

# Advances in detection, prevention and treatment of heart failure in type 2 diabetes: part I

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## Abstract

Management of heart failure (HF) in diabetes has previously centred on aggressive control of cardiovascular risk factors. The benefits of this approach are modest. In the past decade, however, there have been numerous advances in our understanding of HF prevention, detection and treatment which are particularly relevant to people with type 2 diabetes. This review is the first of two that summarise these advances, with Part I focusing on HF prevention and detection.

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**Key words:** type 2 diabetes, heart failure, heart failure prevention

## Introduction

The 2017-18 UK National Diabetes Audit identified heart failure (HF) as the commonest and deadliest major complication of diabetes; even if all major cardiovascular (CV) risk factors are optimised, people with diabetes still have twice the risk of developing HF.<sup>1-5</sup> Among the plethora of multisystem diabetes-related complications, HF remains the leading cause of hospitalisation.<sup>2</sup> Moreover, for a person with type 2 diabetes (T2DM), rates of death in the year following HF admission are 2-5 times higher than that of the general population.<sup>2</sup> The major contribution of HF to morbidity and mortality in people with diabetes was highlighted by the American Diabetes Association in a recent consensus report recognising HF as “an underappreciated complication of diabetes”.<sup>6</sup>

## Classification of HF

Several methods of classifying patients with HF have been proposed, including: categorisation according to symptom severity,<sup>7</sup> ejection fraction (EF),<sup>8</sup> or a combination of the presence of co-morbidities, symptoms, elevated blood

biomarkers and structural heart alterations.<sup>9</sup> Most widely applicable is the combined approach described by the American Heart Association, American College of Cardiology and the Heart Failure Society of America in 2001,<sup>10</sup> which depicts a four-stage HF continuum:<sup>9</sup> Stage A “at risk” includes all people with T2DM given their markedly increased risk; Stage B are those with asymptomatic cardiac structural and/or functional alterations;<sup>11</sup> Stage C represents people with signs and/or symptoms of HF irrespective of left ventricular (LV) EF; and Stage D are those with limiting symptoms and recurrent hospitalisations despite maximally tolerated treatment (Figure 1).<sup>9</sup> Importantly, there is a decline in survival rates from Stages A to D.<sup>12</sup>

## Stage A – prevention of heart failure in at-risk subjects

Early studies that focused primarily on the impact of strict glycaemic and blood pressure (BP) control suggested that the benefits on HF risk reduction were modest.<sup>13-15</sup> The Swedish national diabetes registry has shown that good control of diabetes and CV risk factors negates the increased risk of atherosclerotic disease, but there remains a significant excess risk of hospitalisation for HF.<sup>1</sup> While maintenance of one or more risk factors within target ranges was associated with a stepwise reduction in the risk of HF hospitalisation, this was not to the same extent as the reduction in other CV events.<sup>1</sup> Nevertheless, addressing modifiable risk factors still has an important role to play in treatment for people with T2DM.

