CellPress

Review

Potential Drug Combinations to Reduce Cardiovascular Disease Burden in Diabetes

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The major cause of death and complications in patients with type 2 diabetes (T2DM) is cardiovascular disease (CVD). More than 60% of all patients with T2DM die of CVD, and an even greater percentage have serious complications. The impact of glucose lowering on cardiovascular complications is a hotly debated issue and recent large clinical trials reported no significant decrease in cardiovascular events with intensive glucose control. Risk remains high even after correcting diabetes-associated dyslipidemia with drugs such as fibrates and niacin. Data from several clinical studies show that postprandial glucose and lipids have a strong predictive value on myocardial infarction (MI) and mortality. However, strategies to reduce postprandial hyperglycemia and/or lipemia through increased utilization of glucose and/or triglycerides (TG) have been shown to not be effective in reducing the CVD burden. In this review, I discus the preferred ways to reduce postprandial glucose and TG with combinations of currently marketed drugs with potential benefit in CVD.

Trends

Lowering plasma TG or increasing high-density lipoprotein (HDL) do not seem to offer benefits above the standard of care in diabetics.

Therapeutic targets that prevent glucose and lipid absorption appear to be promising in reducing CVD burden in patients with diabetes.

Emerging data suggest that mechanisms that promote glucose removal through the kidney appear to show cardiovascular and mortality benefits in patients with diabetes.

Reducing sustained vascular stress under postprandial conditions is a promising therapeutic approach to reduce cardiovascular disease burden in patients with diabetes.

Diabetes and CVD

Adults with T2DM are two to four times more likely to have heart disease or a stroke than adults without diabetes, and approximately 65% of patients with T2DM will die from CVD [1]. Risk of MI, stroke, microvascular events, and mortality are all strongly associated with hyperglycemia [hemoglobin A1c (HbA1c)] and epidemiologic analyses suggest that each 1% increase in HbA1c increases the risk for CVD by approximately 18% [2]. In addition to hyperglycemia, patients with T2DM often present with additional risk factors that predispose them to CVD. These include insulin resistance, obesity, hypertension, and dyslipidemia. Although patients with diabetes in general do not have high low-density lipoprotein (LDL), the results of statin trials support the importance of the intensive control of LDL in patients with T2DM [3]. However, CVD remains high and the event rates in the statin-treated subgroups of patients with diabetes are generally higher than those in the treated subgroups of patients without diabetes.

Although HbA1c levels are strongly associated with CVD, it is not clear whether hyperglycemia per se promotes CVD. While trials such as the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) showed that tight control of blood glucose reduces the development of the microvascular disease (nephropathy and retinopathy) [4,5], the relations between blood glucose control, cardiovascular events, and all-cause mortality are controversial. While The Veterans Affairs Diabetes Trial (VADT) showed no significant effect of intensive glucose control on cardiovascular outcomes [6], intense glucose lowering in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed an unexpected increase in all-cause mortality [7]. What is also interesting is that intensive multifactorial risk factor management (i.e., lifestyle interventions, blood glucose, blood pressure, and cholesterol control, as well

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as the prescription of daily low-dose aspirin) also does not seem to significantly reduce the risk of first, second, or third cardiovascular events, compared with standard diabetes care, according to a subanalysis of the ADDITION-Europe trial [8]. A Cochrane systematic review [9] of intensive glycemic control versus conventional glycemic control involving 20 randomized clinical trials that included 29 986 participants with T2DM did not show significant differences for all-cause mortality and cardiovascular mortality. Similarly, another analysis that included 13 studies and 34 533 patients showed no significant benefits of intensive glucose-lowering treatment on all-cause mortality and deaths from cardiovascular causes [10].

The experience was similar with lipid trials, in that several recent trials addressing diabetic dyslipidemia (high TG and low high-density lipoprotein; HDL) also did not show encouraging data. Fibrates (gemfibrozil and fenofibrate) belong to a class of drugs that exert their effects by activating peroxisome proliferator-activated receptor (PPAR)-α. These drugs reduce the concentration of plasma TG by 30–50% and raise the level of HDL cholesterol (HDL-C) by 2–20%. In earlier trials, such as the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) and Helsinki heart study, subgroup analysis showed that, in men with coronary heart disease (CHD) and a low HDL, gemfibrozil use was associated with a reduction in major cardiovascular events in persons with diabetes and in nondiabetic subjects with a high fasting plasma insulin level [11,12]. However, more recent trial data (FIELD and ACCORD trials) show no benefit of dyslipidemia treatment on CVD in patients with diabetes [13,14]. In the ACCORD-Lipid trial involving 5518 patients over 4.7 years, fenofibrate treatment showed no significant benefit on total cardiovascular events or mortality. As a result, information from the trial was added to the physician label and patient medication guide for fenofibrate, which is currently marketed in the USA as Trilipix. In the AIM-HIGH trial [15], which involved 3414 patients (approximately 30% of whom had diabetes), adding niacin (1500–2000 mg/day) had no beneficial effect over simvastatin therapy alone despite significant improvements in TG and HDL. Moreover, there was a trend toward increased risk of ischemic stroke in the niacin-treated group. Thus, it is inconclusive whether treating dyslipidemia will reduce CVD in patients with diabetes.

Postprandial Phenomena

It is clear that addressing fasting plasma glucose (FPG), or dyslipidemia did not provide convincing evidence for CVD protection. In this review, I focus on postprandial glycemia and lipemia and discuss their relation to CVD and ways to reduce the postprandial burden.

Postprandial Glucose

The phenomenon of postprandial glucose (PPG) was addressed in detail by Schrot [16]. Postprandial hyperglycemia is one of the earliest abnormalities observed in patients with T2DM and is defined as a plasma glucose level exceeding 7.8 mM glucose (140 mg/dl). Changes in PPG, as determined by a 2-h glucose tolerance test (GTT), often precede FPG changes in the natural history of T2DM. Studies showed that PPG elevations (> 200 mg/dl) occurred in approximately 39% of patients whose HbA1c levels were optimal (< 7%) [17,18]. In patients using oral agents, PPG elevation occurred in 63% of those with HbA1c < 7%. In patients with normal or near-normal FPG and a HbA1c that remained high, the 2-h PPG becomes a good index of glycemic control. Thus, PPG elevation is a frequent finding even when HbA1c goals are achieved [19]. Controlling PPG at this point would likely lead to a reduction in HbA1c to further below 7%.

Elevated PPG has long been considered an independent risk factor for CVD and death [20–24]. Earlier studies that used 1-h post-meal numbers predicted a relation between PPG and CVD. A study involving Hawaiian Japanese subjects showed that death from all causes, CVD, and coronary heart disease were significantly higher in men with glucose intolerance [25]. Similarly,