HF have shown similar mortality benefits, in

addition to reduction in morbidity and rate of hospitalisation<sup>32</sup> (see table 3).

On the basis of the available data, patients with diabetes and HF should be considered for beta-blocker therapy. Choices are limited, though the most appropriate ones would be carvedilol, extended release metoprolol or bisoprolol from available trial data. The drugs must be introduced cautiously in patients who are hypotensive and in those with poor hypoglycaemic awareness.

**Angiotensin receptor blockers.** Angiotensin receptor blockers provide an alternative to ACE inhibitors to inhibit the renin-angiotensin system. The Val-HeFT demonstrated a significant mortality and morbidity benefit in patients with and without diabetes treated with valsartan.<sup>33</sup> The CHARM (candesartan) trial showed similar benefits<sup>34</sup>. A recent analysis of the LIFE study and the RENAAL study showed losartan significantly reduced the incidence of first hospitalization for HF: adjusted HR 0.74 in RENAAL (losartan vs. placebo); adjusted HR 0.57 in LIFE (losartan vs. atenolol).<sup>35</sup>

**Aldosterone antagonists.** The EPHEsus compared the selective aldosterone inhibitor eplerenone with placebo in patients with LVSD and symptoms of HF following an acute MI. Subjects with diabetes (32% of the population) were

**Table 4.** Possible mechanisms of aspirin resistance

- Increased platelet reactivity via:<sup>41</sup>
  - decreased endothelial nitric oxide production
  - increased platelet turnover
  - altered platelet structure as a result of dyslipidaemia
  - disproportionate increase in intra-platelet calcium concentration
- Hyper-sensitivity of platelets to  $\gamma$ ADP (*in vitro* studies)<sup>42</sup>
- Oxidative stress via a COX independent mechanism contributing to aspirin-insensitive TXA<sub>2</sub> biosynthesis<sup>43</sup>
- Hyperglycaemia in diabetes can cause glycation of platelets and fibrinogen as opposed to acetylation, which improves platelet response and enhances fibrinolysis<sup>44</sup>

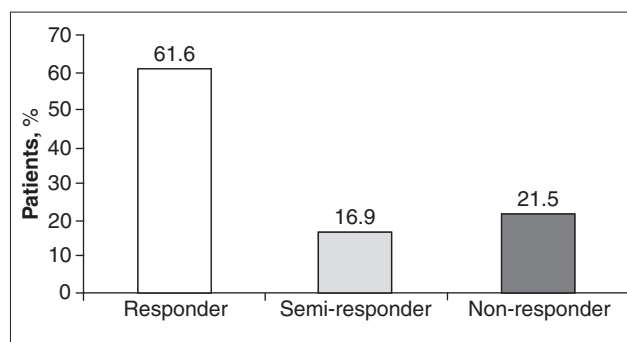
enrolled with LVSD alone regardless of symptoms.<sup>36</sup> Treatment with eplerenone resulted in a significant reduction in all-cause mortality (ARR, 2.3%; RR, 0.85; 95% CI, 0.75–0.96) as well as the risk for cardiovascular death and hospitalisation or sudden cardiac death. Subgroup analysis showed similar benefits in patients with diabetes.

The RALES showed spironolactone had benefits in patients with HF, but subgroup analysis in patients with diabetes was not performed.

Aldosterone antagonists should be commenced in patients with NYHA class III–IV HF, in the absence of contraindications and in the presence of normal serum potassium. It is important to be aware of the fact that patients with diabetes and renal dysfunction can have renal tubular acidosis type IV, which increases the risk of hyperkalaemia with concomitant ACE inhibitor therapy. Regular monitoring is advised and the aim should be to keep the serum potassium <5 mmol/L.

**Diuretics.** There is no strong evidence confirming additional benefit of diuretic therapy in diabetes patients with HF compared with patients without diabetes. However, their benefit in managing pulmonary oedema and fluid overload is well established, and should be used in such circumstances. Thiazide diuretics can potentiate hyperglycaemia primarily through the reduction in total body potassium and the subsequent decreased insulin secretion. This effect can be reversed by potassium supplementation.<sup>37</sup>

**Aspirin.** Ischaemia is a common cause of diabetic cardiomyopathy. The benefits of aspirin in ischaemic heart disease are well established; however, aspirin resistance has been an issue, especially in patients with diabetes. Numerous mechanisms have been postulated, as listed in table 4. The PPP trial failed to show a clear benefit of aspirin therapy in patients with diabetes with a non-significant reduction of cardiovascular events compared with a significant risk reduction in subjects without diabetes.<sup>38</sup> A cohort study conducted by Cubbon *et al.* showed that aspirin was not associated with a significant reduction in mortality in patients with diabetes



**Figure 1.** Prevalence of aspirin responders, semi-responders and non-responders in type 2 diabetes patients (from Fateh-Moghadam, S *et al.*<sup>40</sup> with permission)

