Trends in Cardiovascular Medicine 26 (2016) 165–179

Available online at www.sciencedirect.com

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Approach to diabetes management in patients with CVD

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ABSTRACT

Epidemiologic analyses have established a clear association between diabetes and macrovascular disease. Vascular dysfunction caused by metabolic abnormalities in patients with diabetes is associated with accelerated atherosclerosis and increased risk of myocardial infarction (MI), stroke, and peripheral arterial disease. Patients with diabetes are at two to four fold higher CV risk as compared to non-diabetic individuals, and CVD remains the leading cause of mortality in patients with this condition. One strategy to reduce CVD burden in patients with diabetes has been to focus on controlling the major metabolic abnormality in this condition, namely hyperglycemia. However, this has not been unequivocally demonstrated to reduced CV events, in contrast to controlling other CVD risk factors linked to hyperglycemia, such as blood pressure, dyslipidemia, and platelet dysfunction. However, In contradistinction, accrued data from a number of large, randomized clinical trials in both type 1 (T1DM) and type 2 diabetes (T2DM) over the past 3 decades have proven that more intensive glycemic control retards the onset and progression of microvascular disease. In this review, we will summarize the key glucose-lowering CV outcomes trials in diabetes, provide an overview of the different drugs and their impact on the CV system, and describe our approach to management of the frequently encountered patient with T2DM and coronary artery disease (CAD) and/or heart failure (HF).

Key words: Type 2 diabetes (T2DM), Coronary artery disease (CAD), Congestive heart failure (CHF), CVD, Peripheral arterial disease (PAD), Thiazolidinedione (TZD), Sulfonylurea (SU), Major adverse CV events (MACE), Impaired glucose tolerance (IGT), Impaired fasting glucose (IFG).

Diabetes mellitus is a chronic disease characterized by hyperglycemia and frequently manifested by both macrovascular [myocardial infarction (MI), stroke, and peripheral arterial disease (PAD)] and microvascular (retinopathy, nephropathy, and neuropathy) complications. Type 2 DM (T2DM) is the most common form, constituting 90–95% of cases worldwide. It results from the combination of insulin resistance in peripheral tissues, due to obesity and genetic factors, with an inadequate pancreatic insulin response (or relative beta-cell failure.) T2DM may well be described as a pandemic of the modern age—the CDC estimates 29.1 million people or 9.3% of the US population as having diabetes in 2014 [1]. Moreover, the risk of CV (CV) morbidity and mortality appears to be magnified by diabetes. The CDC reports an increase in self-reported heart disease or stroke from 4.2 million to 7.6 million in people aged 35 years or older with diabetes from 1997 to 2011 [1] (Fig. 1).

The authors have indicated that there are no conflicts of interest.

Dr. Inzucchi discloses receiving honoraria for consultative/advisory activities with the following companies that manufacture diabetes medications: Merck, Novo Nordisk, Boehringer-Ingelheim Janssen, and AstraZeneca. He is involved in a clinical trial for which Takeda Pharmaceuticals is providing study drug and placebo. Dr. Lathief has nothing to disclose.

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http://dx.doi.org/10.1016/j.tcm.2015.05.005
1050-1738/

