SGLT2-inhibition and Vascular Euphoria: A Reconciliation of Vascular Health and Disease Homeostasis

Mangesh Tiwaskar, Sanjay Kalra, Ganapathi Bantwal, Arpandev Bhattacharya, Manisha Sahay, Uday Jadhav, Ameya Joshi, AK Das, Dinesh Khullar, Manash Baruah, Hitesh Punyani, Uday Jadhav, Ameya Joshi, AK Das, Dinesh Khullar, Manash Baruah, Hitesh Punyani, Kamal Kishor, Kimi Shetty, Jignesh Ved

Abstract

The concept of SGLT2-inhibition, once regarded as a non-physiological approach to glycemia control, now finds a foundational relevance in risk-modification for cardiovascular, kidney, and metabolic outcomes, spanning beyond type-2 diabetes. Major studies have proven meaningful improvements in various clinical outcomes, with different SGLT2-i agents. Apart from glycosuria, SGLT2-inhibition is associated with several patho-physiological effects, which may contribute to the clinical benefits seen with these agents. This narrative review is an attempt to appraise the different patho-physiological effects mediated by SGLT2-inhibition, based on contemporary evidence. The review classifies these effects in the acronym EUPHORIA, and grades the possible relevance of each effect, in improving clinical outcomes.

Interplay of Risk Factors, Vascular Disease, and SGLT2-Inhibition

Our present-day understanding of cardiovascular (CV) risk represents the knowledge accrued over years of observations, research, as well as serendipity. In 1991, a committee led by Prof Victor Dzau and Prof Eugene Braunwald, conceptualized the continuum of CV risk. They described the progressive nature of CV risk, starting from presence of risk factors, to sub-clinical manifestations of CV disease, target-organ damage, events, complications, and mortality. Since then, several discoveries of complex pathological underpinnings have enhanced our understanding of CV risk, as well as yielded opportunities for risk-modification. Historically, serendipitous findings have scripted several landmark chapters in cardiovascular medicine. The discovery of role of LDL receptors in coronary artery disease, or nitric oxide in endothelial dysfunction, or application of balloon in angioplasty procedures, represent some of these key examples. Inhibition of sodium-glucose cotransporter-2 (SGLT2), and resultant improvement in CV outcomes, is a recent addition to this notable list.

The EMPA-REG OUTCOME study represents a key milestone for macrovascular and mortality risk-reduction, in patients with type-2 diabetes mellitus (T2DM) and CV disease. Since then, several major studies with SGLT2-inhibitors, have demonstrated various aspects of CV and kidney risk-reduction. The relevance of cardio-renal risk modification, with SGLT2-inhibitors, now spans beyond T2DM. This development suggests that SGLT2-inhibition mediates cardio-renal risk-modification, independently of glycemia control. Several plausible mechanisms attempt to explain the proven cardio-renal risk-modification with SGLT2-inhibitors. Our understanding of these plausible mechanisms has gradually progressed, but remains inconclusive, at present. The certain aspect is that of clinically meaningful vascular risk-modification, mediated by SGLT2-inhibitors in patients with CV diseases. All the plausible secondary effects of SGLT2-inhibition culminate in beneficial vascular risk-modification. We call this phenomenon as vascular euphoria, to represent a state of positive vascular-homeostasis, prompted by SGLT2-inhibition in patients with CV diseases. The scope of this narrative review includes the available evidence of SGLT2-inhibition, and resultant vascular effects and outcomes.

Mechanisms and Effects of SGLT2-Inhibition in Vascular Disease

Existing evidence recognizes several biological mechanisms, and vascular effects, in association with SGLT2-inhibitors. These mechanisms derive credence from varying extent of supportive information, based on non-clinical or clinical data evolving over time. In line with the theme of vascular euphoria, we summarize the vascular effects of SGLT2-inhibition as an acronym, EUPHORIA (Table 1).

