Diabetes and heart failure

The deadly duo

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Type 2 diabetes is a major risk factor for the development of heart failure. Diabetes and heart failure commonly coexist and adversely affect the prognosis of the other. Patients with diabetes have a high prevalence of risk factors for heart failure, with coronary artery disease and hypertension being the most important.

Key points

- **Type 2 diabetes is one of Australia's fastest growing chronic diseases and is a major risk factor for the development of heart failure.**
- **Treatment of systolic heart failure in people with diabetes follows the same principles as for those without diabetes.**
- **Patients with diabetes are at increased risk of diastolic heart failure, but the optimal management for this condition remains unknown.**
- **Trials are underway to investigate the cardiovascular safety of the newer glucose lowering therapies, such as the dipeptidyl peptidase-4 inhibitors, the glucagon-like peptide-1 analogues and the sodium–glucose cotransporter 2 inhibitors.**

Type 2 diabetes is a coronary heart disease risk equivalent that is associated with a significant cardiovascular disease burden. This includes a two- to three-fold increase in cardiac death and an increased risk of congestive heart failure.[1] Both diabetes and heart failure are common reasons for consultation in general practice, particularly as diabetes is present in one million people in Australia and heart failure is present in half a million people in Australia. Heart failure is a leading cause of hospitalisation and, despite advances in management, the diagnosis of heart failure carries substantial morbidity and mortality.[2] Unfortunately, not only do heart failure and diabetes commonly occur, but their mutual presence confers a significantly higher risk of an adverse cardiovascular event as well as death.[3]

This article discusses the risk factors for developing heart failure in people with type 2 diabetes, how to diagnose heart failure and how to manage people with both heart failure and diabetes. The use of glucose-lowering therapies in people with diabetes and heart failure is also discussed.

ENDOCRINOLOGY TODAY 2014; 3(1): 12-16

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Risk factors and/or markers for developing heart failure in diabetes

Diabetes can affect the heart structure and function through multiple mechanisms. The Figure illustrates the relation between diabetes and the progression to overt heart failure through increased incidence of myocardial infarction and left ventricular hypertrophy.[4] Systolic dysfunction is associated with macrovascular disease, whereas cardiac fibrosis and left ventricular hypertrophy can lead to diastolic dysfunction. Such cardiac abnormalities can remain asymptomatic for many years before the development of clinical heart failure.

The relative risk of heart failure is doubled in men with diabetes and increased five-fold in women with diabetes.[1] Coronary artery disease and hypertension are the most common risk factors for developing heart failure in people with diabetes. Other independent risk factors and markers include obesity, increasing age, duration of diabetes, end-stage kidney disease, microalbuminuria and retinopathy. Hypertension can also accelerate left ventricular hypertrophy, which is itself an independent risk factor for developing heart failure. Patients with diabetes are more likely to develop heart failure after

a myocardial infarction than those without diabetes, and this risk may relate to the preclinical abnormalities of left ventricular structure and function alluded to above.

Diagnosis of heart failure

Heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.[2] The typical symptoms are dyspnoea, fatigue (both of which limit exercise tolerance) and fluid retention, which can lead to pulmonary and peripheral oedema. The traditional system for symptom classification in people with heart failure is the New York Heart Association (NYHA) grading system (Table). The diagnosis of heart failure is often made after a patient presents to hospital with new or worsening symptoms. Diagnostic testing includes an electrocardiogram and a chest x-ray, with a transthoracic echocardiogram being the ideal investigation to assess cardiac structure and function. Plasma brain natriuretic peptide (BNP) levels are increased in people with heart failure; however, BNP is a less useful measurement in people with diabetes due to renal impairment (this increases BNP levels) and in those who are obese (this reduces BNP levels). Female gender and increased age can also lead to increases in plasma BNP levels.

Myocardial ischaemia is a common cause of systolic heart failure (impaired contraction of the heart). Coronary angiography should be considered in patients with heart failure and a history of exertional angina or suspected ischaemic left ventricular dysfunction because prognosis is improved with revascularisation. Half of all heart failure admissions are due to diastolic dysfunction or impaired relaxation of the heart, and this type of heart failure is referred to as diastolic heart failure or heart failure with preserved ejection fraction. Risk factors for diastolic heart failure include diabetes, obesity, hypertension, left ventricular hypertrophy, female gender, increased age and atrial fibrillation. Preclinical or asymptomatic diastolic dysfunction has recently emerged as an important risk factor for the development of heart failure in people with diabetes.[5]

Morbidity and mortality of heart failure in diabetes

People with diabetes are commonly hospitalised with heart failure. Although not all trials of glucose-lowering therapy reported on heart failure admissions as an end-point, in those that did, the risk of hospitalisation for heart failure was as high as for myocardial infarction and stroke.

