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Review Article

Raising the Bar When Assessing Cardiovascular Disease Outcome When Studies with Patients with Type 2 Diabetes Mellitus are Constructed: Revisiting ASCEND

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Abstract

The emergence of Type 2 Diabetes Mellitus (T2DM) as a clinical syndrome deviating from rudimentary models including "glucose-insulin" disparities to a clinical syndrome impinged upon hyperactivation of inflammatory-mediated signaling pathways, maladaptive pathophysiological changes, and pleiotropic sequelae has not only changed the nature of discussions regarding diabetes in academic circles, but also the treatment of T2DM clinically. The new challenges faced in preventing the advancement of T2DM coupled with the management of associated chronic disease states have impelled avenues for innovative treatments for T2DM sequelae while also ensuring glycemic control. For example, Sodium-Glucose Transport 2 inhibitors (SGLT2i) and Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA), in addition to passing mandated Food and Drug Administration (FDA) Cardiovascular Outcome Trials (CVOT), have displayed positive outcomes with respect to cardiorenal considerations in patients with T2DM. Such performances have recently elevated these pleiotropic medications to higher tiers of recommendations by medical societies such as the American Diabetes Association and the American College of Cardiology. Moreover, the tandem of the notion that pleiotropic pharmacotherapeutic options with an expanded understanding of T2DM on the epigenetic, molecular, and cellular domains have galvanized researchers to explore pharmacologic mechanisms in the context of our ever-changing model in T2DM. In this communication, we would like to use lessons from the "Effects of aspirin for primary prevention in persons with diabetes mellitus" (ASCEND) trial to implore aspiring researchers and practitioners to explore, or at least consider external factors of the T2DM patient populous when reporting findings of cardiovascular clinical endpoints for proper context.

Keywords: Ascend; Statin; T2dm; Aspirin; Vascular; Mace; Heart; Cardiovascular

Background

The intimate association between uncontrolled T2DM and macrovascular complications culminating in Major Adverse Cardiovascular Events (MACE) has been well studied. Evidence for this can be appreciated in a longitudinal study of 29,863 patients (5,501 diagnosed with T2DM and 24,632 control patients). In this study, a statistically significant relative risk afflicting T2DM patients was shown, elucidating a 1.10, 1.53, 1.58, and 2.12 fold increase for lifetime disease burden of Coronary Artery Disease (CAD), Myocardial Infarction (MI), stroke, and Heart Failure (HF), respectively [1,2]. A substantial amount of disease burden associated with cardiovascular disease morbidity and mortality occurs by why of deficits in vascular biology, which are compromised across multiple axes in T2DM [3]. These deficits in vascular biology have deleterious ramifications such as the mitigation of oxygen flux (with consequences in tissue metabolism and subsequent maladaptive phenotype acquisition), serving the role as the nidus for atherosclerosis with concomitant complications (coronary artery disease or CAD, stroke, etc.), or hypertension [4-8]. All of the latter are implicated in one form in another in the cardiovascular deficits studied by Straka et al. A visual reference to illustrate the importance of the vasculature as the interface of cardiovascular disease can be found in Figure 1.

If the road between vascular biology deficits and MACE is set by T2DM, then Reactive Oxygen Species (ROS) is the cement that makes such a road traversable. Hyperglycemia from T2DM promotes the formation of ROS via the mitochondria through an array of mechanisms [9]. One method is through the status of insulin resistance, which causes increased serum glucose, leading to the propensity to undergo non-enzymatic condensation reactions between glucose and amine residues of proteins and some other macronutrients, such as lipids and nucleic acids. Such constituents are dubbed Advanced Glycation End Products (AGEs). In one study by Morita et al. it was shown that AGEs activates nuclear factor-κB (NF-κB) in human aortic endothelial cells through the modulation of signaling pathways [10]. NF-κB is a transcription factor which has the propensity to modulate multiple genes. Namely, NF-κB has been demonstrated to be paramount in the proliferation of Smooth Muscle Cells (SMCs) that is crucial in the process of arteriosclerosis within

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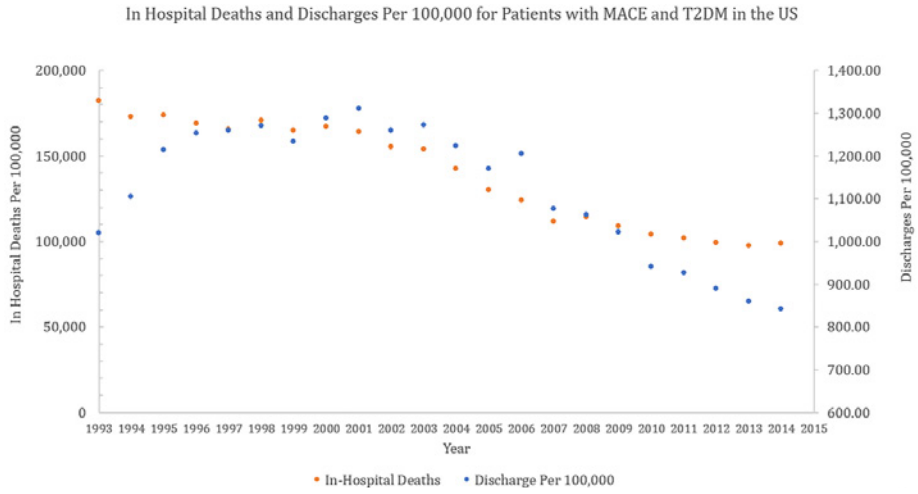