This review describes a brief summary of the wealth of evolving knowledge on this topic. Based on the evidence available for various mechanisms and effects, we have also evaluated the quality of evidence, using GRADE criteria, as described
well as sirtrulin-1 (SIRT1). The regulator, adenosine monophosphate at the cellular level, this effect may reduction with these agents (GRADE Cardiovascular and kidney risk-which may possibly contribute to improvement in vascular function, and resultant cardiovascular and kidney outcomes with SGLT2-inhibition. Overall, SGLT2-inhibition may result in improved uric acid levels, which can possibly contribute to cardiovascular and kidney risk-reduction with these agents (GRADE Rating: Low).

**Utilization of Energy-substrates**

The possible effect of SGLT2-inhibition on cellular energetics and metabolism has been a topic of clinical interest. The primary mechanism of glycosuria results in calorie-restriction mimicry, which can have several corollary implications at various levels. A substrate switch, resulting in increased utilization of adipose tissue for meeting energy requirements, with resultant weight-loss and improved insulin sensitivity, has been well recognized. At the cellular level, this effect may result in stimulation of the key energy-regulator, adenosine monophosphate activated protein kinase (AMPK), as well as sirtulin-1 (SIRT1). The stimulation of AMPK / SIRT1 pathway is implicated in not only improved cellular energetics, but also improved autophagy and mitophagy, resulting in possible cardiovascular benefits.

Further, at the level of heart, in Table 2.

**Endothelial Function Improvement**

Non-clinical evidence suggests that SGLT2-inhibition results in recovery of reactivity of blood vessels, and endothelial cells, in T2DM. Human studies evaluating SGLT2-inhibition and endothelial function have demonstrated mixed results. Reduction in serum uric acid level has been a consistent finding with SGLT2-inhibition. Metabolism of uric acid results in inflammation and oxidative stress, which contribute to endothelial dysfunction. Reduction in serum uric acid levels may mediate improvement in vascular function, and resultant cardiovascular and kidney outcomes with SGLT2-inhibition. Overall, SGLT2-inhibition may result in improved uric acid metabolism and vascular endothelial function, which may possibly contribute to cardiovascular and kidney risk-reduction with these agents (GRADE Rating: Low).

**Table 1: Vascular Mechanisms and Effects of SGLT2-inhibition**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>E- Endothelial function improvement</td>
<td></td>
</tr>
<tr>
<td>U- Utilization of energy-substrates</td>
<td></td>
</tr>
<tr>
<td>P- Pressure and Volume off-loading</td>
<td></td>
</tr>
<tr>
<td>H- Hemoconcentration</td>
<td></td>
</tr>
<tr>
<td>O- Oxidative stress reduction</td>
<td></td>
</tr>
<tr>
<td>R- Reverse LV remodeling</td>
<td></td>
</tr>
<tr>
<td>I- Inflammation control</td>
<td></td>
</tr>
<tr>
<td>A- Autonomic balance</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: GRADE Certainty Ratings**

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>The true effect is probably markedly different from the estimated effect</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect might be markedly different from the estimated effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>The authors believe that the true effect is probably close to the estimated effect</td>
</tr>
<tr>
<td>High</td>
<td>The authors have a lot of confidence that the true effect is similar to the estimated effect</td>
</tr>
</tbody>
</table>

Further, in patients with diabetic cardiomyopathy, the heart is known to be over-dependent on fatty-acid metabolism. SGLT2-inhibition has demonstrated increased cardiac utilization of glucose, in patients with T2DM. A study in patients with T2DM and CV disease, did suggest SGLT2-i mediated modification of the metabolic signature. This effect included stimulation of Kreb's cycle, with utilization of fatty acids, branched-chain amino acids, lysine, and ketone-bodies, as substrates. However, studies like DAPACARD and EMPA-PET, which involved patients with T2DM without significant CV disease, failed to demonstrate meaningful improvements in cardiac energetics with SGLT2-inhibition. These observations contrast with the risk-reduction for heart failure and kidney outcomes, observed with SGLT2-inhibition consistently across the CV disease status, in patients with T2DM.

