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2018 Clinical Practice Guidelines

Treatment of Diabetes in People With Heart Failure

Diabetes Canada 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.
- 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.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Heart failure is a type of heart disease in which the heart no longer pumps sufficient blood to meet the body's needs. Diabetes is a risk factor for heart failure.
- Symptoms of heart failure include shortness of breath, persistent coughing, fatigue, chest pain, weight gain or swelling of the feet, ankles and legs.
- A number of effective drug treatments are available to keep heart failure in check. Your health-care provider will discuss these with you.
- Certain glucose-lowering medications have the potential to worsen or help heart failure. If you have heart failure, this will influence which glucose-lowering medications your health-care provider selects for you.

Introduction

Type 2 diabetes often occurs in association with other cardiovascular (CV) risk factors, such as hypertension, dyslipidemia, smoking and obesity, which, together, are strongly associated with atherosclerosis, ischemic heart disease and left ventricular (LV) dysfunction (1). 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 (2). 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]) (2). 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 left ventricular ejection fractions (LVEF), 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 (3). However, the practicing health-care provider 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. Because of this, many studies have explored the clinical utility of screening people 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. A recent analysis of the Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE) study assessed a number of biomarkers, including high sensitive C-reactive protein (hs-CRP), highly sensitive troponin T (hs-TnT) assay and interleukin 6. In a cohort of 3,098 participants in the ADVANCE study who underwent a nested case-cohort study, only NT-pro-BNP strongly and consistently improved the prediction of heart failure (4).

Diabetes is associated with increased prevalence of heart failure, both systolic (commonly defined as LVEF <40% or heart failure with a reduced ejection fraction) and diastolic (commonly defined as LVEF >50%, but also referred to as preserved systolic function or heart failure with preserved EF). However, the overlap between heart failure with preserved EF and reduced EF is considerable, and many people have a combination of systolic and diastolic dysfunction, although one 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

Conflict of interest statements can be found on page S199.

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cardiomyopathy (5). 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 (6,7). 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 (8–12), no prospective study to date has demonstrated that improved glycemic control significantly reduces the incidence of heart failure (13). Albuminuria is also an independent risk factor for heart failure, especially in people with diabetes. In individuals with and without diabetes, an increasing urinary albumin to creatinine ratio (ACR) is associated with a stepwise increase (2- to 4-fold) in the risk of heart failure development (10,14). Blockade of the renin angiotensin aldosterone system (RAAS) has been shown in large clinical trials of participants with cardiovascular disease (CVD) or diabetes to lower the risk of new-onset heart failure (15–17).

Treatment of Individuals with Both Diabetes and Heart Failure

In nearly every clinical trial involving people with heart failure, diabetes is present in over one-third of subjects. In the large landmark clinical trials of heart failure, subgroup analysis of populations with diabetes has shown that, despite their increased risk of morbidity and mortality, they derive greater absolute benefit from efficacious therapies as compared to people without diabetes (17–19). This was again demonstrated in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial in which 8,442 participants with class II, III or IV heart failure and an EF of ≤40% were randomized to receive either LCZ696 (sacubitril/valsartan at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to routine heart failure therapy. The primary outcome was a composite of death from CV causes or hospitalization for heart failure. LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure ($p<0.001$) (20). An analysis of 4,013 participants in the trial who had a diagnosis of diabetes based on A1C or prior history demonstrated that LCZ696 remained similarly efficacious, regardless of glycemic status (21). A similar finding was observed with the Systolic Heart failure treatment with the I_f inhibitor ivabradine (SHIFT) trial (22), a randomized trial of ivabradine vs. placebo in 6,505 participants with sinus rhythm, systolic heart failure, ejection fraction <35% and a resting heart rate >70 bpm. There were 1,979 participants with diabetes who achieved the primary composite endpoint of hospitalization for worsening heart failure or CV death more frequently than those without diabetes (Hazard Ratio [HR] 1.18, 95% Confidence Interval [CI] 1.07–1.31, $p=0.001$). Serious adverse events were not different between the ivabradine or placebo group, regardless of diabetes status. Overall, ivabradine is effective in this patient group irrespective of diabetic status. As such, heart failure in people with diabetes should be treated similarly to those without diabetes (23).

Therapeutic Considerations for Individuals with Both Diabetes and Heart Failure

People with diabetes are at increased risk for development of hyperkalemia and worsening renal dysfunction in the setting of RAAS blocking agents (24–29). Clinicians should be aware of this potential complication, especially in view of current guidelines advocating the expanded use of combined RAAS blockade in people with mild-to-moderate heart failure and low EF.

Three beta blockers have been shown to reduce morbidity and mortality for people with heart failure, reduced EF and diabetes: carvedilol, bisoprolol and metoprolol succinate. While overall glycemic control generally improves as heart failure is treated with evidence-based therapies, (30–32), carvedilol, in comparison to other beta blockers, has been shown to specifically improve glycemic control (19,33). For this reason, some clinicians prefer carvedilol as the beta blocker of choice in people with diabetes and heart failure. While there is a theoretical concern for the occurrence of severe hypoglycemia without awareness associated with the use of non-selective 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 people 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 people with heart failure and diabetes in comparison to unselected heart failure populations. As such, health-care prescribers must be diligent in providing these therapies.

Antihyperglycemic Agents and Heart Failure

Despite substantial understanding of the impact of antihyperglycemic therapy upon glucose control and microvascular disease, the heart failure specific response to intensive glycemic control and the various antihyperglycemic agents (discussed below) remains poorly understood (34).

Metformin

Metformin is an effective noninsulin 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 (35,36). In fact, CV outcomes in people with heart failure taking metformin were better than in those taking other conventional antihyperglycemic agents (37). The current evidence suggests that people 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 (eGFR >30 mL/min) (37). As such, metformin should still be considered as first-line therapy in people with diabetes with heart failure with mild-to-moderate renal dysfunction (38).

Thiazolidinediones

Thiazolidinediones (TZDs) are known to cause fluid retention, although this is generally mild. Recent studies suggest that this is not a direct toxic effect on the myocardium. The Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE) study of pioglitazone in individuals at risk of cardiac ischemic events showed that TZDs were associated with fewer cardiac ischemic events, but at the cost of an increase in heart failure hospitalizations (2% absolute excess over 2.8 years, or <1% per year) (39). Similarly, The Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) study demonstrated a small excess of new-onset heart failure (0.4% absolute excess).

The RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) was a multicentre,