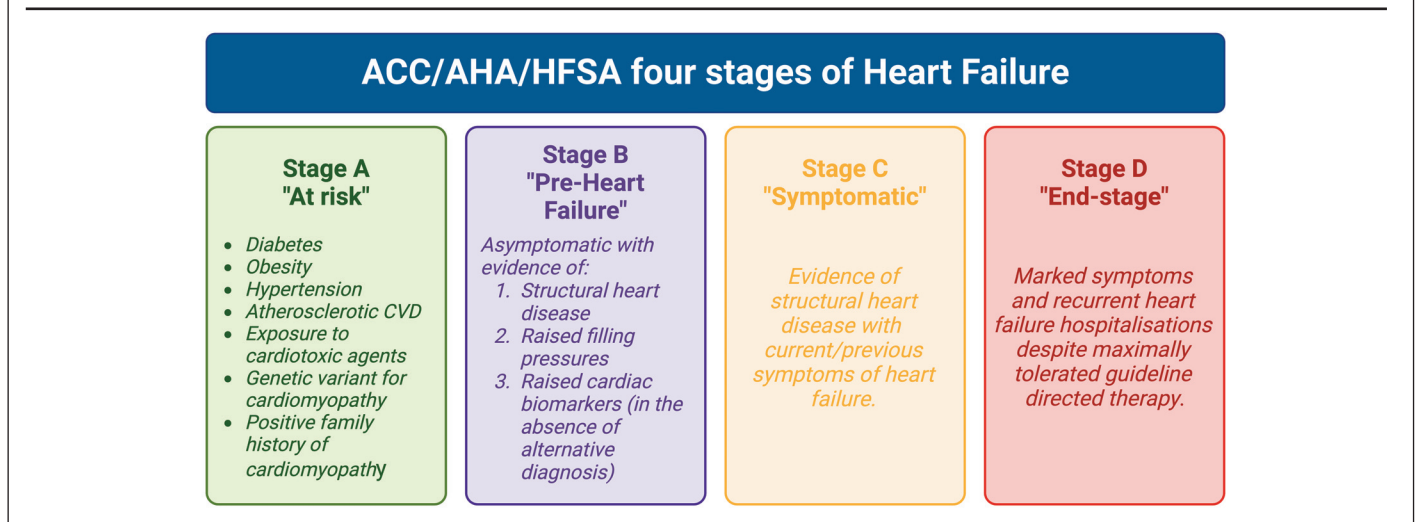
## Smoking cessation

Multiple studies have reported an increased risk of incident HF in smokers,<sup>16-18</sup> and a dose-response relationship between smoking exposure, brain natriuretic peptide (BNP) levels and incident HF hospitalisation.<sup>16</sup> Longitudinal observational data have shown that smoking cessation can reduce the downstream risk of HF, with former smokers (who have ceased smoking >15 years previously) having a similar risk of HF incidence and all-cause mortality to people who have never smoked.<sup>19</sup> The benefits of smoking cessation are attenuated in people with a history of heavy smoking ( $\geq 32$  pack years), who have a higher risk of HF and all-cause mortality compared to never smokers, but remain at a lower risk of death when compared to current smokers.<sup>19</sup> The emergence of e-cigarettes as “safe alternatives” to tobacco smoking has been the subject of much debate. However, a growing evidence base indicates

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**Figure 1.** The four-stage heart failure continuum as described by the American College of Cardiology (ACC)/American Heart Association (AHA)/ Heart Failure Society of America (HFSA).<sup>10</sup>



that e-cigarettes are likely to have multiple deleterious effects on general and CV health, particularly increasing BP and atherogenesis.<sup>20</sup> In a recent large-scale US observational registry study (n=175,667, average age 52 years, 61% female, median follow-up duration 45 months) specifically evaluating risk of HF, e-cigarette use was associated with a 19% excess risk of incident HF and particularly heart failure with preserved ejection fraction (HFpEF), even after adjustment for age, sex and traditional CV risk factors.<sup>21</sup> Although this study included people with and without T2DM, it is reasonable to conclude that e-cigarettes should not be considered an alternative to tobacco smoking in people who have never smoked and may not be a harm-reduction alternative to tobacco smoking in current smokers. Further work is needed to elucidate the precise mechanisms by which e-cigarettes potentiate CV risk and HF in all groups, including people with T2DM.

### Physical activity

Large observational prospective cohort studies have shown that greater physical activity is associated with significantly lower CV and overall mortality in men and women with diabetes.<sup>22,23</sup> Similarly, higher levels of physical activity and fitness have been shown to reduce the risk of HF.<sup>24-29</sup> This was demonstrated specifically in people with T2DM in a subgroup analysis of the ARIC study, which confirmed that increased physical activity reduces the risk of HF in T2DM.<sup>30</sup> Exercise training has also consistently been found to lower haemoglobin A1c (HbA<sub>1c</sub>) by 0.6-0.7%, with greater effects reported with higher exposure to exercise, and benefits observed irrespective of weight loss.<sup>31,32</sup> In health, guidance suggests a minimum of 150 minutes/week moderate-to-vigorous intensity aerobic exercise for adults, supplemented with two to three resistance sessions/week.<sup>1,2,6,7,33,34</sup> The European Society of Cardiology (ESC) expand on this to suggest that structured exercise programmes should be introduced for people with T2DM and established CV disease, and that exercise interventions should

be adapted in patients with T2DM-associated complications, including frailty.<sup>34</sup> Similarly, the World Health Organization states that those with chronic disease (e.g. T2DM) may increase moderate-intensity aerobic activity to >300 minutes (or >150 minutes of vigorous-intensity activity) per week.<sup>1</sup> Although individuals are encouraged to work towards these recommendations, physiological benefits can be achieved at levels below and above these thresholds, depending on CV and metabolic training goals; therefore, individualised exercise training programmes are advocated in people with T2DM.<sup>35</sup>

