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Clinical Practice Guidelines

Treatment of Diabetes in People with Heart Failure

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Heart failure is still under-recognized and misdiagnosed. This has significant clinical implications as the prognosis of untreated or undertreated heart failure is poor, and yet very effective proven therapies are widely available to most physicians.
- Diabetes can cause heart failure independently of ischemic heart disease by causing a diabetic cardiomyopathy that may manifest in the setting of normal or reduced left ventricular ejection fraction. The incidence of heart failure is 2- to 4-fold higher in people with diabetes compared to those without and, when present, occurs at an earlier age.
- Even though heart failure in people with diabetes should be treated similarly to heart failure in those without diabetes, they are less likely to receive appropriate therapies. The presence of diabetes should not affect the decision for treatment of heart failure.
- Comorbidities, such as renal dysfunction and propensity for hyperkalemia, are more prevalent in people with diabetes and may influence heart failure drug doses and monitoring of therapy but not therapeutic targets.

Introduction

Type 2 diabetes often occurs in association with other cardiovascular risk factors, such as hypertension, dyslipidemia, smoking and obesity, which together are strongly associated with atherosclerosis, ischemic heart disease and left ventricular (LV) dysfunction. LV dysfunction can be clinically silent or associated with the typical clinical signs and symptoms of heart failure (e.g. peripheral edema, shortness of breath, fatigue), although the elderly may have atypical symptoms (1). These symptoms need to be differentiated from other conditions that may have similar presentations, such as chronic obstructive pulmonary disease, pneumonia, anemia, varicose veins, depression, etc.

Heart Failure in People with Diabetes

The diagnosis of heart failure is made by association of typical clinical signs and symptoms with objective evidence, such as that obtained from a chest x-ray, an echocardiogram or plasma natriuretic peptide testing (brain natriuretic peptide [BNP] and prohormone of BNP [NT-pro-BNP]) (1). Documentation of systolic and diastolic myocardial function is recommended at the time of diagnosis of heart failure or with any significant change in clinical stability. Heart failure can occur over the entire range of LV ejection fractions (LVEFs), from <10% to >60%. The measurement of plasma BNP and NT-pro-BNP, which are acutely released by ventricular myocytes when the myocardium is stretched due to increased filling pressures, may help make an accurate diagnosis where clinical uncertainty exists (2). However, the practising physician may still under-recognize and misdiagnose heart failure. This has significant clinical implications as the prognosis of untreated or undertreated heart failure is poor, yet very effective proven therapies are widely available to most physicians. Because of this, many studies have explored the clinical utility of screening patients with diabetes for the presence of reduced LV function with BNP/NT-pro-BNP testing. The results to date are mixed, with no clear consensus to institute this strategy. Diabetes is associated with increased prevalence of heart failure, both systolic (commonly defined as LVEF <40%) and diastolic (commonly defined as LVEF >50%, but also referred to as preserved systolic function or preserved EF). However, the overlap between systolic and diastolic heart failure is considerable, and many people have a combination of systolic and diastolic dysfunction, although 1 is often reported to be predominant. Current tests, such as echocardiography, do usually fully characterize all aspects of systolic and diastolic dysfunction in individuals.

It is recognized that diabetes can cause heart failure independently of ischemic heart disease by causing a diabetic cardiomyopathy (3). Epidemiological studies have shown that the incidence of heart failure is 2- to 4-fold higher in people with diabetes compared to those without diabetes (4,5). Additionally, studies have shown the occurrence of asymptomatic abnormalities of ventricular systolic and diastolic function, independently from ischemic heart disease or systemic hypertension. While an increase in glycated hemoglobin (A1C) among individuals with diabetes is a recognized risk factor for heart failure (6–10), no prospective study to date has demonstrated that improved glycemic control significantly reduces the incidence of heart failure (11). Microalbuminuria is also an independent risk factor for heart failure, especially in people with diabetes. In individuals with and without diabetes, increasing urinary albumin-to-creatinine ratio is associated with a stepwise increase (2- to 4-fold) in the risk of heart failure development (8,12). Angiotensin-converting enzyme (ACE) inhibitors significantly reduce urinary albumin excretion, and, in large clinical trials of subjects with cardiovascular disease or diabetes, they have been shown to lower the risk of new-onset heart failure (13–15).

