Perry M. Elliott, MD, The Heart Hospital, University College London, London, United Kingdom, presented some of the new recommendations concerning the symptoms in HCM, such as chest pain, dyspnea and arrhythmia that may be explained by decreased myocardial perfusion and the resultant myocardial ischemia:

- assessment of coronary anatomy with computed tomographic angiography is reasonable for HCM patients with chest discomfort and a low likelihood of coronary artery disease (CAD) to assess for possible concomitant CAD (Class IIa; LoE C)
- the assessment of ischemia or perfusion abnormalities suggestive of CAD with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) myocardial perfusion imaging (MPI) is reasonable in patients with HCM with chest discomfort and a low likelihood of CAD to rule out possible concomitant CAD (Class IIa; LoE C)
- recommendations do not support the use of routine SPECT MPI or stress echocardiography for detection of "silent" CAD-related ischemia in patients with HCM who are asymptomatic; nor is the use of PET to detect the presence of microvascular ischemia recommended for the prognosis of HCM (Class III; LoE C)

Overall there is a low annual rate of mortality from sudden cardiac arrest due to HCM. However, unacceptable death rates in the HCM population remain even in those being treated with medications, explained Matthew W. Martinez, MD, Lehigh Valley Health Network, Allentown, Pennsylvania, USA. Implantable cardioverter-defibrillators (ICDs) are a useful treatment option in patients who are at high risk of SCD, defined as young patients with a positive family history of SCD, unexplained syncope, left ventricularwall thickness >30 mm, associated CAD, nonsustained ventricular tachycardia, exercised-induced hypotension, or fibrosis detected by MRI (Class Ib; LoE B).

Paul Sorajja, MD, Mayo Clinic, Rochester, Minnesota, USA, comparing the outcomes from myectomy and septal ablation, reported that myectomy is the recommended standard treatment for HCM (Class IIa; LoE C), as it offers low immediate post-operative risk, a >95% chance of symptom relief and superb long-term survival benefits. Septal ablation works well if patients are carefully selected (Class IIa or IIb; LoE B) but has higher acute complications, often including heart block, hence the need for a pacemaker following ablation. The two procedures appear to be comparable in terms of gradient relief, symptom relief, and early survival; however, there continues to be concern regarding the potential long-term consequences of the ablation-induced infarction, including data from ICD monitoring that suggest an increased risk of ventricular arrhythmia among HCM patients post ablation compared with septal myectomy. A definitive randomized trial that compared long-term outcomes between these two procedures has yet to be performed.

New Anti-Diabetes Agents Offer Promise in the Fight Against CVD

Written by Rita Buckley

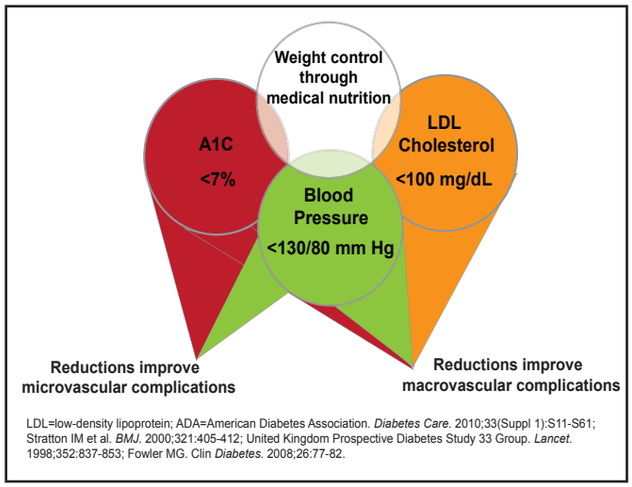
Type 2 diabetes mellitus (T2DM) is a major risk factor for ischemic heart disease, and cardiovascular disease (CVD) is the leading cause of morbidity and mortality for individuals with T2DM [McEwen LN et al. *Diabetes Care* 2012]. CVD is also the largest contributor to direct and indirect medical costs that are associated with T2DM. Common conditions that coexist with T2DM (eg, hypertension and dyslipidemia) are clear risk factors for CVD; however, a diagnosis of T2DM itself confers independent risk [Whittington HJ et al. *Cardiol Res Pract* 2012].

Numerous studies have demonstrated the efficacy of targeting and controlling individual CV risk factors (eg, blood pressure less than 130/80 mm Hg, low-density lipoprotein cholesterol less than 100 mg/dL, HbA1C <7%) in preventing or slowing the progression of microvascular and macrovascular disease in patients with T2DM [American Diabetes Association Standards of Medical Care in Diabetes—2012. *Diabetes Care* 2012] (Figure 1). Larger benefits are seen when multiple risk factors are globally addressed in patients with T2DM [Buse JB et al. *Diabetes Care* 2007; Gaede P et al. *N Engl J Med* 2008].

