SGLT-2 Inhibitors and Peripheral Artery Disease: A Statistical Hoax or Reality?

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Abstract: Inhibitors of sodium-glucose cotransporters type-2 are the most recent addition to the armamentarium of oral antidiabetic agents. This class of drugs has shown promising results in glycemic control and most importantly to reduce cardiovascular disease (CVD) mortality risk. Despite the encouraging data, there is concern regarding their potential for causing or worsening peripheral artery disease (PAD), which may increase the risk of lower extremity amputations. Following the publication of results of CANVAS and CANVAS-R trials, which revealed that leg and mid-foot amputations occurred about twice as often in patients treated with canagliflozin compared to placebo, the Food and Drug Administration (FDA) in the United States issued a black box warning of leg and foot amputations associated with canagliflozin use. In this article, our main aim is to review the available evidence in preclinical and clinical studies regarding SGLT-2 inhibitors and PAD events, the possible mechanisms related to increased risk of amputation, to evaluate whether it is a class effect or individual drug effect, and most importantly, implications for their continued use as antidiabetic agents. It

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also raises the issue of including PAD events among the end-points when assessing future antihyperglycemic agents. Thus, we also tried to analyze whether outcomes of SGLT2 inhibitors trials mostly focused on stroke, myocardial infarction, heart failure, and peripheral vascular disease-related outcomes remained underrated. (Curr Probl Cardiol 2019;44:207−222.)

Introduction

Type 2 diabetes mellitus (DM; T2DM) is a malady which is the characterized by insulin resistance, impaired glycemic control and plethora of metabolic pathways. It is associated with increased risk of atherosclerosis and increased cardiovascular (CV) disease (CVD) complications.[1] Peripheral artery disease (PAD) is one of the most frequent CVD complications in patients with DM since 20% of all symptomatic PAD patients are diabetic.[2] The presence of PAD indicates increased risk of significant atherosclerosis in other vascular beds, including coronary and cerebrovascular disease, and is an independent predictor of CVD death.[3] Patients with PAD develop nonhealing foot ulcers, gangrene, and need for amputations. The likelihood of nontraumatic lower extremity amputations (LEAs) is 15 times higher in DM patients. In the United States (US), 80,000 LEAs are performed each year in DM patients and mortality after one, and 5-year post-LEAs are 10%-50% and 30%-80%, respectively.[4]

Although insulin still holds a prominent place in T2DM management, its long-term CV safety is uncertain.[5] After the rosiglitazone saga, the US Food and Drug Administration (FDA) made postmarketing surveillance of CV safety mandatory for any new DM medication.[6] Inhibitors of sodium-glucose cotransporters type-2 are a promising new class of medications. The results with these agents are encouraging for diabetes management, especially in those with heart failure (HF).[7] Despite the benefit of these drugs among patients with DM and CVD, a few notable adverse events of SGLT-2 inhibitors are euglycemic diabetic ketoacidosis, increased fracture risk, urinary tract infections, male and female genital mycotic infections, acute kidney injury and added most recent to that list, nontraumatic LEAs. In May 2017, the US FDA issued a black box warning of LEAs associated with canagliflozin use, and this has stimulated new criticism and concern.[8] In this manuscript, our main aim is to review the available evidence, the possible mechanisms leading to amputation, to evaluate whether it is a class or individual drug effect, and its implications on the end-point determination in future diabetes medications and CVD outcome trials.

SGLT-2 Inhibitors: Molecular Mechanism of Action

The SGLT-2 inhibitors, currently approved in the US are canagliflozin, dapagliflozin, and empagliflozin. More recently ertugliflozin has been approved by the FDA for use in T2DM.[9,10] Luseogliflozin[11] and ipragliflozin[12] have been approved in Japan for their favorable results in the Japanese population.