Figure 1: Morbidity of Heart Disease with T2DM in the United States between 1993 and 2015.

the vascular injury process as well as lesion acquisition resulting in increased thrombosis risk, pathways central to MACE incidents [11,12]. For example, NF-κB is regulates Vascular Cell Adhesion Molecule (VCAM)-1, which plays a role among other proteins in the promotion of cytokine and inflammatory adhesion of leukocyte mediated adhesion to vessels, which has the propensity to degranulate cytotoxic elements on damaged vasculature [13]. The damaged intima is especially susceptible to the accumulation of Low-Density Lipoprotein (LDL) in the subendotheolial space, where circulating ROS promotes pathologic plaque formation [14]. There is a tendency for these lesions to promote induction of inflammatory cytokines and chemokines, which has systemic influence as well as local formation of atherogenic structures that may embolize leading to MI, or en route to such process, promote stenotic phenotypes [15]. Moreover, hyperglycemia that has not undergone the glycosylation process has the propensity to induce ROS in mitochondria by increasing expression of ROS ligands, making the ROS accumulated throughout T2DM more viable in their downstream effects [16]. Non-glycosylated hyperglycemia also induces vascular damage through the production of TNF-α, a cytokine employed by the immune system with vast clout in the domain of human cell signaling pathway induction, and within the interest of this review, vascular tone.

In vitro studies have shown that the immunoreceptor motif CD33, which has been shown to downregulating TNF-α production, statistically significantly increases TNF-α when cultured in higher glucose concentrations via motif downregulation, with the theory that hyperglycemia overloads the electron transport chain of the mitochondria, causing the production of radicals that induce oxidative stress, stimulate cytokine production, and promote CD33 downregulation [17,18]. This process is critical as TNF-α promotes arginase activity, an enzyme that has competitive actions against Endothelial Nitric Oxide Synthase (eNOS) [19]. As the name implies, eNOS produces Nitric Oxide (NO), which leads to the W of vascular tone through vasodilation by cGMP mediated smooth muscle cell relaxation. By indirectly decreasing vascular tone homeostasis, hyperglycemia mediated TNF-α reduces endothelial cell NO and promoting endothelial cell dysfunction with a net contractile phenotype [20]. Studies of the vascular endothelium note that their neuronal innervation are dense in mitochondria, implying a reliance on oxidative phosphorylation for metabolic homeostasis [21-24]. Unfortunately, the same oxidative constituents that promote deleterious tissue metabolism in oxidative stress also lead to autonomic dysfunction in these sensitive neuronal innervation networks [25,26]. The ramifications of oxidative stress and damage of endothelium mediated vascular tone is a constriction that decreases the flow rate of oxygen, causing a vicious cycle of hypoxia and endothelial cell dysfunction [4,27,28]. The resultant hypoxia has the propensity to result in cardiomyocytes death, with the concomitant abnormalities in the myocardium hampers the coupling process of electromechanical physiology with consequences in arrhythmias, thrombus and emboli advancement, and the development of processes central to MACE [29-33].

The following dialogue raises an inquiry as to the viability of prophylactic pharmacotherapeutic protection of the vascular architecture in patients with T2DM, given their tendency to be prolific producers of ROS, have higher risks of MACE at baseline, and generally carry comorbidities that are problematic for the maintenance of long-term adequate cardiovascular history [34,35]. Such a solution would have severe ramifications in mitigating hospitalizations and deaths in patients with T2DM for MACE, of which such burden at least in the United States can be visualized in Figure 1. While there is a slight downtrend in the magnitude of the patient flux in admissions according to the National Inpatient Sample, the degree of morbidity remains high [36]. In reference to the proposition raised at the beginning of this paragraph, such a relationship and the viability of such an option has been pursued, and we will appraise the design and lessons learned from such trials. Moreover, these trials have relative distinctions in their constructs and mainstream adoption of their results. Revisiting such distinctions, especially when discussed in tandem with the severity of vascular complications in patients with T2DM as described above, will culminate in recommendations for the communications of proceedings regarding therapeutic approaches for the clinical cardiovascular sequalae of T2DM. We hope such a commentary will not only expand our knowledge of T2DM, vascular biology, and the translational biology of cardiovascular health, but will help push for contextual annotations of prospective works