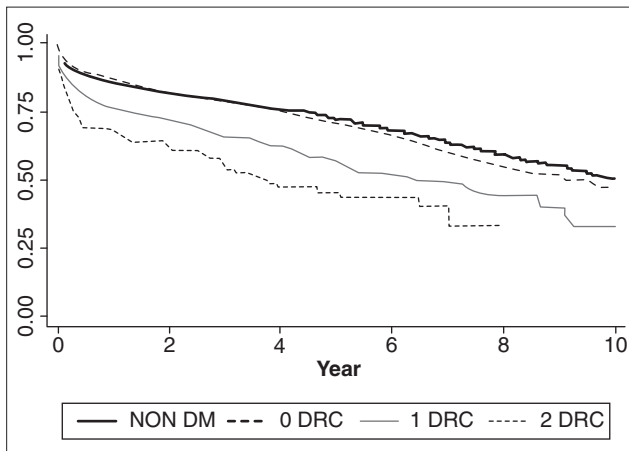
compared with non diabetes patients.<sup>39</sup> In a study of 172 patients with type 2 diabetes and concomitant cardiovascular risk factors, Fateh-Moghadam *et al.* found that a substantial number of patients with type 2 diabetes are resistant (21.5%) or semi-resistant (16.9%) to chronic aspirin treatment (figure 1).<sup>40</sup>

The role of aspirin in patients with diabetes and HF has so far not been studied. Existing antiplatelet trials and numerous large meta-analyses have not revealed any specific outcome data supporting its use in chronic HF. However, given its benefit in ischaemic heart disease, aspirin is still currently recommended in patients with diabetic ischaemic cardiomyopathy. The recent WATCH trial has shown no mortality benefit of warfarin or clopidogrel over aspirin in chronic HF.<sup>45</sup>

### Non-pharmacological therapy

**CRT.** CRT reduces symptoms and improves left ventricular function and prognosis in many patients with moderate-to-severe HF due to systolic dysfunction and cardiac dyssynchrony.<sup>46–48</sup> An analysis of the CARE-HF trial conducted by Hoppe *et al.*<sup>49</sup> looked at mortality and morbidity benefits of CRT in patients with diabetes versus patients without diabetes. Patients with advanced HF and diabetes treated with insulin had a markedly worse prognosis. CRT was equally effective in reducing mortality and in improving clinical outcomes in patients with diabetes compared with those without diabetes.

**Myocardial revascularisation.** Coronary artery disease is commonly seen in patients with diabetes, and myocardial revascularisation can improve prognosis and reduce symptoms in the group that develop ischaemic cardiomyopathy. However, the available data is limited and the optimal therapeutic strategy is still a matter of debate. The BARI study compared 7-year mortality in patients randomised to CABG versus PTCA in patients with or without diabetes and with or without evidence of LVSD. At 7 years, the



**Figure 2.** Kaplan-Meier survival analysis after cardiac transplantation among non-DM and DM stratified by number of DRCs (from Russo, MJ *et al.*<sup>51</sup> with permission)

survival of patients with diabetes and LVSD was better with CABG compared with PTCA. There was no significant difference in the two strategies in patients without diabetes<sup>50</sup>.

The main current drawback of the BARI study is the fact that it was performed nearly a decade ago, and newer modalities and techniques of coronary intervention have since developed. However, increased risk of contrast-induced nephropathy and in-stent re-stenosis still remain.

**Cardiac transplantation.** Cardiac transplantation offers substantial benefits to patients with end stage HF. In the past, diabetes was a relative contraindication to heart transplantation, but studies have shown that well-selected patients with diabetes can achieve similar survival to those without diabetes.<sup>51</sup> Russo *et al.* conducted an analysis of the United Network of Organ Sharing Database and found that recipients with more severe diabetes did suffer a dramatic decrease in survival; among patients with diabetes with one diabetes-related complication and with two or more diabetes-related complications, post transplant survival was 6.7 and 3.6 years less than in patients without diabetes, respectively<sup>51</sup> (see figure 2). Also, infection rates are higher in patients with diabetes, as are complications such as renal failure.

From the available evidence, cardiac transplantation is not advisable in patients with diabetes-related complications along with multiple cardiac risk factors.

## Management of Diabetes in HF

Numerous anti-diabetic drugs are used in the treatment of diabetes in HF. However, side-effect profiles and a lack of prospective randomised trials looking at clinical effectiveness limit their use.

**Table 5.** Key points in diabetes and HF

- DM and HF commonly co-exist and are inter-related through various complex patho-physiological mechanisms
- Risk stratification and early management are crucial in order to prolong survival
- Though there is no clear guidance on management of diabetes and HF, aggressive medical therapy remains the mainstay
- The evidence for adequate and appropriate management when the two co-exist is lacking, and further large randomised controlled trials need to be conducted

## Sulphonylureas

Sulphonylureas are frequently used drugs in type 2 diabetes patients. They augment endogenous insulin secretion. The UKPDS 33 showed that sulphonylurea use was not associated with development of HF<sup>52</sup>.