SGLT, a member of the family of sodium glucose cotransporter SLC5, has two isoforms. SGLT-1 is expressed in the small intestine, the S3 segment of the proximal tubule of the kidney, and myocardium. On the other hand, SGLT-2 is expressed in the epithelial cells in S1 and S2 segments of proximal renal tubules.[13] The plasma glucose concentration directly influences the expression and activity of SGLT-2 as evidenced by elevated SGLT-2 mRNA levels found in renal proximal tubular cells of DM patients.[13] SGLT-1 is a low capacity but high-affinity transporter system, paired with high-affinity GLUT1. On the contrary, SGLT-2 is a high capacity, but low-affinity system, coupled with low-affinity GLUT2. Nearly 90% of filtered glucose is reabsorbed through SGLT-2.[14]. Thus, SGLT-2 inhibitors block reabsorption of glucose, increase urinary glucose excretion, and subsequent plasma glucose-lowering effect independent of plasma insulin concentration. An increase in urinary glucose excretion causes negative energy balance by reducing body weight in DM patient.

Pathogenesis of PAD in DM

Clearly, DM is one of the strongest associated risk factor for PAD along with tobacco abuse.[15] Therefore, it will be prudent to discuss pathogenic mechanisms contributing to PAD in DM as well as to explain how SGLT-2 inhibitors may increase the risk of PAD.

Typically, DM is an inflammatory atherothrombotic state associated with a high prevalence of CVD.[16] In patients with DM, the presence of low-grade inflammation is suggested by increased plasma levels of C-reactive protein (CRP), also a marker for increased cardiovascular and PAD risk.[17] CRP promotes endothelial cell apoptosis, dysfunction, and thus increases a chronic inflammatory atherothrombotic vasculopathic state by colocalizing with oxidized low-density lipoprotein cholesterol (LDL-C) in atherosclerotic plaques.[16]

Hyperglycemia inhibits the function of endothelial nitric oxide synthase (eNOS) and promotes the production of reactive oxygen species (ROS).[18] Free fatty acids, which are produced abundantly in insulin-resistant state, activates of protein kinase C (PKC), inhibits phosphatidylinositol (PI)-3 kinase, and produces ROS, which eventually impairs vasodilator

homeostasis.[19] Vascular smooth muscle cells are also affected and express their proatherogenic activity in a similar manner. Platelet uptake of glucose and subsequent oxidative stress is also increased resulting in more expression of glycoprotein Ib and IIb/IIIa receptors, leading to enhanced platelet aggregation and hypercoagulability.[20]

Attenuation of Vascular Risk Factors by SGLT-2 inhibitors: Beyond Antihyperglycemic Effects

Beyond glucose lowering, SGLT-2 inhibitors also modify other nonglycemic CVD risk factors as well as evidenced by multiple preclinical and clinical studies.[7]

Nonglycemic benefits of SGLT-2 inhibitors contributing to improved CVD outcomes are lowering of SBP, improved lipid profile, lowering uric acid level, lower risk of hypoglycemia, reducing epicardial fat, ventricular, and cardiac fibrosis (vide Table 1).

Preclinical Data

It has been demonstrated that phlorizin (a nonspecific SGLT inhibitor) and canagliflozin (an SGLT-2-specific inhibitor) cause relaxation of pulmonary arteries in a dose-dependent manner, with little or no effect on coronary arteries of mice. On the other hand, canagliflozin enhanced sodium nitroprusside-dependent vasodilatation in coronary arteries in DM mice. It has been postulated that SGLT inhibitors may differentially regulate vascular relaxation depending on the location of vascular bed, duration of treatment, and other health conditions, such as DM.[21] This study raises the possibility that canagliflozin may differentially regulate vascular relaxation in coronary arteries vs the peripheral circulation.

Terasaki et al. showed SGLT-2 inhibitors exerted their antiatherogenic actions in DM mice by pure glucose lowering independent of insulin action. Macrophage scavenger receptors CD36 and Lox-1 scavenge oxidized-LDL

TABLE 1. Nonglycemic benefits of SGLT-2 inhibitors

1. Reduction of BP
2. Improved lipid profile
3. Reduced serum uric acid
4. Reduced visceral and subcutaneous adiposity
5. Weight loss
6. Reduced clinically measurable inflammatory markers, like CRP
7. Reduced CV events and mortality

leading to foam cell formation and atherosclerosis. Treatment with SGLT-2 inhibitors attenuated the upregulated gene expression of CD36 and Lox-1.[22]

Empagliflozin was shown to improve pericoronary vascular fibrosis, oxidative stress, and partially reverse the impairment of vascular relaxation among diabetic mice.[23] With long-term use in Zucker DM fatty (ZDF) rats, empagliflozin enhanced endothelial function, and attenuated oxidative stress in the aorta.[24]

