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Evolution in Understanding of Cardiovascular Outcomes in Diabetes

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Abstract

Eighty percent mortality occurs in patients with type 2 diabetes mellitus due to cardiovascular (CV) events like myocardial infarction, stroke and peripheral vascular disease. We learned from United Kingdom Prospective Diabetes Study (UKPDS) that lowering HbA1c reduces both micro and macrovascular complications. However, more recent studies have provided insight that HbA1c reduction may exert only a modest effect in lowering macrovascular complications. In fact, treating hypertension and dyslipidemia may provide a greater benefit in reducing CV events. The last 10 years have changed our understanding of cardiovascular disease (CVD) risk in type 2 diabetes. Earlier it was believed to be due to atherosclerotic cardiovascular disease which was exaggerated by hyperglycemia. Additionally, some antidiabetic medications were also implied to contribute to cardiovascular illness and mortality. It is plausible that insulin resistance may play a significant role in cardiovascular complications as well since it induces endothelial dysfunction much earlier before type 2 diabetes is diagnosed. Many patients manifest CVD in form of either atherosclerotic cardiovascular disease (ASCVD) or heart failure prior to diagnosis of diabetes. Amelioration of insulin resistance may be the management key in type 2 diabetes and can be very well achieved with modern drugs although attaining and maintaining desirable glycemic control may be as crucial as noted in type 1 diabetes.

Keywords

Type 2 Diabetes Mellitus, CVD, Hyperglycemia, ASCVD, Heart Failure

1. Introduction

Cardiovascular disease (CVD) is a major contributor to morbidity and mortality among patients with diabetes. People with type 2 diabetes mellitus (T2DM) have twice the risk of manifesting cardiovascular ailments including myocardial in-

farction (MI), stroke and peripheral vascular disease which account for eighty percent mortality [1]. A population-based study has demonstrated that cardiovascular deaths occur 7.5 times more in patients with type 2 diabetes who never had a myocardial infarction compared to people who never had diabetes or myocardial infarction [2]. 52.9% mortality due to cardiovascular disease has been suggested in patients with diabetes by Chennai Urban Population Study which was significantly higher (P = 0.042) than those who did not have diabetes (24.2%). One year mortality rate after myocardial infarction was 44% in males and 36% in females, while it was 32% in males not having diabetes and 20% in non-diabetic females [3]. Apart from this, ten-year risk of developing coronary heart disease in patients having diabetes is reported to be more than 20 percent in comparison to non-diabetic population [4]. Considering these facts, Adult Treatment Panel III of the National Cholesterol Education Program has declared type 2 diabetes mellitus as coronary heart disease risk equivalent [5].

Many clinical trials have proven that HbA1c reduction in type 2 diabetes has no [6] or only a modest [7] [8] effect on reducing cardiovascular (CV) risk which is certainly not more than what is achieved by amelioration of hypertension and dyslipidemia. Intensive glycemic control of diabetes substantially reduces the microvascular complications but not the occurrence of macrovascular events like myocardial infarction or strokes. Stringent glucose control from the onset of the diagnosis certainly reduces macrovascular events and all-cause mortality later in life, "legacy effect" [9]. Lipid lowering and control of hypertension also play a key role in the primary prevention of cardiac risk in patients with type 2 diabetes mellitus [10]. It adds clinically significant reduction in deaths and manifestations due to cardiovascular causes. Tight blood pressure control significantly reduced the risk of any diabetes related end point by 24% (P = 0.0046), mortality by 32% (P = 0.019), stroke by 44%, microvascular end points by 37% (P = 0.013) and heart failure by 56% (P = 0.0043) [11]. Hyperglycemia is not always the culprit to cause cardiovascular adverse outcomes. Instead, hypoglycemia or certain antidiabetic therapies may contribute to adverse CV outcomes.

2. Hypoglycemia: Does It Induce CVD?

Hypoglycemia induces many indirect changes including inflammatory cytokine secretion, endothelial dysfunction, exacerbated coagulation, and fibrinolysis with potential of promoting adverse effects on cardiovascular morbidity and mortality [12]. Acute hypoglycemia induces significant sympatho-adrenal responses, because of enhanced autonomic activity with increased adrenaline secretion. It provokes hemodynamic changes to increase heart rate and peripheral systolic blood pressure, fall in central blood pressure, lowering of peripheral arterial resistance, increase in myocardial contractility, stroke volume and cardiac output. These changes lead to the development of transient, but markedly increased workload on the heart, which may have adverse outcomes in elderly type 2 diabetes patients, many of whom already have coronary heart disease. Evidences from

clinical and experimental trials have shown that hypoglycemia may cause abnormal electrical cardiac activity. Resulting in ST wave alterations with increasing QT interval and cardiac repolarization [13].

