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Review

Impact of Sodium–Glucose Cotransporter 2 (SGLT2) Inhibitors on Arterial Stiffness and Vascular Aging—What Do We Know So Far? (A Narrative Review)

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Abstract: Vascular aging, early vascular aging or supernormal vascular aging are concepts used for estimating the cardiovascular risk at a certain age. From the famous line of Thomas Sydenham that "a man is as old as his arteries" to the present day, clinical studies in the field of molecular biology of the vasculature have demonstrated the active role of vascular endothelium in the onset of cardiovascular diseases. Arterial stiffness is an important cardiovascular risk factor associated with the occurrence of cardiovascular events and a high risk of morbidity and mortality, especially in the presence of diabetes. Sodium–glucose cotransporter 2 inhibitors decrease arterial stiffness and vascular resistance by decreasing endothelial cell activation, stimulating direct vasorelaxation and ameliorating endothelial dysfunction or expression of pro-atherogenic cells and molecules.

Keywords: vascular aging; arterial stiffness; SGLT2 inhibitors; early vascular aging; diabetes mellitus; cardiovascular risks

Citation: Adam, C.A.; Anghel, R.; Marcu, D.T.M.; Mitu, O.; Roca, M.; Mitu, F. Impact of Sodium–Glucose Cotransporter 2 (SGLT2) Inhibitors on Arterial Stiffness and Vascular Aging—What Do We Know So Far? (A Narrative Review). *Life* **2022**, *12*, 803. https://doi.org/10.3390/life12060803

Academic Editor: Panagiotis Georgianos

Received: 1 May 2022
Accepted: 25 May 2022
Published: 27 May 2022

1. From Vascular Aging to Arterial Stiffness

Vascular aging affects large elastic arteries, the main changes identified in the vascular wall being luminal enlargement with wall thickening and a reduction in elastic properties also known as stiffening [1]. From the famous line of Thomas Sydenham that *"a man is as old as his arteries"* to the present day, clinical studies conducted in the field of molecular biology of the vasculature have demonstrated the active role of the vascular endothelium in maintaining general homeostasis, as well as in the onset and progression of CVD [2–4]. With advancing age, the amount of elastin in the central arteries decreases, leading to fiber fatigue and fracture, which contributes to arterial aging, along with vascular calcification and endothelial dysfunction [5]. This article aims to review the beneficial effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors on vascular function, which has been little studied so far but has promising results in in vitro studies.

The relationship between arterial ageing and arterial stiffness is bidirectional. Hypertension, diabetes mellitus, dyslipidemia or obesity are cardiovascular risk factors that accelerate the process of arterial stiffening and ageing. Additionally, arterial stiffening per se may be considered an independent risk factor in the development of atherosclerosis and, consequently, lead to various cardiovascular diseases (CVD) [6–8]. Arterial stiffness leads to increased pulse wave velocity and pulse pressure, which are markers of the pulsatile energy content of the pressure waveform. An increase in this leads to additional stress on the heart [9]. There is a directly proportional relationship between pulse pressure and the

risk of cardiovascular disease, with increased pulse pressure associated with an increased risk of myocardial infarction, heart failure, arrhythmias and stroke [10–13].

Medial degeneration is the key factor that causes arterial stiffness [14]. The structure of the media, which is made up mainly of collagen fibers, elastin and vascular smooth muscle cells (VSMC), degenerates, causing muscle fiber rupture over time [15]. In certain pathological situations (such as in hypertension or atherosclerosis), proteins in the cellular matrix structure undergo proteolysis, generating bioactive fragments with an active role in vascular remodeling processes [4,16]. Extracellular matrix molecules (elastin, collagens, proteoglycans or glycoproteins) synthesized during the growth period ensure tissue homeostasis [17]. Elastic fibers are considered to be the strongest structures, with an estimated durability of about 40 years [18]. In the adult period, there is a decrease in their activity with a very low turnover rate for elastin and collagen fibers, leading to the disruption of homeostasis and the appearance of morphological and functional disorders exacerbated in the context of the presence of related pathologies such as CVD [19] (Figure 1). Their degradation occurs naturally with advancing age or as a result of excessive mechanical stress that stimulates the appearance of a permanent inflammatory environment, which stimulates vascular calcification processes [20]. Besides mechanical stress, telomere dysfunction, oncogene activation or deoxyribonucleic acid (DNA) damage contribute to cellular senescence, exacerbating the arterial aging process [21]. Vascular fibrosis is characterized by the accumulation of extracellular matrix, especially collagen fibers, contributing to the remodeling process in hypertension, restenosis or atherosclerosis [22–25].