### Weight loss

The Framingham Heart Study reported that for every unit increase in body mass index (BMI) there is an associated 5-7% increased risk of HF.<sup>36</sup> Furthermore, there was evidence of a sex-specific interaction between BMI and HF risk, with a linear association observed in men and a J-shaped association in women.<sup>37</sup>

The metabolic benefits of weight loss in T2DM, including remission of diabetes, are now well established.<sup>38</sup> Observational studies have shown that dietary weight loss in people with diabetes is associated with improvement in a range of associated CV risk factors (e.g. low-density lipoprotein [LDL] cholesterol, BP and glycaemia), with the magnitude of weight loss generally being associated with greater risk factor reduction.<sup>39</sup> Historically, this was observed to be associated with lower all-cause and CV mortality,<sup>40</sup> although the impact on risk of incident HF was not specifically examined. The randomised controlled Look AHEAD trial compared intensive lifestyle intervention (a combination of a dietary weight loss and exercise programme) versus a diabetes support programme.<sup>41</sup> In 5,145 overweight/obese people with T2DM (mean age 58.7 years, diabetes duration five years, BMI 36 kg/m<sup>2</sup>) there was no difference in the rate of CV events or HF development over a median follow-up duration of 9.6 years,<sup>41</sup> despite greater weight loss (8.6% vs. 0.7% at one year; 6.0% vs. 3.5% at study end),

increased fitness and improved glycaemic control in the intensive lifestyle intervention arm.<sup>42</sup> Intensive medical management of CV risk factors was delivered to both intervention groups, which may account for the limited treatment effect. In participants who achieved >10% weight loss, a secondary analysis of the trial cohort found 24% reduced incidence of CV disease (although the composite primary and secondary outcomes were largely comprised of atherosclerotic CV events), highlighting that more modest weight loss may not be sufficient to mitigate CV disease development.<sup>43</sup> This is supported by a further subgroup analysis of the same trial, which showed that reducing fat mass and waist circumference (but not lean mass) in the intensive lifestyle intervention arm was associated with lower risk of incident HF.<sup>44</sup> At one-year follow up, a 10% reduction in fat mass was associated with 22% lower risk of HFpEF and 24% lower risk of heart failure with reduced ejection fraction HFrEF.<sup>44</sup> A recent meta-analysis of >220,000 people with T2DM confirms that concomitant weight loss and reductions in HbA<sub>1c</sub> are effective at lowering risk of CV disease (including HF) and death.<sup>45</sup>

For overweight/obese people with T2DM who are unable to achieve weight loss with lifestyle modification, newer pharmacotherapies and bariatric surgery should be explored.

### Pharmacologic weight loss therapies

Advances in our understanding of gut hormones and the existence of bidirectional gut-brain interactions in regulating appetite, gastric emptying and pancreatic hormone secretion have led to the development of novel and effective anti-obesity medications, with positive safety profiles. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and therapies in combination with other incretin hormones have emerged. Using these agents, body weight reductions between 10-25% have been demonstrated in phase 3 randomised placebo-controlled trials in people with obesity, with or without T2DM, with associated improvements in cardiometabolic risk factors.<sup>46-51</sup> The first CV outcomes trial of a long-acting GLP-1 RA (semaglutide 2.4 mg/week) in overweight/obese adults was published this year,<sup>52</sup> but participants with diabetes were excluded and the study cohort comprised only those with established CV disease (which included a combination of participants with stages A and B HF). Nevertheless, the potential beneficial secondary CV effects are the subject of intense interest.