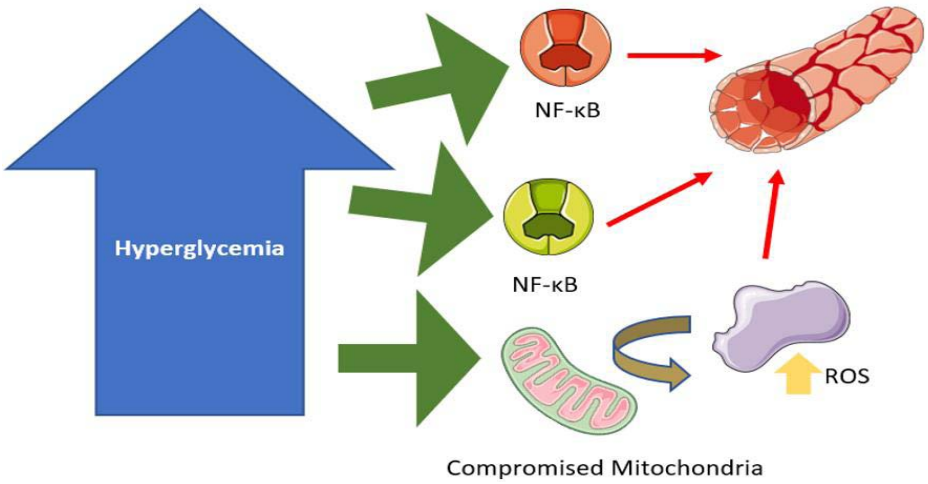

Figure 2: A Review of the Ramifications of Hyperglycemia on Vascular Dynamics Hyperglycemic Patient with Implications for Vascular prophylaxis. Adapted from Servier Medical Art by Servier, which is licensed under a Creative Commons Attribution 3.0 Unported License.

of literature discussing cardiology in patients with T2DM. In this commentary, we will discuss the ramifications of the results of the ASCEND t trial and the consequences it has in reporting results in T2DM and MACE concordance.

ASCEND Trial

The ASCEND (Effects of aspirin for primary prevention in persons with diabetes mellitus) trial was a trial conducted in 2018 that sought to answer the question, "In patients with T2DM without atherosclerotic disease, can low dose aspirin be used as a prophylactic compound to mitigate vascular events relative to placebo?". The interest in this research was spurred considering that T2DM conveys a 2-4 times increase of vascular incidents according to some studies [37] through the array of mechanisms as discussed previously and can be found succinctly in Figure 2.

The ASCEND trial recruited 15,480 patients with T2DM randomized to receive primary prevention prophylaxis with aspirin or placebo, with subsequent assessment of vascular incidents. After a subsequent follow-up of 7.4 years, there was a 1.1% absolute reduction in vascular events in patients randomized to receive aspirin prophylaxis (NNT=91 at 7.4 years). However, one major point to note was over half of the patients recruited (roughly 51%) had a defined "controlled diabetic" status with an HgbA1C of <8% (only 12% had a higher threshold). With this comes a reduction in the sequelae of diabetes as reductions of HgbA1C (or on the converse their increase) have microvascular and macrovascular ramifications as per UKPDS, one a series of trials conducted in the United Kingdom to assess the burden of T2DM on systemic sequelae such as microvascular and macrovascular events [38,39]. Another criticism of ASCEN was that nearly 75% of the patients were on statin therapy, which has been recommended by societies such as the American Diabetes Association (ADA) in mitigating vascular decline, and has molecular evidence backing the pleiotropic effects of statins in not only reducing atherosclerotic disease, but through other signaling pathways, maintaining vascular integrity [40,41]. Some of these are through modulation of the family of rho-associated protein kinases (ROCKs) [42]. Such ramifications include maintenance of endothelial cell integrity through mitigation of harmful reactive oxygen species caused by hyperglycemia and vascular pliability needed to control for an array of blood pressures [43]. Evidence in trials shows that aspirin is associated with an increase risked in bleeding, however, the friability of vessels due to uncontrolled T2DM and its sequelae such as Hypertension (HTN) may mask the use of aspirin as a prophylactic in the early stages of metabolic derangement diagnosis before the latter syndromes become too detrimental to the health of a patient. Due to these findings, USPSFTF guidelines recommend aspirin prophylaxis in a very narrow grow (age 50-50, with estimated 10-year ASCVD risk <10%) [44].

Conclusion

In cardiovascular diabetology and endocrinology, we are entering a new era of therapeutics that target the overlap of sequelae of T2DM and heart disease (for example, sodium-glucose 2 inhibitors and GLP-1 receptor agonists) [45-47]. However, due to the systemic effects of T2DM, and the sequelae it induces such as HTN and atherosclerosis, it is prudent for researchers who are exploring the pleiotropic effects of pharmacotherapeutics to reduce overall cardiovascular morbidity. The ASCEND trial is an example of which the background populous of a patient can lead to underwhelming results of other prophylaxis to reduce vascular effects associated with diabetes. Reconsiderations may be warranted given the ubiquity of aspirin usage in patients with Cardiovascular Disease (CVD) and the overlap of T2DM, of which there is a close association in the western world. These measures can help communicate the underlying effects of whether or not vascular mitigations are at their true proclivity or are merely masked by other ASCVD risk reduction co-therapeutics taken with patients (i.e, statins or glucose-controlling agents).

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