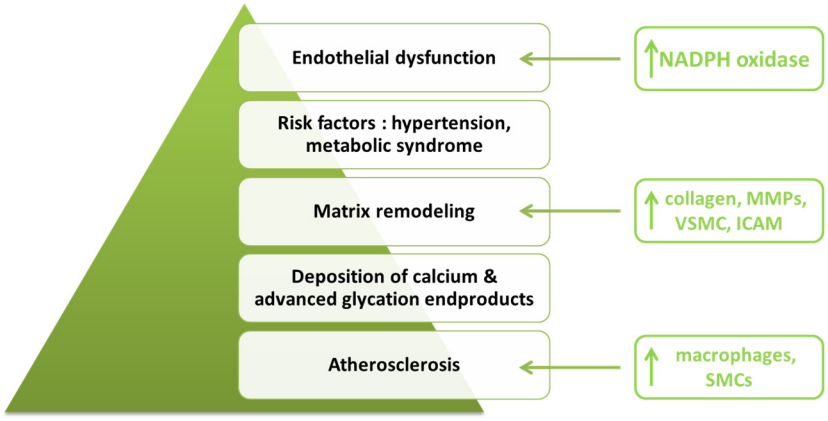

Figure 1. Factors contributing to arterial aging (adapted after [1]). (NADPH: nicotinamide adenine dinucleotide phosphate oxidase; MMPs: matrix metalloproteinases; VSMC: vascular smooth muscle cells; ICAM: intercellular adhesion molecule; SMCs: smooth muscle cells).

The deposition of calcium and advanced glycation end products reduce arterial distensibility, particularly after the 5th decade [26]. Calcification occurs predominantly in the intimal plaques and the medial elastic fiber network [26,27]. The calcification of medial elastic fibers, also known as elastocalcinosis, occurs independently of the calcification of atheromas [28]. Medial elastocalcinosis mainly affects elastic fibers [29], and over time, their fragmentation has been observed in the coronary arteries [30]. Peripheral artery calcification is associated with an increased risk of limb acute events in patients with peripheral artery disease [31–33]. Zettervall et al. [31] demonstrated significant correlations between the risk of ischemia and age, diabetes duration, hypertension, the artery occlusion score and peripheral artery calcification. The identification of potential biomarkers associated with vascular calcification, as well as the understanding of the molecular mechanisms underlying pathophysiological changes, are research directions that have been increasingly addressed in recent years [34,35]. Chen et al. [34] compared the genes of subjects with normal arteries to those of patients with significant vascular changes and demonstrated the presence of genetic changes associated with the development and progression of vas-

cular calcification. They identified genes with a significantly high expression in vascular calcification, which can be seen both as potential biomarkers and future therapeutic targets.

Peripheral resistance associated with endothelial dysfunction occurs as a consequence of altered motor function with advancing age. Simultaneously, there is a disturbance of the balance between antioxidant status and oxidative stress [36,37]. Tobacco smoking, one of the most common cardiovascular risk factors, causes the appearance of oxygen free radicals, thus further contributing to the accentuation of oxidative stress [38]. Aging is considered a major determinant of CVD-related events [37], altered mitochondrial functions and oxidative stress (apoptosis, bioenergetics or inflammation) being factors associated with the occurrence of heart failure, cardiac hypertrophy or diabetic cardiomyopathy [39–41]. Oxidative stress promotes vascular inflammation even in the absence of risk factors associated with atherogenesis via reactive oxygen species [42–44].

Arterial stiffness is an important cardiovascular risk factor associated with the occurrence of cardiovascular events and a high risk of morbidity and mortality [45,46]. Pulse pressure and mean arterial pressure are its main determinants, themselves having both prognostic and therapeutic value for predicting CVD-associated risk in patients with diabetes mellitus [47–49]. Mean arterial pressure and pulse pressure have a proven beneficial role in assessing prognosis, the risk of hospitalization for heart failure ($p < 0.002$) or that of all-causes mortality ($p < 0.007$) in heart failure patients with preserved ejection fraction [48,50,51]. Arterial stiffness accelerates the onset and progression of neuropathy, nephropathy and retinopathy in patients with type 2 diabetes mellitus [52–55].