The relevance of cardiac-energetics with SGLT2-inhibition, in improving the cardio-renal outcomes in patients with T2DM, remains a moot question. Further, plausible differences in significance of this mechanism, in patient-groups based on their status of T2DM or CV disease, need further understanding (GRADE Rating: Low).

**Pressure and Volume Off-loading**

SGLT2-inhibition has been consistently associated with meaningful reductions in fluid volume, as well as blood pressure. Through modest natriuresis as well as osmotic diuresis, these agents reduce the volume overload. Mathematical modelling, supported by some non-clinical evidence, suggests that SGLT2-inhibition may exert more prominent interstitial fluid-volume reduction, than blood-volume. Further, the RECEDE CHF study performed in patients with T2DM and chronic HF, demonstrated that concomitant use of empagliflozin and loop-diuretic, resulted in increased electrolyte-free water clearance. The possible implications of electrolyte-free water clearance, on clinical effects like reduction in interstitial edema and improved oxygenation, are worthy of further exploration. Volume-reduction with SGLT2-inhibitors, in patients with heart failure, is associated with modest improvements in NT-proBNP levels. This suggests that the pronounced clinical benefits of SGLT2-inhibition, in heart failure, are not associated with significant natriuretic mechanism.

Through various interlinked hemodynamic, autonomic, hormonal, and inflammatory pathways, these agents may also have certain benefits on various aspects of hypertension, like nocturnal non-dipping, morning hypertension, or resistant hypertension. Smaller studies as well as observational evidence have demonstrated important leads on these aspects, which are worthy of further exploration. At the level of kidney, reduction in intra-glomerular pressure has been a key mechanism supporting kidney benefits. Natriuresis and resultant correction of tubuloglomerular feedback signal, results in vaso-modulation at glomerular arterioles, reduces glomerular hypertension, and protects the nephrons in long-term. This manifests as an initial dip, and subsequent stabilization of renal function decline, resulting in delayed onset or progression of kidney disease. This clinical benefit is evident in patients with chronic kidney disease, regardless of T2DM.

Reduction in preload, as well as in afterload, have definitive advantages on the risk of heart failure in predisposed patients. Prevention of heart failure hospitalization has been consistently evident with SGLT2-inhibition, in patients with T2DM. Evidence also supports the increasing relevance of SGLT2-inhibition, in the treatment of heart failure, regardless of T2DM. The rapidity of onset of heart-
failure benefits with these agents, also underlines the importance of volume-offloading with SGLT2-inhibition. The possible extension of these benefits, in patients without existing heart failure and T2DM, is an aspect of developmental interest with SGLT2-inhibitors. This may be particularly relevant in predisposing conditions like post myocardial infarction, asciates secondary to liver cirrhosis, idiopathic edema, or syndrome of inappropriate antidiuretic hormone secretion (SIADH). We believe that haemodynamic effects represent important intermediate mechanisms with SGLT2-inhibition, resulting in improved cardio-renal outcomes (GRADE Rating: High).

**Hemoconcentration**

SGLT2-inhibition is associated with a pro-erythropoietic milieu in the kidney.43,44 Plausible vasculo-protective effects, mediated by reduced blood glucose and inflammation in renal blood vessels, reduce the endothelial-to-mesenchymal transition.45 Further, reduced activity of sodium-potassium ATPase pump, in the renal proximal convoluted tubules, indirectly reduces the epithelial-to-mesenchymal transition in renal parenchyma.46 These effects plausibly protect the erythropoietic progenitor cells in the renal parenchyma, in patients with T2DM. An increased oxygen requirement in kidney medulla, secondary to increased downstream sodium reabsorption, is postulated to stimulate erythropoiesis. The net effect of SGLT2-inhibition, in patients with T2DM, is a modest increase in haematocrit.