### Lipid-lowering therapy

The therapeutic benefits of cholesterol management and statin therapy in preventing atherosclerotic CV disease are well established.<sup>53-56</sup> Current guidance recommends the use of statins in people with T2DM based on CV risk,<sup>34,57</sup> although there is limited evidence with regard to the impact of lipid-lowering therapy on HF outcomes. Large-scale, randomised, placebo-controlled trials have reported lower incidence of congestive HF with statin use.<sup>56,58</sup> Furthermore, a meta-analysis of treatment with statins in HF reported improved all-cause mortality, CV mortality and CV hospitalisation in HFpEF.<sup>59</sup> Newer non-statin lipid-lowering therapies such as proprotein convertase

subtilisin/kexin type 9 (PCSK9) inhibitors are now recommended for secondary prevention of atherosclerotic CV disease in certain patients not meeting non-HDL cholesterol targets,<sup>60,61</sup> but their role in primary prevention of CV disease is less clear due to lack of available trial data. There is also debate regarding the potential for harm associated with PCSK9i use in patients with a history of HF, possibly mediated via unwanted effects on cardiac metabolism.<sup>62,63</sup> As yet there is insufficient evidence to advocate non-statin lipid-lowering therapies to mediate HF risk in T2DM, especially in those with no prior history of CV disease. While the benefits of lipid-lowering therapy may extend beyond reduction of atherosclerotic CV events, given that coronary artery disease is a leading risk factor for HF there is sufficient evidence to warrant strict adherence to existing lipid-lowering therapy guidelines.<sup>64</sup>

### Glycaemic control

Large-scale observational studies have found that worsening glycaemic control is associated with increased risk of incident HF development, diagnosis of HF at a younger age and higher rates of hospitalisation for HF.<sup>65,66</sup> Surprisingly, the majority of previous large, multicentre randomised controlled trials did not demonstrate an improvement in macrovascular outcomes with tight blood glucose control.<sup>67-70</sup> Meta-analysis data have revealed no observed benefit of intensive glycaemic control on HF-related outcomes,<sup>14</sup> and just a modest reduction in major adverse CV events, primarily driven by a reduction in myocardial infarction, with no overall benefit on all-cause mortality or CV death.<sup>72</sup> Given that the excess risk of HF is mostly apparent when HbA<sub>1c</sub> ≥7.0%,<sup>66</sup> all major national and international guidelines advise aiming for a serum HbA<sub>1c</sub> <7.0% and avoidance of intensive glucose control.<sup>72-75</sup>

Since the publication of the EMPA REG OUTCOME trial, and the CV outcomes trials that followed,<sup>76</sup> management of hyperglycaemia for CV risk and HF prevention in T2DM has become more nuanced. There is now robust evidence to show that sodium glucose co-transporter 2 inhibitors (SGLT2i) give lower rates of HF hospitalisation in people with T2DM with or at high risk of CV disease.<sup>76-79</sup> In the recent ESC guidelines for the management of CV disease in diabetes, SGLT2i are recommended as first-line agents in the vast majority of people with T2DM,<sup>34</sup> highlighting their centrality in the management of diabetes. Similarly, multiple randomised trials have shown lower rates of CV events using GLP-1 RA in people with T2DM, with or at high risk of CV disease.<sup>50,51,80-82</sup> As with SGLT2i, guidelines recommend GLP-1 RA as a preferred medication for people with T2DM.<sup>34</sup> The effect of GLP-1 RA on HF events specifically is less clear, although recent meta-analysis suggested reduced risk of incident HF in people with T2DM without pre-existing HF at baseline.<sup>83</sup>

### Blood pressure control

Cardiac remodelling in hypertension may lead to permanent myocardial ischaemia, independent of epicardial obstruction.<sup>84</sup> Observational studies have reported the well-known link between hypertension and future risk of heart failure.<sup>36,85-87</sup> The ACCORD randomised controlled trial in people with T2DM found

**Table 1.** Recommended echocardiographic and blood biomarker criteria for diagnosing Stage B HF and major limitations. Adapted from references 7 and 10

