Palliative care and heart failure in diabetes

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Abstract
Heart failure is a major cause of morbidity and mortality in diabetes and once established the mortality is very high. There is evidence for a U-shaped association between HbA1c and risk of mortality with the lowest risk associated with an HbA1c of 6.5–7.5% (48–58mmol/mol). Guidelines for management of chronic heart failure recommend palliative care for end-stage disease, but because of the unpredictable trajectory of heart failure it can be difficult to decide exactly when palliative care should be introduced. Despite the frequent combination of diabetes and heart failure, end of life guidelines for each condition fail to provide recommendations for management when they coexist.

While no class of cardiac failure medication is contraindicated in diabetes, some blood glucose lowering agents may have an adverse effect on heart failure. Cardiovascular outcome studies have linked pioglitazone, saxagliptin and possibly alogliptin with increased risk of heart failure and these drugs should be avoided once the condition is diagnosed. Blood glucose targets should aim for avoidance of hypoglycaemia (increased risk of arrhythmias) and hyperglycaemia (increased risk of dehydration and renal impairment when combined with diuretics). Despite the usual advice to reduce blood testing to a minimum in palliative care, monitoring of both the blood glucose and renal function may be needed to ensure optimal symptom control.

Multidisciplinary heart failure and diabetes teams should be trained to provide palliative care and should use their combined skills to optimise care. They should aim to alleviate symptoms and to address the anxiety and depression often associated with heart failure. Both family and patient should be supported to deal with the uncertainty associated with the unpredictable trajectory towards death. Authors of guidelines should collaborate to produce recommendations for management of the combination of end-stage heart failure and diabetes.

Key words
diabetes; heart failure; end of life

Introduction
Heart failure is the most common cardiovascular complication of diabetes. More than 40 years ago, the Framingham Heart Study showed that, compared with non-diabetic controls, heart failure was twice as high in diabetic men and five times higher in women; this was independent of other risk factors such as hypertension and hyperlipidaemia. This probably explains why diabetes has been over-represented in several studies of patients with heart failure. A US study of 9591 patients with type 2 diabetes reported a heart failure prevalence of 11.8% in the diabetic cohort compared with 4.5% in matched controls. Over 30 months of follow up, the incidence of heart failure was 7.7% in those with diabetes versus 3.4% in controls. The combination of the two conditions leads to worse outcomes; a meta-analysis of mortality in people with diabetes and heart failure, compared with heart failure alone, demonstrated a hazard ratio of 1.34. As the population ages, and effective risk factor modification reduces mortality from coronary artery disease, the prevalence of heart failure in the diabetic population is rising. Once heart failure develops in people with diabetes the prognosis is poor; mortality increases 10-fold and five-year survival is only 12.5%.

Glycaemic control
The relationship between the incidence of heart failure and HbA1c was examined in 20 985 patients with type 1 diabetes. The authors compared two groups, with HbA1c ≥10.5% (91mmol/mol) and <6.5% (48mmol/mol); the hazard ratio for mortality in the poorly controlled group was 3.98 when adjusted for age, duration of diabetes, cardiovascular risk factors and other comorbidities. Data from the UK Clinical Practice Research Datalink showed that once heart failure has developed, the relationship between HbA1c and mortality forms a...
Palliative care and heart failure

As the prevalence of heart failure increases in the general population, both SIGN9 and NICE10 guidelines for management of heart failure now advise palliative care for end-stage disease. The essential features of all palliative care are communication, shared decision making, symptom relief, psychological support, advance planning and support for families. Palliative care has expanded from its origins in cancer care to include a range of chronic, progressive conditions including heart failure but cancer patients still make up the majority of referrals to the specialist palliative care team. By default, responsibility for palliation of heart failure usually falls to the multidisciplinary heart failure team and it is essential that team members have an understanding of how and when to deliver palliative care. A survey of palliative care teams in 2015 found that 47% of the 499 responders (response rate 42%) received fewer than 10 referrals for heart failure per annum, with little interdisciplinary collaboration.11

A major difference between heart failure and cancer is that, in the former, the trajectory at the end of life is unpredictable; while a proportion of patients (estimated at 40–50%12) will die suddenly of a cardiac arrhythmia (Figure 2A), others will experience progressive pump failure with a variable and unpredictable time course and the possibility of a significant recovery from a life-threatening episode (Figure 2C). This makes it very difficult to identify people who are truly at the end of their life so the decision to introduce palliative care should be based on symptoms rather than life expectancy. People with heart failure tend to be older, frailer and with comorbidities; it is essential that a multidisciplinary approach is taken to ensure that the care provided is holistic and takes into account the high levels of anxiety and depression associated with this condition.9

Despite the high prevalence of heart failure in people with diabetes, and vice versa, the SIGN heart failure guideline does not include diabetes in the list of comorbidities requiring specific consideration; NICE simply provides a link from the heart failure guideline to type 2 diabetes guidance (NG28) without further comment. The recently revised Diabetes UK guideline for end of life care and diabetes13 does not include heart failure as a specific condition. This suggests that, in spite of the frequency with which the two conditions are found together, there is no perceived need for shared guidelines. In our local

U-shaped curve.8 Compared with people without diabetes, the hazard ratio for mortality was 1.30 for HbA1c >9.5% (80mmol/mol), 1.1 for HbA1c 6.5–7.5% (48–58mmol/mol) and 1.29 for HbA1c <5.5% (37mmol/mol). (Figure 1.)