However, randomized clinical trials have also suggested the limits of intensive CV risk factor control in T2DM [The ACCORD Study Group. *N Engl J Med* 2010; Duckworth W et al. *N Engl J Med* 2009; ADVANCE Collaborative Group. *N Engl J Med* 2008]. In particular, achieving intensive glucose control alone may be insufficient to reduce major CVD events. A new medication class that may reduce CVD in patients with T2DM uses molecules that activate the incretin system to raise or mimic glucagon-like peptide-1 (GLP-1). In a recent review, Motta et al. [*Recent Pat Cardiovasc Drug Discov* 2012] reported that incretin-based agents improve glycemic control by mechanisms

that minimize hypoglycemia and that some agents also improve lipoprotein profiles, blood pressure control, and weight loss.

Figure 1. Metabolic Components of Diabetes: ADA Treatment Recommendations.



LDL=low-density lipoprotein; ADA=American Diabetes Association. *Diabetes Care*. 2010;33(Suppl 1):S11-S61; Stratton IM et al. *BMJ*. 2000;321:405-412; United Kingdom Prospective Diabetes Study 33 Group. *Lancet*. 1998;352:837-853; Fowler MG. Clin *Diabetes*. 2008;26:77-82.

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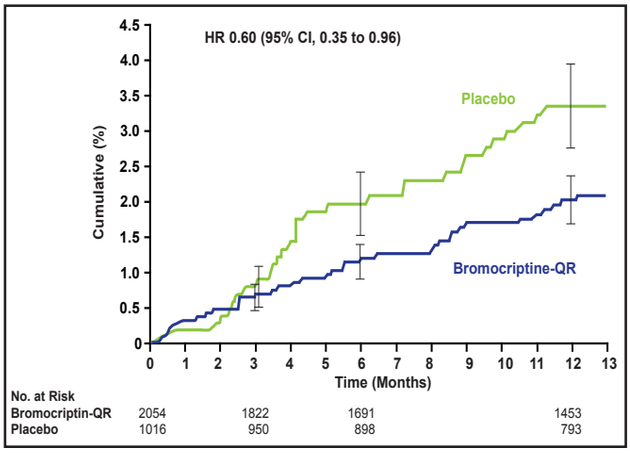
GLP-1 receptors have been discovered on cardiac myocytes and endothelial cells [Ban K et al. *Circulation* 2008; Bose AK. *Diabetes* 2005], and intravenous GLP-1 acutely improves left ventricular ejection function (LVEF) and reduces BNP levels in heart failure patients [Sokos GG et al. *Card Fail* 2006]. A 72-hour GLP-1 infusion also improved left ventricular wall motion abnormalities and LVEF in patients with a history of myocardial infarction (MI) [Nikolaidis LA et al. *Circulation* 2004]. Given all of these favorable effects on surrogate outcomes, there are currently large ongoing trials of GLP-1 agonists in patients with T2DM that are studying their ability to reduce CV endpoints [LEADER, NCT01179048; EXSCEL, NCT01144338].

Dipeptidyl peptidase 4 (DPP-4) inhibitors are another form of incretin-based therapy that indirectly increase endogenous GLP-1. Evidence shows that GLP-1 receptor agonists and DPP-4 inhibitors are capable of preserving myocardial function and protecting cardiac myocytes from ischemic damage, independent of their glucose-lowering function [Mannucci E, Dicembrini I. *Curr Med Res Opin* 2012].

Mannucci and Dicembrini note that both classes of drugs enhance endothelial function. In addition, DPP-4 inhibitors increase the availability of endothelial progenitor cells via a GLP-1 receptor-independent pathway. Taken together, available experimental evidence, with a few pilot studies in humans, suggests that incretin-based therapies could prevent CVD [Monami M et al. *Exp Diabetes Res* 2011; Phung OJ et al. *JAMA* 2010; Frederich R et al. *Postgrad Med* 2010]. As a result, there are several large randomized clinical trials studying the effects of DPP-4 inhibitors in patients with T2DM to reduce incident and recurrent CV events [TECOS, NCT00790205; EXAMINE, NCT00968708; SAVOR-TIMI 53, NCT01107886].

Neuroendocrine-based therapies are another approach of interest for reducing CVD in patients with T2DM. Quick-release bromocriptine (bromocriptine-QR) is a D2 dopamine receptor agonist. The Cycloset Safety Trial, a 52-week, randomized, double-blind, multicenter trial demonstrated the potential CV safety and efficacy of this novel therapy for T2DM (Figure 2) [Gaziano JM et al. *Diabetes Care* 2010]. Fewer people reported a CVD end point (the composite of MI, stroke, coronary revascularization, and hospitalization for angina or congestive heart failure) in the bromocriptine-QR group (1.8%) versus placebo group (3.2%; HR, 0.60; 95% two-sided CI, 0.35 to 0.96; Figure 2). The frequency of serious adverse events (SAEs) was comparable between the groups (8.6% vs 9.6%; HR, 1.02; 96% one-sided CI, 1.27).

Figure 2. CV Endpoints – Reported SAEs.



Reproduced from Gaziano JM et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care* 2010. Jul;33(7):1503-8. With permission from the American Diabetes Association.

Incretin- and neuroendocrine-based therapies for patients with T2DM are exciting new developments; with the potential to improve overall CVD risk based on experimental and early clinical data. Although these early developments are promising, we await the results of the ongoing large multicenter clinical trials that are designed to determine whether these therapies reduce CV events in patients with T2DM.