3. Antidiabetic Therapies and CVD

Commonly used oral antidiabetic drugs like sulfonylureas and thiazolidinediones may develop certain cardiovascular issues like hypoglycemia-induced ischemia and arrhythmia. In heart tissues, sulfonylureas bind to the channels blocking the following three beneficial mechanisms, 1) vascular smooth muscle cells relaxation that improves coronary blood flow, 2) limitation of myocardial damage during ischemia, and 3) protection of energy producing mitochondria in cardiomyocytes. Monotherapy with 1st and 2nd generation sulfonylureas have been associated with significant higher risk (24% to 61%) for all-cause mortality while monotherapy with 2nd generation sulfonylureas were associated with significant excess risk (18% to 30%) for congestive heart failure [12].

Thiazolidinediones are known to be associated with occurrence of heart failure due to fluid retention increasing the risk of myocardial infarction. Biguanides are associated with improved cardiovascular outcomes. However, they may induce lactic acidosis and hence should not be used in patients with acute or unstable heart failure. Alpha Glucosidase inhibitors are found to improve CV outcome without any adverse impact by lowering post-prandial glucose excursions especially in carbohydrate eating populations [14].

Chronic hyperinsulinemia is a thought to be atherogenic and thus may offset the benefit conferred by modest glycemic improvement with administration of insulin. Insulin therapy may promote cardiovascular risks like smooth muscle cell proliferations, vasoconstrictions especially in large conduit arteries, monocyte adhesions, fluid retention and prothrombotic activities due to increased level of plasminogen activator receptor-1 (PAI-1), endothelin-1 receptors and adhesion molecules. Hyperinsulinemia in the presence of insulin resistance can overstimulate the intracellular mitogen signaling pathway in endothelial cells. This condition, together with impaired phosphatidylinositol 3-kinase activation of nitric oxide synthase, could lead to an atherogenic state [15].

4. Glycemic Variability & CVD

Glycemic variability is considered not only the 4th pillar of glycemic control but also yet another important determinant for cardiovascular safety. In fact, it is implicated as an independent risk factor for cardiovascular complications in patients with and without diabetes [16]. Post prandial excursion plays an important role in glycemic variability. Although a simple and a standard tool to measure glycemic variability is yet to be established, Mean Amplitude of Glycemic Excursions (MAGE) reduction is documented to lower oxidative stress and inflammatory markers in type 2 diabetic patients and consequently, the cardiovascular risks [17]. Therefore, cardiovascular risk has been found to be reduced

with antidiabetic drugs with efficacy to maintain glycemic variability at its lowest level.

5. What Is Cardiovascular Outcome Trial (CVOT)?

In an endeavor to identify antidiabetic drugs with maximum safety with the least cardiovascular risks, the Food and Drug Administration (FDA) and the European Medicines Agency simultaneously revised their approval processes in 2008, so that all new glucose lowering molecules prove their cardiovascular safety before granting approval. As per these guidelines, an upper limit of the 95% confidence interval (CI) for the risk ratio for cardiovascular events of <1.3 is recommended as a key criterion for excluding unacceptable CV risk for recent treatment modalities against type 2 diabetes pending approval. Regulatory agencies require enrollment of patients with relatively advanced CV disease, elderly and patients with some degree of renal impairment. The requirements also include CV safety data with a prospective, independent adjudication of CV events in all phase 2 and 3 studies over a minimum duration of 2 years. Regulatory agencies demand that adjudication events include CV mortality, acute coronary syndrome and stroke requiring hospitalization, urgent revascularization procedures, and possibly other end points. Moreover, the agencies stipulated new statistical guidelines regarding the analysis of cardiovascular safety data in order to satisfy upper limit of CI with submission of New Drug /Biologic License Application. The accepted methodology consists of meta-analysis of all placebo-controlled trials, add-on trials (drug vs. placebo, each added to standard therapy), prospective randomized placebo controlled trials or an additional single large safety trial alone, or combined with other trials. Most new drugs received approval only after going through this process [18].