Despite advances in therapy and management, heart failure remains a deadly clinical syndrome, particularly when diabetes and heart failure coexist.[3] Diabetes is an independent predictor of mortality in population studies, as well as in clinical trials of medications for heart failure, such as renin-angiotensin system (RAS) blockers and β-blockers. Patients with diabetes in the type 2 Diabetes, Hypertension, Cardiovascular events and Ramipril (DIABHYCAR) trial who developed heart failure had a 12-fold increase in mortality compared with those with diabetes who did not develop heart failure (36% *v.* 3%).[6]

Management of heart failure in diabetes

Management of patients with both diabetes and heart failure essentially follows the same principles as used for those without diabetes. This includes prevention, early detection, slowing of disease progression, symptom relief and prolongation of survival.[2]

Nonpharmacological management

The use of multidisciplinary heart failure clinics reduces admissions by providing patients with access to nurses, pharmacists and other allied health professionals, in addition to physicians. These programs reinforce to patients the need for fluid and salt restriction, daily weight monitoring, cessation of cigarette smoking and restriction of alcohol intake. Exercise training programs in patients with stable chronic heart failure have been shown to improve exercise capacity and reduce hospitalisations.[7]

Pharmacological management

Diabetes specific

Glycaemic control is important in reducing morbidity and mortality in patients with diabetes. However, in patients with both diabetes

Table. New York Heart Association (NYHA) heart failure classification system

NYHA class	Description
Class I	No limitations. No symptoms of heart failure with ordinary activity (asymptomatic left ventricular dysfunction)
Class II (mild)	Slight limitation of physical activity. Symptoms of heart failure with moderate exertion (such as walking two blocks or climbing two flights of stairs)
Class III (moderate)	Marked limitation of physical activity. Symptoms of heart failure with mild exertion (such as walking one block or climbing one flight of stairs)
Class IV (severe)	Unable to carry out any physical activity without discomfort. Symptoms of heart failure at rest

and heart failure, the impact of glucose-lowering drugs on heart failure outcomes is limited. Evidence for the use of commonly used drugs (i.e. metformin, sulfonylureas and insulin) comes from registries, observational data and subgroup analysis. Prospective randomised trials of the optimal glucose-lowering strategy in patients with diabetes and heart failure are needed.

Metformin is commonly used in people with type 2 diabetes and observational studies have shown better clinical outcomes in patients with heart failure taking metformin compared with other hypoglycaemic agents.[8] Metformin should be avoided in patients with unstable or decompensated heart failure, particularly in the presence of haemodynamic instability and renal impairment because of the increased risk of lactic acidosis.

Thiazolidinediones (TZDs) cause sodium and water retention, leading to oedema, weight gain and precipitation or worsening of heart failure. Large randomised controlled trials have reported an increased incidence of heart failure in patients taking TZDs. TZDs are contraindicated in patients with symptoms of heart failure on minimal exertion (NYHA III/IV) because of the increased risk of hospitalisation due to heart failure or death. If TZDs are given to patients at high risk of heart failure, low doses should be used with close monitoring for symptoms and signs of heart failure, including weight gain from fluid retention.

Dipeptidyl peptidase-4 inhibitors are enzymes that metabolise endogenous glucagon-like peptides. Agents in this class include sitagliptin, linagliptin, saxagliptin, alogliptin and vildagliptin. Due to the adverse cardiovascular effects observed with the TZDs, the FDA has mandated that new diabetes drugs undergo cardiovascular outcomes trials. The first to report on this were the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53 trial) and the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE trial). In the SAVOR-TIMI 53 trial, patients treated with saxagliptin had a 27% increased risk for heart failure hospitalisation compared with placebo-treated patients.[9] A post-hoc analysis indicated a higher, albeit nonsignificant increase in heart failure admissions with use of alogliptin (unpublished data). Results from ongoing randomised controlled trials such as the Sitagliptin Cardiovascular Outcome Study (TECOS) and the Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) are awaited to see if the heart failure signal is an effect with just one drug or a class effect.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors increase urinary glucose excretion and reduce hyperglycaemia. The SGLT2 inhibitors canagliflozin and dapagliflozin are available in Australia, and trials are underway to address the cardiovascular safety of these compounds. In the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) trial, more than 17,000 patients will be followed for four to five years to ascertain whether dapagliflozin is associated with increased risks for cardiovascular events, liver problems or malignancies. Information on long-term cardiovascular outcomes with canagliflozin will be available on the completion of the Canagliflozin Cardiovascular Assessment Study (CANVAS).