## Metformin

Metformin, a biguanide, is an ‘insulin sensitiser’. It prevents hyperglycaemia by affecting hepatic gluconeogenesis. However, there are variable views on the use of metformin in HF. The primary concern has been that of lactic acidosis developing as a side effect of treatment. However, compared with phenformin, metformin has a much lesser incidence of lactic acidosis.<sup>53</sup> Two studies conducted in 2005 clearly show the benefits of metformin in HF and also its safety.<sup>54,55</sup> The evidence base against prescribing metformin is not strong and it is recommended to treat patients with type 2 diabetes with metformin. Prospective trials are yet to be conducted to draw definitive conclusions about its use.

## TZDs

TZDs are widely used oral antihyperglycemic drugs that facilitate insulin action, increase insulin-stimulated glucose disposal and thereby decrease insulin resistance. They act via the PPAR- $\alpha$ , are effective in lowering HbA<sub>1c</sub> levels and also may have beneficial beta-cell and vasculo-protective effects.<sup>56</sup> Fluid retention and weight gain remain a primary concern, and numerous mechanisms have been postulated to explain this, including altered renal sodium handling by the amiloride-sensitive endothelial sodium channel in the collecting duct, which is activated by TZDs via the PPAR- $\alpha$ .<sup>57</sup>

*So should TZDs be used to treat patients with diabetes and HF?* A teleo-analysis conducted by Singh *et al.* confirmed the increased magnitude of HF with TZDs.<sup>58</sup> However, whether or not the increased risk of HF leads to a higher chance of death is unclear. In the absence of insufficient data, it would be appropriate to avoid using TZDs in NYHA class III/IV HF. This is the current recommendation of the AHA and ADA.<sup>59</sup> A detailed discussion regarding TZDs has been published in another article in this journal.

**Abbreviations and acronyms**

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ADA	American Diabetes Association
AHA	American Heart Association
ARR	absolute relative risk
CABG	coronary artery bypass grafting
CRT	cardiac resynchronisation therapy
DM	diabetes mellitus
DRC	diabetes related complications
HF	heart failure
HR	hazard ratio
LVSD	left ventricular systolic dysfunction
MI	myocardial infarction
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PTCA	percutaneous transluminal coronary angioplasty
PPAR- $\gamma$	peroxisome proliferator-activated receptor-gamma
PPP	primary prevention project
RRR	relative risk reduction
TZD	thiazolidinedione

**Studies/trials**

ALLHAT	Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial
BARI	Bypass Angioplasty Revascularisation Investigation
CARE-HF	Cardiac Resynchronisation in Heart Failure
CIBIS-II	Cardiac Insufficiency Bisoprolol Study-II
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
DIABHYCAR	Type 2 Diabetes Hypertension, Cardiovascular events And Ramipril
FREEDOM	Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease
LIFE	Losartan Intervention For Endpoint reduction in hypertension
MERIT-HF	Metoprolol Extended-release Randomized Intervention Trial in Heart Failure
RALES	Randomized Aldactone Evaluation Study
RENAAL	Reduction in Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
SAVE	Survival and Ventricular Enlargement
SOLVD	Studies of Left Ventricular Dysfunction
TRACE	Trandolapril Cardiac Evaluation
UKPDS	United Kingdom Prospective Diabetes Study
Val-HeFT	Valsartan Heart Failure Trial
WATCH	Warfarin and Antiplatelet Therapy in Chronic Heart Failure

**Insulin**

The role of insulin in HF patients with type 2 diabetes remains controversial. No doubt diabetes itself is associated with increased mortality in HF patients, but a study conducted by Smooke *et al.* revealed insulin-treated diabetic patients with HF had a markedly increased risk of

mortality compared with patients without diabetes and patients with diabetes and HF not treated with insulin.<sup>60</sup> There is a possibility of complex patho-physiological mechanisms being involved, or insulin could be considered a marker for longer duration of diabetes. Compliance to treatment may be an issue as well.

**Future Prospects**

The FREEDOM trial is currently underway, assessing CABG versus PCI in subjects with diabetes. If conducted, it will be interesting to see what the outcome of subgroup analysis of patients with LVSD and diabetes would be.

**Summary**

Key points regarding diabetes and HF are listed in table 5.

**Conclusion**

Unfortunately, despite advances in diabetes and cardiovascular research, treatment options which may lead to improved prognosis of patients with diabetes and HF remain limited. Well-powered prospective randomised controlled trials are essential to look at the mortality and morbidity benefits of various HF treatment modalities in subjects with diabetes, in addition to the impact of diabetic treatment on cardiovascular risk factors.

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