6. Is Insulin Resistance the Main Culprit?

During follow up of participating subjects for several years after completion of UKPDS, the importance of early aggressive glycemic control in improving CV outcomes was documented (legacy effect). However, the role of moderate to severe insulin resistance was being established in onset of multiple CV risk factors like obesity, dyslipidemia, hypertension, endothelial dysfunction and pro-coagulant state. Therefore, the importance of multifactorial intervention was recognized for improving CV risk factors. Furthermore, the molecular mechanisms responsible for insulin resistance, independent of metabolic abnormalities were documented to directly contribute to pathogenesis of atherosclerosis [19]. Finally, individuals manifesting insulin resistance syndrome without diabetes were noted to present increased risk for CVD similar to patients with T2DM thus supporting the concept that hyperglycemia is not the lone major risk factor for CVD in subjects with diabetes [20]. Therefore, reducing blood pressure to the optimum level and improving the lipid profile leads to greater reduction in CVD risk than lowering plasma glucose alone in T2DM patients. So, conceptually, the anti-diabetes

agents like insulin or insulin secretagogues (e.g. sulfonylureas, GLP1 receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors) which lower plasma glucose without an effect on insulin resistance, should not lower CV risk and mortality in type 2 diabetes mellitus. However, the data from UKPDS as well as GLP1 RA trials are contradictory to this concept. On the other hand, treatment with metformin, the most effective insulin sensitizer lowered CV outcomes in UKPDS as well [9]. Alternatively, the data regarding glitazones which improve insulin sensitivity is inconsistent. Pioglitazone may have a favorable effect on CV risk in type 2 diabetes mellitus, independent of its glucose-lowering action as suggested in PROactive trial which showed marginal reduction in secondary endpoints alone including MACE (CV death, nonfatal myocardial infarction [MI], nonfatal stroke) by 16% ($P < 0.027$) [21]. Role of improving insulin sensitivity in reducing the incidence of recurrent stroke and MI by therapy with pioglitazone in individuals with insulin-resistance without diabetes was evident in IRIS [22]. However, therapy with Rosiglitazone, another insulin sensitizer appeared to increase adverse CV outcomes in subjects with diabetes [23] [24] [25].

7. Effect of GLP1 RA

Three point MACE has been found to be reduced by 15% in a meta-analysis of the two long-acting GLP-1 RAs liraglutide and semaglutide with similar and significant benefit for all three components: nonfatal stroke, nonfatal MI and mortality by 18%, 16%, and 13%, respectively. LEADER and SUSTAIN-6 have highlighted that patients at higher cardiovascular risk benefited more from GLP-1 RA treatment. The benefit of liraglutide and semaglutide has been quite visible maximally for optimal control of traditional CV risk factors. However, it is worth noticing the finding in LEADER that 23% of patients without prior cardiovascular event, did not show MACE reduction. In SUSTAIN-6, there was a greater fall in HbA1c of the treatment group although hyperglycemia was not considered a major risk factor for cardiovascular disease. There were more incidences of serious eye complications like vitreous hemorrhage, blindness, and photocoagulation [21].

8. Empa-Reg Outcome Study

In EMPA-REG OUTCOME, empagliflozin reduced 3 point MACE by 14% ($P = 0.04$ for superiority) in more than seven thousand type 2 diabetes patients with established cardiovascular disease for more than three years [21]. Many outcomes were different from LEADER, SUSTAIN-6, PROactive, and IRIS. The primary outcome was a robust 38% decrease in CV mortality ($P = 0.001$). Surprisingly, the reduction in primary outcome was early at 3 months after starting treatment [21]. However, reduction in all three points of MACE did not match similar patterns. Nonfatal MI decreased only slightly with hazard ratio HR (0.87) which was not statistically significant ($P = 0.22$). Alternatively, nonfatal stroke HR (1.24) increased slightly but not significantly ($P = 0.22$).