**Figure 1.** HbA1c adjusted associations with all-cause mortality in people with type 2 diabetes and heart failure, compared with non-diabetic controls. (Reproduced from: Lawson CA, et al. JACC Heart Fail 2018;6:18–26)

**Figure 2.** Trajectories at end of life. (Reproduced from: ‘End of Life Care in Advanced Kidney Disease: A Framework for Implementation’. © Copyright NHS Improving Quality, 2015)
experience, where both heart failure and diabetes teams operate in the community, it is uncommon for both teams to be involved in the care of an individual patient. This implies, but does not prove, that treating the combination does not cause management dilemmas and the potential benefits of shared care are not recognised.

### Diabetes treatments and heart failure

#### Evidence from studies

The relationship between blood glucose lowering agents and cardiovascular outcomes has been a controversial area for decades, with several drugs associated with increased risk of cardiovascular events, including heart failure. As a result of this, regulatory authorities have required cardiovascular outcome studies for new diabetes treatments since 2008. Pioglitazone, saxagliptin and alogliptin have been associated with increased risk of hospitalisation for heart failure and these drugs are contraindicated in established heart failure. See ‘The treatment of diabetes in heart failure’ on pages 123–126 of this issue of Practical Diabetes for a summary of the results of these outcome trials.

Systematic reviews and observational studies based on records from GP databases have been used to gain further insights into the effect of blood glucose lowering treatments on heart failure. A meta-analysis of heart failure associated with a range of comorbidities found nine studies looking at the effect of diabetes on heart failure mortality. Diabetes was present in 16% (13–47%) of the 135 402 patients studied. The hazard ratio for mortality was 1.35 in the diet alone group, 1.38 in those treated with oral agents (NS) and 2.11 in those taking insulin (p<0.01), an increase of 78% when compared with the diet alone group. The reason for this is uncertain but could be due to: (1) clinicians preferring to use insulin in those with severe heart failure; (2) increased risk of cardiac arrhythmias secondary to hypoglycaemia in insulin treated patients.

In the observational case control study based on data from general practice, mortality was also stratified by diabetes treatment, with slightly different findings; the adjusted odds ratio for all-cause mortality was lower for those treated with oral agents (1.16) or oral agents plus insulin (1.19) compared with those on no treatment (1.31) and those on insulin (1.43). A recent reduction in diabetes treatment was associated with a significant increase in mortality compared with those in whom treatment was unchanged (adjusted OR 2.09 versus 1.20). This may reflect the clinician’s response to worsening heart failure (relaxation of targets and de-prescribing in the face of approaching death), rather than an adverse effect of the treatment change.

A general practice database study of 469 688 people with type 2 diabetes looked at risk of heart failure and all-cause mortality and found, counter-intuitively, that use of gliptins and glitazones was associated with reduced risk of heart failure when compared with no treatment (diet only). Combining either of these drugs with metformin, sulphonylureas, or both, also reduced mortality. Treatment with insulin was associated with more comorbidities. As with all observational studies, the explanations for the findings are multifactorial, and require careful interpretation. The study was unable to assess the indications for choice of drug and it is likely that clinicians would have avoided gliptins and glitazones in anyone they considered to be at risk of heart failure.

### Heart failure treatments and diabetes

Several of the drugs routinely used in heart failure (ACE inhibitors, angiotensin receptor blockers, diuretics, beta blockers) are also used in diabetes and have no significant adverse effect on blood glucose control. The most important interaction is the combined effect of diuretics and hyperglycaemia-related dehydration, which can lead to worsening renal failure, a condition associated independently with both heart failure and diabetes. Managing the heart failure while maintaining renal function is a balancing act in which hyperglycaemia may be a tipping factor.

### Palliative care and diabetes management in end-stage heart failure

How can we use the studies and guidelines available to determine how best to manage the individual with end-stage heart failure and diabetes? As with all palliative care, relief of symptoms, both physical and psychological, is the mainstay of treatment. Dyspnoea, oedema, nausea, anorexia, pain, fatigue, anxiety and depression are the predominant symptoms. The specialist heart failure team should take the lead in managing these and there may be a need to reduce treatment depending on the perceived life expectancy. However, because the trajectory of end-stage heart failure

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Risks in heart failure</th>
<th>Recommendations for use</th>
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<tbody>
<tr>
<td>Metformin</td>
<td>• Avoid if eGFR &lt;30&lt;br&gt;• No longer contraindicated in HF&lt;br&gt;• May exacerbate GI symptoms of HF</td>
<td>Monitor renal function</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>• Increased risk of HF</td>
<td>Avoid</td>
</tr>
<tr>
<td>Gliptins</td>
<td>• Increased risk of HF with some gliptins</td>
<td>Avoid saxagliptin and alogliptin</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>• Dehydration and impaired renal function&lt;br&gt;• Hypotension</td>
<td>Monitor renal function</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>• Increased risk of hypoglycaemia</td>
<td>Monitor blood glucose</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>• GI symptoms of HF exacerbated&lt;br&gt;• Weight loss effect undesirable in end-stage HF</td>
<td>Avoid</td>
</tr>
</tbody>
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**Table 1. Selection of non-insulin blood glucose lowering treatments in end-stage heart failure**

HF = heart failure; eGFR = estimated glomerular filtration rate; GI = gastrointestinal.