The EMPA-HEART study has proven that early increase in erythropoietin secretion is the key mechanism responsible for increased erythropoiesis, with SGLT2-inhibition, in patients with T2DM.45 CREDENCE, EMPEROR-REDUCED, and DAPA CKD studies have demonstrated meaningful improvements in anemia, following SGLT2-inhibition in the respective study participants.46,47,15

Modest hemoconcentration may benefit the failing myocardium, by increasing oxygen supply. This effect, when combined with reduced myocardial oxygen demand secondary to improved energy homeostasis, as well as improved myocardial perfusion secondary to possible reverse remodeling, may generate a favourable metabolic milieu in myocardium. The secondary analysis of EMPA-REG OUTCOME study has demonstrated significant 21% lower risk of total myocardial infarction events (p<0.05), with empagliflozin in patients with T2DM and atherosclerotic CV disease.48 This effect included a consistent reduction in risk of type-1 (atherosclerotic plaque related), as well as type-2 (oxygen demand-supply imbalance related) myocardial infarction (MI) events.49 The secondary analysis of DECLARE TIMI,50 suggested a similar effect with dapagliflozin in patients with T2DM and prior MI, but not in those patients with atherosclerotic CV disease without prior MI.50 This evidence suggests meaningful benefit of SGLT2-inhibition, on reducing the risk of MI, plausibly through a simultaneous interplay of various favourable mechanisms. Further, anaemia is closely related to adverse outcomes in heart-failure.51 Improved erythropoiesis may thus have meaningful relevance in improving heart-failure outcomes, regardless of T2DM.

We believe that hemoconcentration resulting from increased erythropoiesis, may partly contribute to the clinical cardiac benefits observed with SGLT2-i agents (GRADE Rating: High).

**Oxidative Stress Reduction**

A recent review summarizes the pathophysiological evidence of SGLT2-inhibition, and amelioration of oxidative stress.52 Evidence suggests pleiotropic effects of SGLT2-inhibitors, on reducing oxidative stress in patients with T2DM. Stimulation of biological anti-oxidative mechanisms through reduced generation and increased scavenging of free radicals, facilitate reduced oxidative damage to the blood vessels. Reduction of glycemia itself plays an important role in alleviating glucose-mediated oxidative stress. Reduction in uricemia, and resultant lower endothelial uric acid metabolism, may also plausibly reduce oxidative stress. Further, calorie-restriction mimicry secondary to SGLT2-inhibition may influence autophagy of damaged organelles and improve cellular biological processes in blood vessels. The net effect is a reduction in vascular damage, and improvement in vascular stiffness. Several mechanistic studies have demonstrated improvements in pulse-wave velocity, with the use of SGLT2-inhibitors, in patients with T2DM.53-55 Reduced vascular resistance may have relevant implications in patients with T2DM and comorbid hypertension, or atherosclerotic CV disease.

We believe that mitigation of oxidative stress, may partly explain the vascular effects of SGLT2-i agents, with modest influence on long-term CV risk reduction (GRADE Rating: Moderate).

**Reverse LV Remodeling**

The EMPA-HEART, EMPA-TROPISM, DAPA LVH, REFORM, and SUGAR DM HF studies are randomized controlled trials, which characterize the cardiac effects with various SGLT2-i agents, using cardiac magnetic resonance (CMR).56-60

SGLT2-inhibition has demonstrated regression of left-ventricular mass-index, in EMPA-HEART, EMPA-TROPISM, and DAPA-LVH studies, but not in REFORM study with dapagliflozin. In EMPA-HEART as well as EMPA-TROPISM studies, empagliflozin use also demonstrated reduction in myocardial extracellular volume, indicative of reduced matrix expansion and myocardial fibrosis. These studies suggest possible reversal of pathological myocardial remodeling with empagliflozin, in patients with T2DM and coronary artery disease, as well as in patients with HFrEF without T2DM, respectively. The EMPA-TROPISM and SUGAR-DM HF studies also demonstrated significant improvements in left ventricular volumes. Further, the EMBRACE HF and EMPIRE HF studies also demonstrated significant improvements in pulmonary circulation, with the use of empagliflozin in patients with heart failure.55,62 Assessing long-term effects of SGLT2-inhibition, on cardiac structure and function, is an aspect of further academic interest. The collective evidence suggests improvement in cardiac structure and function, in patients with cardiac diseases regardless of T2DM, with the use of these agents (GRADE Rating: Moderate).