9. How Did Our Understanding of Cardiovascular Outcome Change over the Years?

Insulin resistance is a core defect in type 2 diabetes mellitus which is associated with multiple metabolic and cardiovascular risk factors. The role the molecular physiology of insulin resistance in pathogenesis of atherosclerosis is relatively well documented [19]. Therefore, interventions which improve insulin sensitivity may reduce CV events in subjects with type 2 diabetes. However, most of the CV outcome trials except IRIS did not determine insulin resistance or its surrogate markers. It is plausible that improvements in CV outcomes in clinical trials using GLP-1 RAs, sodium-glucose cotransporter 2 inhibitors (SGLT2 I) and pioglitazone may have been mediated via increase in insulin sensitivity [25] [26]. Pioglitazone is a powerful insulin sensitizer in skeletal muscle, liver, and adipocytes [25]. GLP-1 RAs may increase insulin sensitivity through weight loss, though its major effect is noted in both type 1 and 2 diabetes enhanced insulin secretion, an "incretin" effect. Treatment with dapagliflozin for as little as 2 weeks modestly increases insulin-mediated glucose disposal secondary to reversal of glucotoxicity [26]. However, improvement in cardiovascular outcomes in type 2 diabetes cannot be entirely attributed to lowering insulin resistance since decline in CV outcomes noted in Extension of diabetes Control Complication Trial (EDIC) in type 1 diabetes was attributed to aggressive glycemic control, "metabolic memory effect" [27]. Moreover, the relationships between the declines in adverse CV outcomes and lowering of HbA1C in these CV trials are almost identical when compared to the data in UKPDS and EDIC [10] [28] [29] [30] [31]. Finally, it is likely that almost all manifestations including complications and metabolic abnormalities noted in both type 2 and 1 diabetes are consequences of multicellular dysfunction secondary to lack of entry of glucose, the most efficient fuel caused by insulin resistance and insulin lack respectively [32]. The hypothesis is further established by improvement in manifestations by facilitating glucose entry into cells by amelioration of insulin resistance and relative decline in insulin secretion in type 2 and insulin administration in type 1 diabetes.

The beneficial effect of empagliflozin on cardiovascular events appears to be unique from that of pioglitazone and GLP-1 RAs as robust reduction in CV mortality is rapid in onset, together with a marked decrease in hospitalization for heart failure. Proposed mechanisms for the impressive reductions in both mortality and onset of heart failure may be reductions in "afterload" following rapid simultaneous lowering of blood pressure as well as "preload" and arterial stiffness by declining intravascular volume; *i.e.* hemodynamic effects and not by slowing the process of atherosclerosis. Alternatively, reduced left ventricle mass index and improved diastolic dysfunction following empagliflozin treatment for 3 months documented in a recent preliminary study may have contributed to improvement in CV outcomes [33]. Increased blood ketone levels, reduced uric acid, and increased angiotensin and angiotensin type 2 receptor activity are also suggested to be responsible for beneficial CV effects in EMPA-REG OUTCOME

[34]. However, the main contributor to the improvement in heart failure is likely to be diuretic activity of glycosuria [31].

10. Are These Benfits Additive?

As the beneficial cardiovascular effects of empagliflozin are hemodynamically mediated and those of GLP-1 RAs and pioglitazone are direct action on the vasculature to reduce atherogenesis, it is plausible that combination therapy with empagliflozin plus pioglitazone and/or a GLP-1 RA may exert an additive, even synergistic, CV benefit. Empagliflozin profoundly reduced CV mortality, whereas pioglitazone and GLP-1 RAs primarily reduced the risk of nonfatal MI and nonfatal stroke, so addition of empagliflozin to pioglitazone or a GLP-1 RA may produce a robust reduction in all three MACE components. However, this hypothesis requires examination.

11. Summary

Insulin resistance is the core defect in metabolic syndrome, prediabetes and type 2 diabetes. It initiates endothelial dysfunction before onset of T2DM. It may be an important risk factor for CVD since almost all insulin resistant states e.g. hypoglycemia, aging, obesity, dyslipidemia and hypertension are contributors to CVD morbidity and mortality. Enhancement of insulin sensitivity may be of equal or even greater influence in preventing or delaying CVDs in comparison to attaining and maintaining desirable glycemic control. However the role of hyperglycemia in onset of cardiovascular complications can not be denied. Finally, occurrence of hypoglycemia as a consequence of treatment and various treatment modalities themselves may contribute to increasing cardiovascular risk as well.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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