Cardiac alteration	Criteria	Limitations
Morphological	LA enlargement (indexed LA volume $\geq 29$ mL/m <sup>2</sup> ).	T2D is associated with smaller LA volumes. <sup>101</sup>
	Increased LV mass (indexed LV mass $>116$ g/m <sup>2</sup> in males and $95$ g/m <sup>2</sup> in females).	Indexing LV mass to body surface area, as is clinically routine, incorrectly "permits" higher LV mass in overweight and obese subjects.
	Concentric LV remodelling (relative wall thickness $>0.42$ ).	Poor sensitivity and not reported in a minimum echo dataset. <sup>102</sup>
	LV hypertrophy (absolute wall thickness $\geq 12$ mm).	Sex- and ethnic-specific criteria needed.
Ventricular systolic function	LV ejection fraction $<50\%$ .	Challenging to measure in subjects with overweight and obesity due to poor acoustic windows.
	Global longitudinal strain $<16\%$ .	Strain is not routinely measured. Existing cut-offs are arbitrary and not sex- and ethnicity- specific.
Ventricular diastolic function	Increased LV filling pressure (average E/e' $\geq 15$ ).	Highly age-dependent. Modest association with invasive LV filling pressures. Although prognostic value in population studies, application in individual patients is highly problematic. <sup>103</sup>
	Impaired LV relaxation (septal e' $<7$ cm/s and/or lateral e' $<10$ cm/s).	
	Tricuspid regurgitation velocity $\geq 2.8$ m/s.	Not a clinically validated measure of diastolic dysfunction.
	Estimated pulmonary artery systolic pressure $>35$ mmHg.	Not specific to LV diastolic dysfunction and may be due to intrinsic lung disease.
Blood biomarkers	Elevated natriuretic peptides (BNP $\geq 35$ pg/mL, NT-proBNP $\geq 125$ pg/mL).	Often low in overweight/obesity and T2D. Undetectable in up to one third of people with HFpEF. <sup>104</sup>
	Raised high sensitivity troponin ( $>$ 99th centile upper reference limit).	Undetectable levels do not exclude Stage B HF and have not convincingly been shown to predict incident HF. <sup>105</sup>

BNP=brain natriuretic peptide; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; LA=left atrium; LV=left ventricle; T2DM=type 2 diabetes.

no difference in mortality or HF hospitalisation with intensive BP management,<sup>15</sup> and a significant increase in serious adverse events has been reported with intensive therapy.<sup>15,88</sup> Current guidance recommends a tailored approach to patients, giving particular consideration to frailer individuals, who may benefit from a higher BP target.<sup>34,75,89</sup> Lastly, non-adherence to antihypertensives remains a major challenge to maintaining adequate BP control and is common in people with T2DM, especially in younger age groups who have the highest lifetime risk of HF; more than 80% reportedly had low adherence in one study.<sup>90</sup> A key risk factor for non-adherence particularly relevant to people with T2DM is polypharmacy,<sup>91</sup> and suboptimal BP control in people taking multiple antihypertensives should alert clinicians to the possibility of medication non-adherence. Whilst there are several available methods for identifying non-adherence, liquid chromatography-tandem mass spectrometry techniques are now available for detection of antihypertensive medications in urine or other body fluids and should be considered in patients presenting with persistent uncontrolled BP.<sup>92</sup>

### Stage B – early detection of subclinical cardiac dysfunction

One third of people with T2DM have asymptomatic cardiac structural and/or functional alterations that precede HF symptomatology.<sup>11,93</sup> Stage B HF is a dynamic phenomenon, with potential for both progression to overt symptomatic HF and reversal to Stage A. In a meta-analysis of 11 cohort studies

comprising 25,369 subjects with an average ~8 years follow-up, rates of progression from Stage B HF to symptomatic HF were almost five-fold higher for systolic dysfunction and 1.7 higher for diastolic dysfunction than in those without stage B HF.<sup>94</sup> Diabetes was a major predictor of HF progression, along with age, sex, BP and BMI.<sup>94</sup> Conversely, a subset of the Olmsted County Heart Function Study, 8% of whom had diabetes, identified regression of Stage B HF to stage A HF or 'normal' in 39% of subjects who underwent repeat echo after four years.<sup>95</sup> Individuals who regressed had lower troponin and natriuretic peptide levels, higher LV ejection fractions and lower indexed left atrial volumes.<sup>95</sup>

Given that Stage B HF is potentially reversible, early diagnosis is desirable. Current recommendations for diagnosis of Stage B HF are based solely on transthoracic echocardiography or blood biomarker criteria (Table 1). These will not, therefore, routinely be available in asymptomatic individuals, nor are the echocardiographic parameters always detailed or easily accessible in standard clinical reports. Numerous additional early deleterious effects on cardiac structure and function have been reported in T2DM, including smaller cardiac chamber volumes, impaired myocardial energy utilisation, coronary microvascular dysfunction, myocardial steatosis, focal and diffuse fibrosis, and dysregulated myocardial calcium handling,<sup>96,97</sup> that are not included in the current classification of Stage B HF or detectable with echocardiography.<sup>11</sup> This will undoubtedly lead to under-estimation of the prevalence of Stage B HF and missed