2. Effects of SGLT2 Inhibitors on Vascular Aging

2.1. Cardiorenal Benefits of SGLT2 Inhibitors

Renal glucose reabsorption is crucial in maintaining adequate glycemic control. Clinical studies have identified three families of glucose transporters in humans: glucose facilitators, sodium-glucose cotransporter and sugars that will eventually be exported transporters (SWEETs) [56–58]. Among these, sodium-glucose cotransporter mediates most of the glucose reabsorption process in the early proximal tubule via an insulin-independent mechanism [59]. By reducing hyperglycemia, SGLT2 inhibitors also reduce glucotoxicity in both kidney and extrarenal organs [60–62]. The pleiotropic effects such as reducing blood pressure, weight loss or the inhibition of hyperuricemia contribute to cardiovascular protection [60,63] (Figure 2). SGLT2 inhibitors' contribution to erythropoietin production, extracellular volume homeostasis or interaction with the angiotensin system and the renal sympathetic nervous system were also investigated [63].

Until the development of SGLT2 inhibitors, glucose-lowering agents had little or no impact on CVD progression in patients with diabetes mellitus [64]. Of all the agents in this class, dapagliflozin is the only one approved for the treatment of patients with type 1 diabetes in the European Union to date [64]. Fibroblasts in the interstitial tubules are responsible for the synthesis of erythropoietin, the production of which is mediated by the hypoxia-inducible factor in the presence of oxygen [65,66]. In patients with diabetes mellitus, tubulointerstitial hypoxia occurs as a result of excessive oxygen consumption in the process of impaired glucose reabsorption [67]. SGLT2 inhibitors relieve hypoxia in the interstitial tubules by decreasing workload at this level, thereby improving erythropoietin production in fibroblasts. Clinical studies in the literature report an average increase in hematocrit value of 2–4% compared to a placebo [68]. Hematocrit changes are influenced by the degree of renal dysfunction in patients treated with empagliflozin. In this regard, Sano et al. [68] emphasize the beneficial effect of administering this SGLT2 inhibitor to diabetic patients with chronic kidney disease stages 2 and 3, with no beneficial effects observed in patients with severe renal impairment.

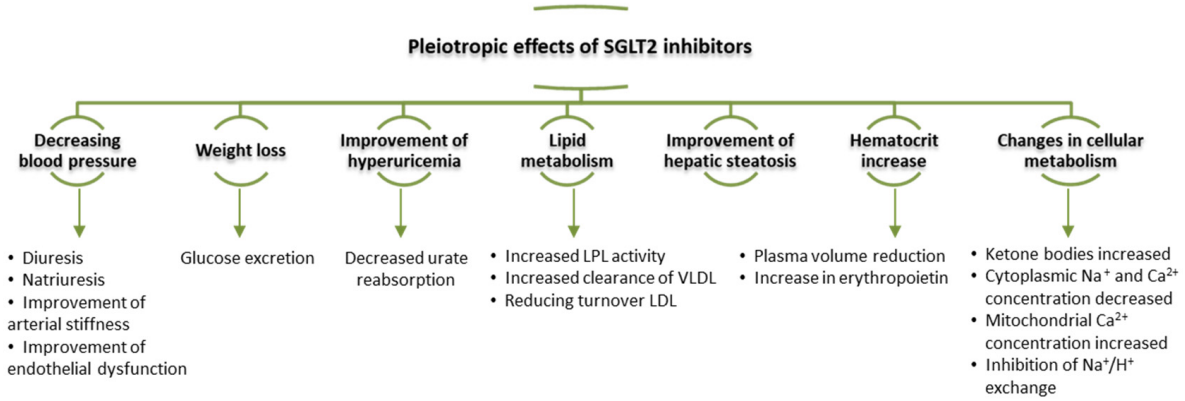

Figure 2. Pleiotropic effects of SGLT2 inhibitors (adapted after [69]) (LPL: lipoprotein lipase; VLDL: very low density lipoprotein; LDL: low density lipoprotein).