An in vitro study with dapagliflozin showed attenuation of tumor necrosis factor-α and hyperglycemia-induced increase in intercellular adhesion molecule-1, vascular cell adhesion molecule-1, plasminogen activator inhibitor type 1 and NFκB expression. Administration of dapagliflozin improved endothelial function, caused vasorelaxation and significantly reduced vascular adhesion molecule expression, phospho-IκB expression and macrophage infiltration in the vessel wall.[25] In another study[26] dapagliflozin treatment reversed the formation of atherosclerosis, inhibited macrophage infiltration, and increased plaque among diabetic ApoE mutated mice.

All of these preclinical data prompt us to believe that SGLT-2 inhibitors halt the progression of atherosclerosis and inflammation in vascular beds, which are the most important risk factors for macrovascular complications of DM. However, dedicated in vitro and animal studies involving models representing peripheral vascular systems are needed to evaluate whether these molecular interactions hold in the pathogenesis of PAD. In fact, a recent study involving a murine surrogate model of severe limb ischemia showed canagliflozin-treated mice demonstrated enhanced vascular perfusion recovery and increased capillary regeneration.[27]

Table 2 depicts the possible pathophysiological pathways through which SGLT-2 inhibitors possibly halt the progression of PAD

Clinical Data

Empagliflozin has been found to reduce arterial stiffness in patients with T1DM.[28] Emerging evidence suggests that SGLT-2 inhibitors help

TABLE 2. Probable mechanisms by which SGLT-2 inhibitors decrease risk of PAD

1. Vasodilatation by relaxing vascular smooth muscles
2. Decreased atherogenic lipid molecules
3. Reduction of oxidative stress
4. Attenuation of regulated gene expression of CD36 and Lox-1, key molecules in foam cell formation
5. Reduced expression of vascular and intercellular adhesion molecules
6. Reduced expression of prothrombotic molecules, like- PAI-1, NF- κB, TNF- α

lower blood pressure (BP),[29] an important risk factor for PAD. This effect is due to the combination of diuretic action, weight loss, remodeling of the nephron, and arterial stiffness reduction.[30] It has been shown that SGLT-2 inhibitors also lead to improvements in plasma lipids.[31,32] Dapagliflozin induces a 4.8% reduction of LDL-C level and 6.9% elevation of high-density lipoprotein cholesterol (HDL-C). It also leads to a reduction in CRP levels,[33] an important cytokine involved in atherosclerosis. Canagliflozin also reduces serum uric acid levels, which may be associated with improved endothelium function, decreased inflammation and atherosclerosis.[34] In fact, applying the Archimedes model, dapagliflozin has been shown to reduce foot amputations by 13% when compared with standard of care.[35] Dapagliflozin is also associated with body weight reduction (by both fluid and nonfluid mediated mechanisms), visceral adiposity, and subcutaneous fat mass,[36] which ultimately reduce atherogenic burden.[37]

Critical Analysis of CVD Data With a Focus on PAD From Recent CVD Outcomes Trials of SGLT-2 Inhibitors

EMPA-REG OUTCOME

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial[38] was a multicenter, randomized, double-blind placebo-controlled to study the effect of empagliflozin on 7028 patients at high risk of CVD, of whom 21% had PAD, over about 3.1 years of follow-up. The study assessed the effect of empagliflozin (10 mg or 25 mg once daily) added to standard of care compared with placebo added to standard of care treatment. The EMPA-REG OUTCOME trial revealed that empagliflozin was significantly beneficial in improving CVD outcomes, in all subgroups, including in individuals with PAD. Empagliflozin significantly decreased the risk of CVD death, nonfatal myocardial infarction (MI) or nonfatal stroke by 14% vs placebo. The risk of CVD death was reduced by 38%, with no significant difference in the risk of nonfatal MI or nonfatal stroke. Hospitalization for HF was reduced by 44%, while nephropathy was decreased by 46%. The difference in outcome between empagliflozin and placebo occurred early, and reduction in the primary outcome was evident by the third month. Interestingly, empagliflozin did not reduce the incidence of nonfatal stroke and nonfatal MI or unstable angina. Critics have suggested that it is less likely that the decrease in major CVD events (MACE) in the EMPA-REG OUTCOME trial resulted from attenuating the

atherosclerotic process by empagliflozin.[39] Importantly, no amputations were reported. However, none of the primary or secondary outcomes (composite of CVD death, MI, stroke, HF, unstable angina) included PAD. EMPA-REG OUTCOME was not a primary prevention trial, but a secondary one. Therefore, it is unknown whether low-risk patients would experience similar benefits.

