Managing Dysglycemia in Diabetic Patients With Heart Failure

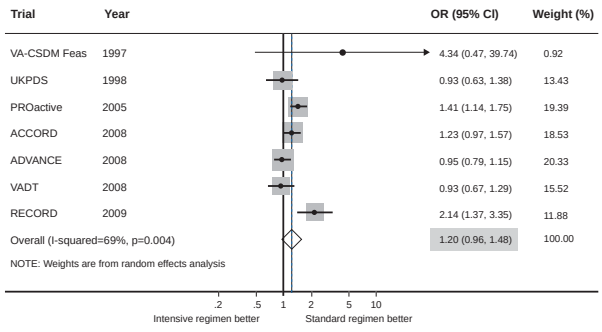
Written by **Maria Vinall**

Selecting the right antidiabetic therapy for patients with heart failure (HF) and type 2 diabetes mellitus (T2DM) can be challenging. Miles Fisher, MD, Glasgow Royal Infirmary, Glasgow, United Kingdom, reviewed approaches to managing dysglycemiain patients with HF.

INTENSIVE VERSUS LESS INTENSIVE CONTROL

To-date the data remain questionable regarding the prevention of HF by managing dysglycemia. A meta-analysis of eight randomized controlled trials comparing more versus less intensive glucose lowering in patients with T2DM reported that a more intensive control strategy did not reduce the occurrence of HF (OR, 1.20; 95% CI, 0.96 to 1.48; Figure 1) [Castagno D et al. *Am Heart J* 2011].Although randomized controlled trial data are scarce for this population of patients, in general, hyperglycemia in patients with T2DM should be treated to appropriate guideline-recommended targets and hypoglycemia should be avoided [Gitt AK et al. *Eur J Heart Fail* 2012]. Near-normal glycemic targets should be the standard for younger patients with relatively recent onset of T2DM and little or no micro- or macrovascular complications, while somewhat higher targets should be considered for older patients with long-standing diabetes and evidence of cardiovascular disease [Ismail-Beigi F et al. *Ann Intern Med* 2011].

Figure 1. Intensive Versus Less Intensive Glycemic Control



Reproduced from Castagno D et al. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: Evidence from a 37,229 patient meta-analysis. *Am Heart J* 2011;162(5):938-942. With permission from Elsevier.

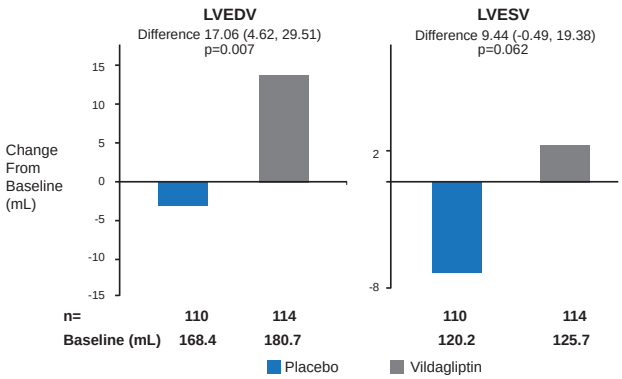
TREATMENTS

In a case-control study of patients with T2DM and HF matched for age, sex, clinic site, calendar year, and duration of follow-up, only metformin monotherapy (OR, 0.65; 95% CI, 0.48 to 0.87) or metformin in combination with other drugs (OR, 0.72; 95% CI, 0.59 to 0.90) was associated with reduced HF-related mortality compared with diabetic patients who were not exposed to antidiabetic drugs [MacDonald MR et al. *Diabetes Care* 2010].

A systematic review and meta-analysis of the seven randomized double-blind clinical trials of drug-related congestive HF in diabetic patients given thiazolidinediones (either rosiglitazone or pioglitazone) showed these agents increased the risk of developing congestive HF across a wide background of cardiac risk (RR, 1.72; 95% CI, 1.21 to 2.42; p=0.002) [Lago RM et al. *Lancet* 2007].

The SGLT2 inhibitors may offer benefits in terms of fluid volume reduction, but it is just as possible that they may cause additional harm in terms of volume depletion in vulnerable patients. In very recent trial, vildagliptin was shown to have glycemic benefit in patients with T2DM and HF but its cardiovascular safety remains unclear. Although there was no difference in left ventricular ejection fraction compared with placebo, there was an unexpected significant increase in left ventricular end-diastolic volume and a nonsignificant increase in left ventricular end-systolic volume in the vildagliptin group (Figure 2) [McMurray J et al. Heart Failure Congress 2013 (abstr 99)]. According to Prof. Fisher, use of DPP-4 and SGLT2 inhibitors remains questionable until more HF patients are included in randomized controlled trials.