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is more variable than cancer, it may be difficult to predict the remaining lifespan; treatment of both the diabetes and the heart failure should be focused on alleviating symptoms with a view to reducing fluctuations as much as possible (Figure 2C). This may require more monitoring of blood glucose and renal function than would be normal towards the end of life.

In line with the guidelines for management of diabetes in end of life care, the first aim of diabetes treatment should be to avoid hyperglycaemia (target blood glucose above 6mmol/L) because of the increased risk of hypoglycaemia-induced arrhythmia and sudden death. Hyperglycaemia has the potential to worsen renal function and cause postural hypotension, so it is equally important to aim for a blood glucose below 15mmol/L.

**Choice of medication**

Pioglitazone and some gliptins should be avoided because of the increased risk of heart failure. Although GLP-1 agonists have evidence for reduced incidence of heart failure, it is hard to justify their use in a situation where lifespan is limited, given their potential to worsen gastrointestinal symptoms. (Table 1.)

Heart failure-related nausea, vomiting and delayed gastric emptying may necessitate a change of diabetes treatment; metformin can be difficult to tolerate in these circumstances, although past advice that it is contraindicated in heart failure has been rescinded. Sulphonylureas increase the risk of hypoglycaemia, particularly in the presence of reduced food intake and/or poor renal function. SGLT-2 inhibitors have potential benefit in heart failure but must be used with caution because they may lead to dehydration, hypotension and declining renal function. When using these drugs, the margins between fluid retention and dehydration/declining renal function are so fine that frequent monitoring may be necessary.

Treatment with insulin also requires careful monitoring because of reduced food intake and declining renal function, both of which lead to lower dose requirement. Simplifying the insulin regimen is usually a good plan, particularly if food intake is reduced, and once-daily basal insulin may be sufficient, irrespective of the type of diabetes, with degludec particularly useful. However, there are no hard and fast rules about a suitable insulin regimen and clinicians should be guided by the wishes and capabilities of the individual. This may depend on their previous experience of managing their diabetes and how much control they wish to retain. For example, some people with long experience of managing type 1 diabetes may not wish to move to a simpler regimen or to relinquish control to carers with less expertise in their personal diabetes management; others may be weary of day-to-day decision making and keen to reduce the burden by simplifying the regimen and handing the decision making to others. Collaboration between patient, carers and clinicians is crucial. The advent of flash glucose monitors has the potential to make monitoring less invasive in the future.

**Other considerations**

**Footcare.** People with diabetes are very vulnerable to pressure ulcers, particularly when immobile. The National Diabetes Inpatient Audit 2017 found a 1% incidence of new foot lesions during hospital admission and although there has been a downward trend over the last five years, this is still unacceptable. People with heart failure are also at increased risk of pressure ulcers because of peripheral oedema and immobility; it is essential to ensure that feet are protected by assessing the risk (neuropathy and vascular assessment) and by preventing pressure on heels during bedrest or foot elevation.

**Psychological support.** Severe heart failure is frequently associated with anxiety and depression, which need to be recognised and acknowledged. Both the patient and their relatives require support to deal with the uncertainty that accompanies a terminal condition with an unpredictable duration. This may require counselling or medication. Because of the uncertainty, advance planning and decisions about treatment withdrawal – both an integral part of palliative care – may be more difficult than in cancer care; being prepared to recognise the difficulties created by uncertainty and to discuss them openly is a responsibility shared by both the heart failure and the diabetes specialist teams.

**Conclusions**

Despite the frequency of coexistence of end-stage heart failure and diabetes, no specific guidelines exist for management of the combined conditions and this omission should be addressed. Evidence suggests that both hyperglycaemia and hypoglycaemia are linked to worse
heart failure outcomes so pragmatic targets for blood glucose range are 6–15mmol/L. Medications for heart failure are widely used in diabetes and do not require modification but certain blood glucose lowering agents may adversely affect heart failure or exacerbate symptoms, and treatment should be modified with this in mind. In contrast to most palliative care situations, monitoring of blood glucose and renal function may be required. Care should be provided by the specialist heart failure and diabetes teams to ensure that treatment for both conditions is optimised, and specialist teams should pay attention to the psychological needs of the patient and their family.

**Acknowledgement**

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**Declaration of interests**

There are no conflicts of interest declared.

**References**