CANVAS and CANVAS-R

The combined Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R) trial[40] results have studied 10,142 patients with T2DM on canagliflozin 100 mg or 300 mg daily or placebo. It revealed that canagliflozin reduced the primary composite outcome of CVD death, nonfatal MI, and nonfatal stroke by 14% and reduced the rate of renal function decline by 40% among high-risk T2DM patients. Neither of the individual endpoints of all-cause or CVD death was significantly reduced in CANVAS as they were in EMPA-REG. The event curve for the composite endpoint of CVD death, nonfatal MI, and nonfatal stroke could nearly be superimposed between canagliflozin vs placebo among the primary-prevention group of patients. CANVAS differed from EMPA-REG with respect to the fact that the former included approximately one-third of patients with DM but no history of CVD, and this could be the potential reason for the lack of significance in the prevention of death in CANVAS trial. The data, however, suggest a similar pattern of outcomes in both higher- and lower-risk subgroups. There is concern that while canagliflozin's 14% reduction in the primary outcome fulfills the FDA's margin for noninferiority ($P < 0.001$), the P-value of 0.02 for superiority was not strong enough to meet the FDA's statutory criterion for substantial evidence. One of the important and intriguing findings was an increased amputation risk noted among canagliflozin-treated patients (6.3 cases per 1000 patient-years; hazard ratio, 1.97). The amputation issue and PAD outcomes will be discussed in greater detail in subsequent sections.

CVD-REAL

The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 inhibitors (CVD-REAL) study,[41] an observational study compared the risk of hospitalization for HF (the primary endpoint), death, and combined death and HF (the secondary endpoints) in patients with T2DM who were newly initiated with SGLT-2 inhibitors vs some other

glucose-lowering drug across six countries of US and Europe. In the US, most patients (76%), given an SGLT-2 inhibitor received canagliflozin, while in Europe, dapagliflozin was the main agent utilized (92%). While comparing with new users of other glucose-lowering drugs, new users of SGLT-2 inhibitors had a 39% lower rate of hospitalization for HF (HR 0.61, 95% CI 0.51-0.73; $P<0.001$) and 51% lower rate of death from any cause during follow-up (HR 0.49, 95% CI 0.41−0.57; $P<0.001$). The results did not reveal significant geographic heterogeneity. The beneficial effect was also extended to those without CVD at baseline. In those with CVD, there was a 53% reduced risk of all-cause mortality at 8 months compared with patients who were on other glucose-lowering drugs. Similarly, those without baseline CVD who were initiated on SGLT-2 inhibitors had a 46% lower risk of mortality. The findings possibly indicate the potential benefit of this drug class in the primary prevention of CVD among T2DM patients. However, this study has been criticized for being plagued by time-related biases.[42]

DECLARE TIMI 58

Dapagliflozin on the Incidence of Cardiovascular Events-Thrombolysis in Myocardial Infarction-58 (DECLARE-TIMI 58) study will analyze 17,160 patients with T2DM randomized to treatment with dapagliflozin (10 mg/d) or matching placebo. It is expected to conclude by 2019 and to provide important insights into the added effect of dapagliflozin to the standard of care on CVD outcomes among T2DM patients with established CVD or with multiple risk factors.[43]

Amputation Risk With SGLT-2 Inhibitors

Despite the CV and renal effects of canagliflozin, the amputation issue raises concerns. Results from the CANVAS and CANVAS-R showed that rate of occurrence of LEAs was about twice in patients treated with canagliflozin than in the patients treated with placebo.[40] The CANVAS trial revealed that the amputation risk was 5.9 out of every 1000 patients treated with canagliflozin (compared to 2.8 out of every 1000 patients treated with placebo) in 1 year. On the other hand, the CANVAS-R trial demonstrated that the risk of amputation was 7.5 out of every 1000 patients treated with canagliflozin (compared to 4.2 out of every 1000 patients treated with placebo). Toe and mid-foot were the most commonly affected.[44] Based on these results, the European Medicines

Agency (EMA) also issued a warning notice about the risk of amputation with all SGLT-2 inhibitors, specifically canagliflozin.[45]

Having a history of amputation and DM foot disease were strong and independent risk factors for amputation in the CANVAS study.[40] The highest absolute risk for amputation happened among the patients with a history of PAD or amputation, but the relative amputation risk for canagliflozin vs placebo was similar across subgroups.