Figure 2. Change in Left Ventricular Volumes



LVEDV=left ventricular end-diastolic volume; LVESV=left ventricular end-systolic volume.
Source: McMurray J et al. Heart Failure Congress 2013 (abstr 990).

Injected antidiabetic drugs, such as glucagon-like

peptide-1 (GLP-1), may offer some benefits, but, as with the other therapies, data are limited. GLP-1s preserve cardiac function and structure, decrease inflammation, improve glucose metabolism, increase weight loss, reduce blood pressure, and reduce atherosclerotic lesions. Trials are ongoing with these agents.

Prof. Fisher concluded that among the antidiabetic therapies, metformin is probably safe for patients with diabetes and HF while the glitazones are not and the DPP-4 inhibitors are also possibly unsafe. As for the SGLT2 inhibitors and GLP-1 receptor agonists, it is too soon to tell.

New Basal Insulins: The Longer the Better?

Written by **Brian Hoyle**

Luigi Meneghini, MD, University of Miami, Miami, Florida, USA, presented evidence supporting the efforts to develop longer-acting insulin therapy.

The importance of insulin therapy and associated glycemic control is incontestable. Prior to the discovery of insulin in the early 1920s, the life expectancy of a 10-year-old diagnosed with type 1 diabetes was only 2.6 years. In the early years following the introduction of insulin, the life expectancy of a 10-year-old patient with diabetes had increased to 24.3 years and had leapt to 55 years 2 decades later [Joslin EP. *Diabetic Manual for the Doctor and Patient*, 9th Ed. 1957].

Establishing glycemic control early in the course of diabetes reduces vascular complications later in life [UKPDS Group. *Lancet* 1998; Gerstein HC et al. *N Engl J Med* 2008; Duckworth W et al. *N Engl J Med* 2009; ACCORD Study Group. *N Engl J Med* 2010]. However, insulin therapy does have limitations. One is the risk of hypoglycemia. Hypoglycemia, which most often occurs in individuals with diabetes who require insulin, accounted for >95% of all endocrine-related emergency hospitalizations in people aged >65 years in the United States from 2007 through 2009 [Budnitz DS et al. *N Engl J Med* 2011]. The frequency of severe episodes of hypoglycemia rises with duration of both type 1 and type 2 diabetes [UK Hypoglycemia Study Group. *Diabetologia* 2007; Amiel SA et al. *Diab Med* 2008]. There is also increasing awareness of asymptomatic hypoglycemia, especially occurring during the night, as evidenced by data collected through continuous glucose monitoring [Hay LC et al. *Diab Tech Ther* 2003].

Longer-acting (≥24 hours) insulin could be useful especially when accompanied by minimal-to-no peak effect and predictable day-to-day glucose response. Insulin detemir and insulin glargine have shown promise towards these goals, although the peak effect has only been reduced but not eliminated, compared with neutral protamine Hagedorn (NPH) insulin [Heise T et al. *Diabetes* 2004]. Nocturnal hypoglycemia is reduced with insulin glargine and insulin detemir, compared with NPH insulin [Riddle MC et al. *Diab Care* 2003; Philis-Tsimikas A et al. *Clin Ther* 2006].

In seeking to extend the benefits of basal insulin, studies have focused on larger molecules that have a longer duration of action, such as the multihexameric insulin degludec. Insulin degludec attains steady state with 2 to 3 days of once-daily dosing. Compared with insulin glargine, insulin degludec maintains a more sustained serum concentration over time, a longer mean half-life (Table 1).

Table 1. Half-life of Insulin Degludec and Insulin Glargine

	Degludec			Glargine		
	0.4 U/kg	0.6 U/kg	0.8 U/kg	0.4 U/kg	0.6 U/kg	0.8 U/kg
Half-life (hours)	25.9	27.0	23.9	11.8	14.0	11.9
Mean half-life	25.4			12.5		

Compound LY2605541 (pegylated lispro insulin) is another large molecule that is delayed in absorption and clearance, which prolongs its action.

These ultra long-acting insulin preparations have been compared with insulin glargine with regards to efficacy and risk of hypoglycemia. While there is comparable reduction in HbA1C between these longer-acting basal analogs and insulin glargine, there is also a consistent reduction in the risk of nocturnal hypoglycemia associated with the use of these new ultra-long basal insulin preparations [Rodbard HW et al. *Diabet Med* 2013; Bergenstal RM et al. *Diabetes Care* 2012].

Because these longer-acting insulin preparations take ~3 to 4 dosing injections to reach steady state, adjusting the basal insulin dose on a weekly basis to achieve desired fasting plasma glucose targets should allay any potential concerns over stacking of the insulin.

Long-term cardiovascular trials planned for some of these longer-acting basal insulin preparations should be able to address any remaining issues regarding the cardiovascular safety of these novel insulin molecules.