**Table 2.** Impact of key lifestyle and pharmacologic interventions on Stage B HF in people with T2DM

Intervention	Contribution to Stage B HF
Smoking cessation	Current smoking, smoking intensity and smoking burden of ever smokers were all associated with increased BNP levels and incident HF hospitalisation, <sup>16</sup> in addition to increased myocardial extracellular volume, a marker of cardiac interstitial fibrosis. <sup>106</sup>
Physical activity	Improved exercise capacity, measured by cardiopulmonary exercise testing, and peak early diastolic strain rate, measured by cardiac magnetic resonance imaging, have both been reported following supervised aerobic exercise training in obese patients with T2DM. <sup>107</sup>
Weight loss	Incremental unit increases in BMI are associated with a 5-7% increased risk of heart failure. <sup>36</sup> Observational data during follow-up for bariatric surgery showed staggering effects on incident HF (HR 0.33 [CI 0.24, 0.46], $p < 0.0001$ ) and CV mortality (HR 0.36 [CI 0.22, 0.58], $p < 0.0001$ ) with a significant reduction in BMI. <sup>108</sup>
Lipid-lowering therapy	There is limited evidence with regards to lipid-lowering therapy for HF outcomes. However, reduced incidence of congestive HF and improved all-cause mortality, CV mortality and CV hospitalisation in HF have all been reported with statin use. <sup>56,58,59</sup>
Glycaemic control	Worsening dysglycaemia was associated with deleterious cardiac structural changes, including increased LV mass, E/e' (an indicator of diastolic dysfunction) and global longitudinal strain. <sup>109</sup>
Blood pressure reduction	Histopathological processes, including myocyte hypertrophy and apoptosis, arteriolar wall thickening and perivascular fibrosis, interstitial fibrosis and inflammation and reduced capillary density, contribute to a reduction in myocardial perfusion reserve. <sup>84</sup>

opportunities for treatment. Acknowledging that routine screening for Stage B HF is not currently possible, detection should be opportunistic and include early investigation whenever possible.

Surprisingly, very few available risk stratification tools for CV disease in T2DM are calibrated for HF risk estimation.<sup>98</sup> There is a paucity of generalisable or robust T2DM-specific HF risk calculators, such that risk stratification is highly challenging in real-world practice.<sup>99</sup> For this reason, emphasis should be on early initiation and maintenance of the cardio-protective glucose-lowering agents.

Management of Stage B HF follows the same principles as for Stage A. Several studies have shown that lifestyle modification and risk factor control can ameliorate many of the cardiac alterations described in Stage B HF (Table 2). Where evidence of a reduced LV ejection fraction is opportunistically detected, early initiation of guideline-directed medical therapy is strongly encouraged. Conversely, avoidance of thiazolidinediones, dipeptidyl peptidase IV inhibitors and sulfonylureas is advised, given the association with risk of CV events and HF.<sup>6,100</sup> The absolute goal is to prevent deterioration of cardiac dysfunction and progression to symptomatic HF.

## Conclusions

Often underappreciated as a complication of T2DM, HF is one of the commonest and deadliest consequences of the disease. All the available evidence suggests that in people with T2DM and Stage A HF: 1) intensive blood glucose control is not sufficient for HF prevention and a multifaceted approach is likely to have a greater effect; 2) the most compelling evidence for HF risk reduction is for SGLT2i, although GLP-1 RA may also have a role; and 3) patients likely to derive most benefit are those at highest risk of developing overt HF, which probably represents the majority of people with T2DM. Increased awareness and early diagnosis are paramount to establish treatment, and more research is required to identify patients with stage B HF effectively in this at-risk cohort.



## Key message

- ▲ Heart failure is the commonest and deadliest major complication of diabetes.
- ▲ Addressing modifiable risk factors is associated with a stepwise reduction in the risk of heart failure hospitalisation and has an important role to play in treatment for people with type 2 diabetes, but there remains a significant excess risk of hospitalisation for heart failure.
- ▲ Stage B heart failure is a dynamic and potentially reversible phenomenon, as such early detection is desirable.



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