**Inflammation Control**

Several effects mediated by SGLT2-inhibition, result in a state of reduced systemic or tissue inflammation. Reduction in adiposity secondary...
to substrate switch, results in lowered activity of inflammatory adipokines. Improved M2 macrophage polarization, and balance favouring circulating vascular progenitor cells, may improve vascular health in patients with T2DM and CVD. 63 A recent study demonstrated that the effect of empagliflozin on glycemia, uricemia, insulinemia and ketosis, lead to reduced NLRP3-inflammasome activation. 64 This mechanism may have beneficial effect on atherosclerotic CV disease, as well as heart failure, which needs to be characterized further. We believe that inflammation-alleviating effect of SGLT2-inhibition, may partly contribute to the cardiovascular effects seen with these agents (GRADE Rating: Low).

Autonomic Balance

Evidence supports the plausible effect of SGLT2-inhibition, on improving autonomic balance, in patients with T2DM. Volume-depletion and hypotension mediated by these agents, does not result in increased sympathetic activity, and heart rate. Reduced renal cortical oxygen demand, and consequently reduced renal afferent sympathetic activation, are plausible mechanisms of SGLT2-inhibitor related autonomic improvements, supported by limited evidence. 65 Clinical studies have demonstrated alleviation in muscle sympathetic nerve activity, and skin sympathetic nerve activity, following SGLT2-inhibition. 66,67 A restoration of sympathetic-parasympathetic autonomic balance has also been evident. The EMODY study further suggests possible improvement in heart-rate variability, following empagliflozin use in post-myocardial infarction patients with T2DM. 68 This effect may have implications in several clinical conditions, including hypertension, myocardial infarction salvage, arrhythmias, and sudden cardiac death. 69,70 Evidence also suggests possible reduction in the risk of atrial fibrillation, in patients with T2DM and CVD, following SGLT2-inhibition. 71 The EMPA-REG OUTCOME study also demonstrated beneficial effect of empagliflozin, on reduction in sudden cardiac death, in patients with T2DM and CVD. 72 We believe that improvement in autonomic balance may have some possible influence on these clinical outcomes with SGLT2-inhibitors, which prompts further academic exploration.

(GRADE Rating: Moderate).

Way Forward

SGLT2-inhibitors have scripted an optimistic story for vascular disease outcomes, which is gradually spanning beyond T2DM. This SGLT2-1 associated vascular euphoria is still in the evolving phase, with several aspects remaining yet unexplored, uncertain, or elusive. Trials like EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI-58, VERTIS CV, CREDENCE, DAPA-HF, EMPEROR-REDUCED, DAPA-CKD, SCORED, and SOLOIST WHF represent major milestones in the vascular euphoria with SGLT2-inhibition. 6,14

The major clinical expectations, in future, include possible benefits in heart failure and preserved ejection fraction, non-albuniminic chronic kidney disease, post myocardial-infarction related heart failure beyond T2DM. Further emerging evidence in systemic vascular diseases like COVID-19 related multi-organ damage, volume-retention states like refractory ascites, SIADH, or idiopathic edema, may witness increasing optimism influenced by SGLT2-inhibition. The importance of optimizing the clinical translation of SGLT2-1 associated vascular euphoria, for maximizing benefits to the eligible patients along with minimizing risks, also remains a journey in yet evolutionary stage.

Acknowledgements

All authors provided comments and input. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

References