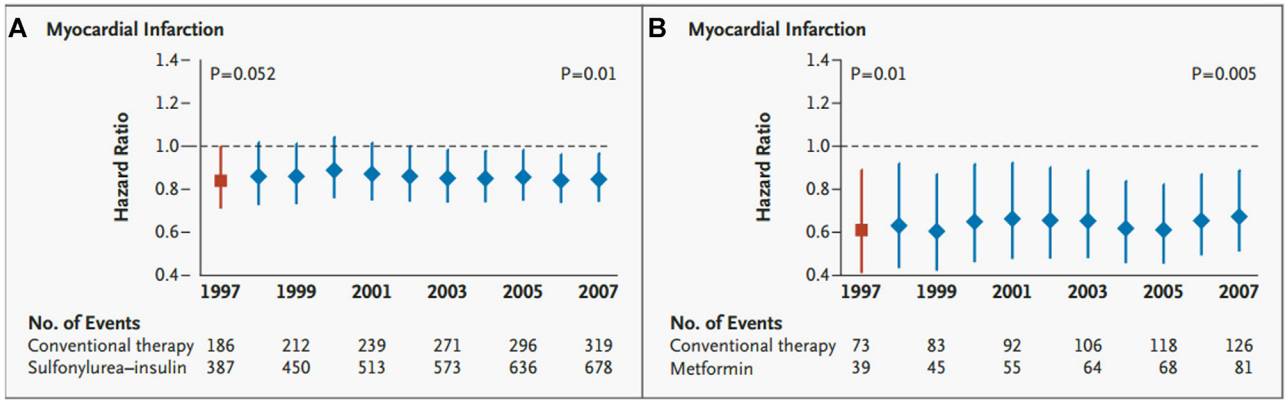

Fig. 1 – Myocardial infarction in the UKPDS. The proportions of patients in the UKPDS who suffered a myocardial. (A) Sulfonylurea–insulin group vs. the conventional-therapy group and (B) Kaplan–Meier plots for cumulative incidence and log-rank. P values are shown at 5-year intervals during a 25-year period from the start of the interventional trial. (Adapted with permission from Holman et al. [41].)

Epidemiology

Patients with diabetes are at two to four fold increased CV risk as compared to non-diabetic individuals [2–4]. The 7-year incidence of first myocardial infarction (MI) in patients with diabetes has been estimated at 20% as compared to 3.5% in non-diabetics in an older population-based study [3]. This report concluded that diabetic patients without any history of MI have equivalent risk for a future acute coronary event as non-diabetic individuals with a prior history of MI, i.e., a "coronary risk equivalent." Subsequent studies, however, have not confirmed this observation, finding that, while clearly higher than in control patients, diabetes does not confer that large a degree of incremental risk [5,6]. Nonetheless, CVD (CVD)—and specifically coronary artery disease (CAD)—remains the major cause for mortality in patients with diabetes [7]. Diabetic participants with a history of CVD at time of enrollment in the Heart Protection Study had a three-fold greater number of CV events than those without such a history [8]. A prospective study analyzing the 2-year CVD outcomes of patients with diabetes admitted with unstable angina or non ST elevation MI found higher incidence of CV mortality, new MIs, heart failure (HF), and stroke in those with diabetes as compared to controls [9]. In the Multiple Risk Factor Intervention Trial, men who reported taking medications for diabetes were three times as likely to develop a stroke [10]. Epidemiological analyses have also identified between a two- and four-fold higher incidence of peripheral arterial disease (PAD) in patients with diabetes [2]. Of note, a causal role for diabetes in the development of CVD has been identified even at a genetic level through Mendelian randomization analyses of single nucleotide polymorphisms [11].

Pathophysiology

The pathophysiology of diabetic vascular disease is complex. It involves endothelial dysfunction which may promote vasospasm, inflammation and thrombosis [2] (Fig. 2). Hyperglycemia inhibits the production of nitric oxide (NO) by inhibiting NO synthase, thereby reducing the availability of this potent vasodilator in the vascular smooth muscle and endothelium [2]. Additionally, hyperglycemia promotes the upregulation of genes responsible for production of pro-inflammatory cytokines and promotion of production of matrix metalloproteinases that render atheromatous plaques more unstable, with greater propensity to rupture, leading to acute thrombosis [2]. Finally, platelet dysfunction and increased production of pro-thrombotic substances like fibrinogen and thrombin contribute to a pro-thrombotic milieu in patients with this condition [2].

Of course, patients with T2DM also have additional risk factors to promote atherosclerosis, including obesity, dyslipidemia, hypertension, and insulin resistance. Data from prior trials have established consensus on the CV benefit of controlling blood pressure, cholesterol, smoking and lifestyle changes in patients with diabetes [12–17]. however, the specific targets and strategies differ between various societies and professional groups.

Dyslipidemia

Diabetic dyslipidemia is characterized by decreased concentrations of high density lipoprotein (HDL)-cholesterol (C), increased triglycerides, and elevated amounts of small, dense low-density lipoprotein (LDL) particles. Increased release of free fatty acids (FFA) from adipose tissue coupled with their impaired skeletal muscle uptake yields greater substrate delivery to the liver and augmented hepatic synthesis of proatherogenic very low-density lipoprotein (VLDL) particles. This is responsible for the major lipid abnormalities in diabetes, since VLDL is the main carrier lipoprotein for triglycerides and increased VLDL, through cholesterol ester transfer protein (CETP), leads to reduced HDL-C concentrations. Diabetic dyslipidemia may be indirectly exacerbated by poor glycemic control, also probably through increase substrate flux. LDL-C concentrations tend not to be higher in diabetic vs. non-diabetic individuals, although LDL particles appear to be more atherogenic. Lipid lowering, specifically LDL-C reduction, has been associated with a substantive CV