In a subanalysis of the EMPA-REG OUTCOME study[46] among patients with PAD, lower-limb amputation occurred in 5.5% of patients enrolled in empagliflozin vs 6.3% assigned to placebo (HR = 0.84; 95% CI, 0.54-1.32). Among patients without PAD, lower-limb amputation occurred in 0.9% vs 0.7%, respectively (HR = 1.3; 95% CI, 0.69-2.46). There is currently no head to head comparative trial of empagliflozin and canagliflozin to assess their relative effects on CVD and LEAs.

Interestingly, the increased amputation risk was not noted in any other canagliflozin trial or other SGLT-2 inhibitors. Potential explanations for the difference may lie in the baseline characteristics of the CANVAS population or the method of drug administration. The potential reasons cited for the differences in LEAs in the CANVAS program may be inherent molecular variation despite being from the same class; differences in amputation event ascertainment; varying populations; and chance.[47] Moreover, the clinical benefit regarding MACE occurred during earlier phases of the study than did the LEAs, which occurred predominantly in the late phase of the study. This finding suggests the presence of other factors which may have led to the increased incidence of LEAs. Adverse events resulting from volume depletion occurred more frequently in the canagliflozin-treated group than in the placebo group. According to Tanaka et al., this might cause or contribute to the circulatory failure in the distal peripheral arterial beds.[47] This hypothesis may be supported by the fact that treatment with thiazide diuretics compared to treatment with other antihypertensive agents was also associated with excess amputations in T2DM patients.[48] However, since the amputations were late event, this hypothesis may be somewhat questionable.[48] An additional factor may be the relatively lower adherence with the study drugs in the CANVAS program compared to EMPA-REG OUTCOME trial. While in EMPA-REG OUTCOME trial, 25% of the participants discontinued treatment, it was somewhat worse at 29% in CANVAS. Therefore, Tanaka et al. hypothesized that discontinuation of the agent erased the potentially beneficial effects of the SGLT-2 inhibitor on endothelial and metabolic function, causing an excess of distal peripheral arteriosclerosis and ischemia.[48] This explanation is also not totally convincing as it does

not address the question of why only amputation risk was increased as opposed to other macrovascular or microvascular complications.

Most recently, a real-world retrospective cohort study[49] demonstrated no increased risk of incidence of below-knee lower extremity (BKLE) amputation among new users of canagliflozin compared to other SGLT-2 inhibitors and non-SGLT-2 inhibitor DM agents. The incidence rates of BKLE amputation were 1.18 and 1.12 events per 1000 person-years with canagliflozin and non-SGLT-2 inhibitor DM agents, respectively (hazard ratio was 0.98). All SGLT-2 inhibitors have consistently shown benefit with risk factors for PAD as discussed earlier. Meta-analyses of SGLT-2 inhibitors have only studied coronary circulation (MI and unstable angina), cerebrovascular bed (stroke), HF, and death. Most SGLT-2 inhibitor trials included CVD outcomes, as well as HF, BP, lipid profiles, uric acid, and CRP. Though these parameters have a profound impact on PAD, a dedicated trial specifically addressing PAD is currently lacking.