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Treatment of Individuals with Both Diabetes and Heart Failure

In nearly every clinical trial involving patients with heart failure, diabetes is present in over one-third of subjects. In the large landmark clinical trials of heart failure, subgroup analysis of diabetic populations has shown that, despite their increased risk of morbidity and mortality, they derive greater absolute benefit from efficacious therapies as compared to patients without diabetes (15–17). As such, heart failure in people with diabetes should be treated similarly to those without diabetes, although comorbidities, such as renal dysfunction and hyperkalemia, may be more prevalent in people with diabetes (http://www.ccsguidelineprograms.ca).

In particular, patients with diabetes are at increased risk for development of hyperkalemia and worsening renal dysfunction in the setting of renin-angiotensin-aldosterone (RAAS) blocking agents (18–23). Clinicians should be aware of this potential complication, especially in view of current guidelines advocating the expanded use of combined RAAS blockade in patients with mild-to-moderate heart failure and low EF.

Three beta blockers have been shown to reduce morbidity and mortality for patients with heart failure and diabetes: carvedilol, bisoprolol and metoprolol. Data to date suggest overall glycemic control for these patients improves as their heart failure syndrome improves on therapy (24–26). Carvedilol, in comparison to other beta blockers, has been shown to be associated with improved glycemic control. In addition, some data suggest the improvement in LVEF is also greater with carvedilol (17,27). For this reason, some clinicians prefer carvedilol as the beta blocker of choice in such patients. While there is a theoretical concern for the occurrence of severe hypoglycemia without awareness associated with the use of nonselective beta blockers, this has not been reported in clinical trials.

Numerous registries and reports indicate that persons with diabetes are less likely than those without diabetes to receive efficacious and evidence-based therapies for systolic heart failure. Perhaps this is due, in part, to the increased incidence of side effects and/or intolerance to RAAS blockade and the increased prevalence of renal disease in patients with diabetes. However, even when controlled for these conditions, the differences persist. This is particularly concerning considering the increased absolute benefit the agents confer to patients with heart failure and diabetes in comparison to unselected heart failure populations. As such, prescribers must be diligent in providing these therapies.

RECOMMENDATIONS

1. Individuals with diabetes and heart failure should receive the same heart failure therapies as those identified in the evidence-based Canadian Cardiovascular Society heart failure recommendations (http://www.ccsguidelineprograms.ca) [Grade D, Consensus].

2. In people with diabetes and heart failure and an estimated glomerular filtration rate <60 mL/min, or if combined renin-angiotensin-aldosterone blockade is employed:
   - Starting doses of angiotensin-converting enzyme inhibitors or angiotensin receptor II antagonists (angiotensin receptor blockers) should be halved [Grade D, Consensus].
   - Serum electrolytes and creatinine, blood pressure and body weight, as well as heart failure symptoms and signs, should be monitored within 7–10 days of any initiation or titration of therapy [Grade D, Consensus].
   - Dose-up titration should be more gradual (with monitoring of blood pressure, serum potassium and creatinine) [Grade D, Consensus].
   - The target drug doses should be the same as those identified in the evidence-based Canadian Cardiovascular Society recommendations on heart failure (http://www.ccsguidelineprograms.ca), if well tolerated [Grade D, Consensus].

3. Beta blockers should be prescribed when indicated for systolic heart failure, as they provide similar benefits in people with diabetes compared with people without diabetes [Grade B, Level 2 (17,27)].

Metformin

Metformin is an effective oral antihyperglycemic agent, but, based on isolated case reports and a biochemical rationale for a risk of lactic acidosis, it is approved for use under a warning in the setting of several conditions, including heart failure. Meta-analyses have evaluated the occurrence of lactic acidosis with the use of metformin (over 70 000 patient-years) or other antihyperglycemic agents (over 55 000 patient-years) and they have consistently shown no increase in lactic acidosis in the metformin group (28,29). In fact, cardiovascular outcomes in heart failure patients taking metformin were better than in those taking other antihyperglycemic agents (30). The current evidence suggests that patients with heart failure fare at least as well, if not better, with metformin than with other antihyperglycemic agents if they have only mild-to-moderate renal dysfunction (estimated glomerular filtration rate >30 mL/min) (30). As such, metformin should still be considered as first-line therapy in heart failure patients with mild-to-moderate renal dysfunction.

A detailed discussion of the rationale and evidence for the treatment approach to heart failure patients is available in the Canadian Cardiovascular Society consensus recommendations (http://www.ccsguidelineprograms.ca) (31).

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