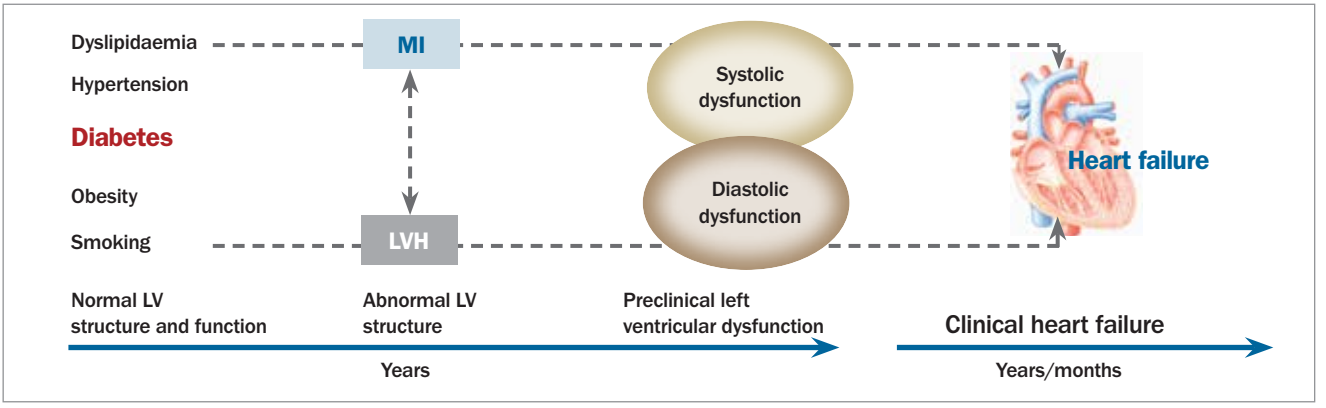

Figure. Progression to heart failure in people with type 2 diabetes.
Adapted from Krum H, Gilbert RE. Lancet 2003; 362: 147-158.[4]
Abbreviations: LV = left ventricle; LVH = left ventricular hypertrophy; MI = myocardial infarction.

Systolic heart failure

Management of systolic heart failure in patients with diabetes is similar to that in patients with heart failure and no diabetes (see the Box). The cornerstone of therapy is based on blockade of the activated renin angiotensin system and sympathetic nervous systems. Treatment should include a RAS blocker, a β-blocker and a mineralocorticoid receptor antagonist (MRA), which all improve survival in patients with heart failure. Diuretics are used to relieve congestion, but do not improve survival.

ACE inhibitors are indicated in people with diabetes and heart failure, with multiple randomised controlled trials showing they prolong survival in all grades of heart failure, reduce readmissions and improve symptoms. If patients are intolerant of ACE inhibitors, an angiotensin receptor blocker (ARB) has similar benefits. ACE inhibitors and ARBs should not be prescribed together. Careful monitoring of potassium and renal function with commencement and dose escalation is required because of the common occurrence of kidney disease in people with diabetes.[2]

A β-blocker should be used in addition to an ACE inhibitor or ARB in all patients with an ejection fraction of less than 40%. The β-blockers carvedilol (β1, β2 and α1 antagonist), bisoprolol (β1 selective antagonist) and metoprolol slow-release (β1 selective antagonist) reduce morbidity and mortality in patients with heart failure who are already receiving an ACE inhibitor. A meta-analysis of six studies of β-blockade in heart failure in which 25% of participants were diabetic has shown beneficial effects of β-blockade (relative risk, 0.84) on mortality and hospitalisation for heart failure.[10]

If patients remain symptomatic (NYHA II to IV, ejection fraction <35%), a low-dose MRA (spironolactone or eplerenone) is recommended in addition to an ACE inhibitor or ARB and a β-blocker because this combination reduces mortality and hospitalisation in those with severe heart failure. Careful monitoring of potassium and renal function with commencement and dose escalation is required because of the common occurrence of kidney disease in people with diabetes.

Ivabradine, a direct sinus node inhibitor, may be added as fourth-line therapy to an ACE inhibitor, β-blocker and MRA in people with diabetes and heart failure who are in sinus rhythm and have a heart rate of more than 70 beats per minute, reduced ejection fraction and persistent symptoms. This recent addition to the heart failure armamentarium results from a trial that reported that use of ivabradine in patients with symptomatic systolic heart failure, sinus rhythm (heart rate >70 beats per minute) and recent (within 12 months) hospitalisation for heart failure led to a reduction in cardiovascular mortality and heart failure hospitalisations. This benefit was additional to patients taking the highest tolerated dose of background RAS and β-blockade.