Conclusions and Future Directions

A relatively small study showed that dapagliflozin acutely improved endothelial dysfunction, reduced aortic stiffness, and renal resistive index in T2DM patients, which occurred independently of changes in blood pressure and natriuresis. This suggests a direct effect on the vasculature, possibly through mitigation of oxidative stress.[50] A prospective, single-center, placebo-controlled, double-blind, randomized crossover phase IIIb study showed that dapagliflozin administered for 6 weeks improved retinal capillary flow and parameters of arteriolar remodeling.[51] Recently, dapagliflozin's effectiveness on vascular endothelial function and glycemic control (DEFENCE) study showed significant improvement of the flow-mediated dilation when dapagliflozin was added with metformin, compared to metformin alone.[52] The Study of Using Tofogliflozin for Possible better Intervention against Atherosclerosis for T2DM patients (UTOPIA)[53] is underway to address the effects of tofogliflozin's effect on the progression of carotid intima-media thickness (cIMT) in subjects with T2DM without a history of CVD. Tofogliflozin is approved for use in Japan. The primary study outcomes are the changes in mean cIMT of the common carotid artery (mean-IMT-CCA) and maximum cIMT of the CCA (max-IMT-CCA) during the 104-week treatment period, measured by carotid arterial ultrasonography. Apart from several secondary outcomes, subsets of the study population are to be enrolled in substudies assessing the effect of the interventions on brachial-ankle pulse wave velocity and ankle-brachial BP index. Following encouraging results

TABLE 3. Lacuna in current CV outcome trials of SGLT-2 inhibitors and possible solutions

1. CV outcome trials mostly ignore PAD data
2. CAD data cannot be taken as a proxy measure for PAD data
3. Dedicated PAD outcome trials are the necessity of the hour

from EMPAREG-OUTCOME trial, the impact of empagliflozin on endothelial function (EMBLEM) trial[54] was designed to specifically evaluate endothelial function. The primary endpoint of the trial is to measure the change in the reactive hyperemia-peripheral arterial tonometry (RH-PAT) derived index at 24 weeks from baseline. This trial is of utmost importance as it is the only trial evaluating the role of empagliflozin in peripheral vascular biology.

Although the logic behind these surrogate end-point studies is promising, prior experience with cholesterol transfer ester protein inhibitor, torcetrapib,[55] suggests that caution is needed in interpretation. A recently performed disproportionality analysis pharmacovigilance study done among all the oral glucose-lowering agents showed that SGLT-2 inhibitors, as a class were associated with lower-limb amputation.[56] Of them, canagliflozin carried the highest risk (proportional reporting ratio, [PPR]-7.09), while PPR for empagliflozin and dapagliflozin was significant. On the contrary, a meta-analysis of 14 randomized control trials concluded that as a class SGLT-2 inhibitors were not associated with amputation risk, with slightly greater incidence among canagliflozin (OR- 1.89).[57]

Most recent addition to the speculation was OBSERVE-4D study presented recently in the conference of American Diabetes Association (ADA). It was a retrospective observational analysis of real-world data involving more than 7 lakhs patients, which showed no evidence of increased risk of amputation with canagliflozin vs dapagliflozin, empagliflozin, and all non-SGLT2 therapies.[58]

An adequately powered multicentered blinded prospective trial to address the PAD outcomes among DM patients treated with canagliflozin and all other SGLT-2 inhibitors is urgently needed to assess further the ongoing canagliflozin-amputation risk controversy following the CANVAS study (vide Table 3).

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Inhibitors of sodium-glucose cotransporters type-2 are the most recent addition to the armamentarium of oral anti-diabetic agents. These agents provide glycemic control but also and more importantly to reduce cardiovascular disease mortality risk. However, there have been data for the potential to causing or worsening peripheral artery disease.

Several perspectives can be taken from this excellent review.

First, the authors state that among all the oral glucose-lowering agents showed that SGLT-2 inhibitors, as a class were associated with lower-limb amputation.

Second, canagliflozin had the highest risk, empagliflozin and dapagliflozin were also significantly associated with risk.

Third, a meta-analysis of fourteen randomized control trials concluded that as a class SGLT-2 inhibitors were not associated with amputation risk, with slightly greater incidence among canagliflozin.

Fourth, a retrospective observational analysis of real-world data showed no evidence of increased risk of amputation with canagliflozin vs. dapagliflozin, empagliflozin, and all non-SGLT2 therapies.

In conclusion, there is controversy regarding SGLT-2 inhibitors and causing peripheral vascular disease and the mechanisms by which this occurrs is not clear. The authors conclude that in the future a multi-centered blinded prospective trial to address the PAD outcomes among DM patients treated with canagliflozin and all other SGLT-2 inhibitors is needed to assess further this controversy.

I will like to thank the author for this interesting review of SGLT-2 inhibitors and peripheral vascular disease.