Diastolic heart failure

In contrast to systolic heart failure, no mortality benefit has yet been established with the use of RAS blockers, β-blockers or MRAs in people with diastolic heart failure, although there is some morbidity benefit in terms of reducing hospitalisations due to heart failure. Management

Management of systolic heart failure in patients with diabetes

Recommended medications

ACE inhibitor

In patients with systolic heart failure and type 2 diabetes, an ACE inhibitor reduces hospitalisation and mortality. Increasing the dose of the ACE inhibitor as tolerated is recommended.

Angiotensin receptor blocker (ARB)

In patients with systolic heart failure and type 2 diabetes, an ARB may be used as an alternative to an ACE inhibitor where an ACE inhibitor is not tolerated.

β-blocker

A β-blocker (bisoprolol, carvedilol or metoprolol extended release) is recommended in addition to an ACE inhibitor (or an ARB) in patients with systolic heart failure and type 2 diabetes to reduce hospitalisation and mortality. Increasing the dose of the β-blocker as tolerated is recommended.

Mineralocorticoid receptor antagonist (MRA)

An MRA (spironolactone or eplerenone) is recommended in patients with persisting heart failure symptoms (NYHA class II to IV) and reduced ejection fraction despite treatment with an ACE inhibitor (or ARB) and a β-blocker to reduce heart failure hospitalisation and mortality.

Direct sinus node inhibitor

Ivabradine may be added to an ACE inhibitor, β-blocker and MRA in patients with diabetes and heart failure in sinus rhythm with a heart rate of more than 70 beats per minute and reduced left ventricular ejection fraction with persistent symptoms.

Diuretic

Loop diuretic or/and thiazide diuretic is used in fluid overloaded patients with diabetes to achieve euvolaemia and relieve symptoms. Diuretics do not improve survival.

Medications to be used with caution

Thiazolidinedione

Thiazolidinediones cause fluid retention and should not be used in patients with diabetes and heart failure.

Nondihydropyridine calcium channel blocker

Nondihydropyridine calcium channel blockers (diltiazem, verapamil) have negative inotropic effects and are contraindicated in patients with systolic heart failure.

Central sympathetic inhibitor with an imidazoline receptor agonist

Moxonidine is contraindicated in patients with heart failure as it is associated with increased mortality.

Note: The optimal management of diastolic heart failure remains unknown; clinical trials of RAS blockers, MRAs and β-blockers have failed to improve survival in patients with diastolic heart failure.

of diastolic heart failure is directed at control of risk factors such as diabetes, hypertension, obesity and atrial fibrillation.

Surgical management

Cardiac resynchronisation therapy has similar benefit in selected patients (those in sinus rhythm, with an ejection fraction of ≤35%, with prolonged QRS on ECG and who are symptomatic with mild exertion despite taking optimal medical therapies) with diabetes compared with those without diabetes.

A cardiac transplant could be considered in patients with systolic heart failure and persistent NYHA class IV symptoms despite maximal medical therapy with left ventricular ejection fraction of less than 20%. Although diabetes is not a specific contraindication, end organ damage such as neuropathy, nephropathy or retinopathy are all relative contraindications for cardiac transplantation.

Prevention of heart failure in diabetes

Screening for preclinical cardiac disease, such as left ventricular hypertrophy and systolic/diastolic dysfunction in people with diabetes is not recommended by diabetes guidelines. Our own data suggest that two-thirds of people with type 2 diabetes have preclinical abnormalities on an echocardiogram that places them at high risk of developing clinical heart failure.[11] It has yet to be investigated if detection of preclinical abnormalities and targeted intensive therapy would assist in preventing the subsequent development of heart failure in people with diabetes.

Conclusion

Type 2 diabetes is one of Australia's fastest growing chronic diseases and is a major risk factor for the development of heart failure. Diabetes and heart failure commonly coexist and adversely affect the prognosis of the other. Patients with diabetes have a high prevalence of risk factors for heart failure, with coronary artery disease and hypertension being the most important.

Treatment of systolic heart failure in people with diabetes follows the same principles as for those without diabetes, and includes three neurohormonal antagonists – an ACE inhibitor or ARB, a β-blocker and a MRA, all of which reduce symptoms and prolong survival. They can be supplemented with the direct sinus node inhibitor, ivabradine. Diuretics are used for symptom relief.

Patients with diabetes are at increased risk of diastolic heart failure, but the optimal management of this condition remains unknown. Clinical trials of RAS blockers, MRA and β-blockers have failed to improve survival in patients with diastolic heart failure.

With regard to safety of glucose-lowering therapy in patients with heart failure, the TZDs are contraindicated. Further outcome data are needed as to the risk of heart failure with use of the newer agents such as DPP-4 inhibitors and the glucagon-like peptide-1 analogues. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: None.

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