Phlorizin was the first SGLT2 inhibitor isolated in 1835 from the bark of an apple tree by a group of French chemists [70,71]. Decades later, Kahn et al. [72] demonstrated in a diabetic rat model that phlorizin causes the decrease in both fasting and postprandial blood glucose levels, independent of insulin secretion. Chasis et al. [73] concluded that the administration of phlorizin leads to lower blood pressure and lower body weight and increases renal glucose excretion, but its use as an oral antidiabetic is not possible due to rapid lactase–phlorizin hydrolase-induced degradation and reduced absorption in the gastrointestinal tract [74]. The protective role in cardiovascular, renal and vascular function modulation is a class one for SGLT2 inhibitors (Figure 3), but in the case of phlorizin, it could only be demonstrated in clinical studies on animals. Shen et al. [75] investigated the effect of phlorizin on vascular complications in an animal model. At a 10-week follow-up, they concluded that its administration to diabetic mice resulted in decreased blood glucose and advanced glycation end products (AGEs) concentration, thus conferring a preventive role for the occurrence and progression of macrovascular complications. In a similar study, Pei et al. [76] emphasized the protective role of phlorizin in preventing the development of diabetic nephropathy by modulating metabolic processes involved in protein and lipid transport and metabolism.

SGLT2 inhibitors are associated with favorable cardiovascular and kidney outcomes in people with or without diabetes mellitus [77]. The main benefits are a reduction in the risk of cardiovascular death and hospitalization for heart failure, regardless of the presence of diabetes or heart failure [69]. Heart failure is one of the most commonly encountered CVD and is considered a public health problem in terms of economic, social and associated medical management implications [78–80]. In the context of the ongoing industrialization of society and the increasing prevalence of cardiovascular risk factors and hence cardiovascular damage, the development and introduction of new therapeutic molecules for patients with heart failure leads to a decrease in the risk of morbidity and mortality [59,81,82]. EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcomes Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose) investigators [83] concluded that diabetic patients with important cardiovascular risk factors had an early reduction in both cardiovascular and renal events following treatment with empagliflozin. Similar results have been reported by other clinical trials such as CANVAS (Canagliflozin Cardiovascular Assessment Study) [84] or CREDENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) [85] for canagliflozin and DECLARE-TIMI 58 (Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes) [86] for dapagliflozin. In addition to the trials mentioned above, other clinical trials demonstrating the cardiovascular protective role by reducing the hospitalization rate in heart failure or optimizing the treatment of these patients (DAPA-HF, DELIVER HFpEF, EMPEROR-Preserved, EMPEROR-Reduced) are cited in the literature [87]. The renal protective role conferred by SGLT2 inhibitors is to reduce the decline in renal function (proven outcome in the CANVAS Program, DECLARE-

TIMI 58 and EMPA-REG OUTCOME trials) or to stabilize and slow the progression of chronic kidney disease in previously diagnosed patients (EMPA-Kidney, DAPA-CKD) [87]. Many of the clinical trials reviewed included patients with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 [88]. A meta-analysis conducted by Lo et al. [89] concluded that cardiorenal protection is maintained in those with renal impairment below the mentioned threshold. The molecular mechanisms in relation to SGLT2 inhibitors involved in modulating the processes of arterial stiffening and vascular aging are complex, currently representing a major interest of the scientific community. Several clinical studies in the field have emphasized the beneficial role of Na^+ homeostasis in cardioprotection and the modulation of vascular function [90]. Thus, the inhibition of essential proteins in the cellular metabolism of Na^+ as well as cardiac Na^+/H^+ exchanger 1 [91–93], Ca^{2+}/calmodulin-dependent protein kinase II [94] and late Na^+ current helps prevent the progression of heart failure [90,95]. In addition to modulating processes involved in Na metabolism, the inappropriate activation of the RAS system, as well as increased sympathetic nervous system activity are processes antagonized by SGLT2 inhibitors in in vitro and in vivo clinical studies [96].

The pathophysiology of chronic heart failure involves various signaling pathways that are not localized to cardiac myocytes, with consecutive involvement of numerous cells such as fibroblasts, vascular cells, cytokines or chemokines [97] that mediate complex processes, stimulating the continuous development of bio-molecular analyzing techniques [98].

SGLT2 inhibitors can be used for both primary and secondary prevention population, the cardiorenal benefits being variable depending on the presence or absence of established CVD [99]. Thus, in diabetic patients with multiple cardiovascular risk factors, SGLT2 inhibitors provide renal protection and decrease the risk of hospitalization due to heart failure but do not decrease the risk of major cardiovascular events, as seen in patients with established CVD [77,100,101]. In a meta-analysis based on the aforementioned clinical trials, Zelniker et al. [101] concluded the beneficial role of SGLT2 inhibitors in decreasing the risk of major cardiovascular events by 11% (p = 0.0014) in patients with atherosclerotic disease than in those with cardiovascular risk factors (p = 0.0501) associated with myocardial infarction (by 11%, p = 0.0177) and cardiovascular death (by 16%, p = 0.0023).

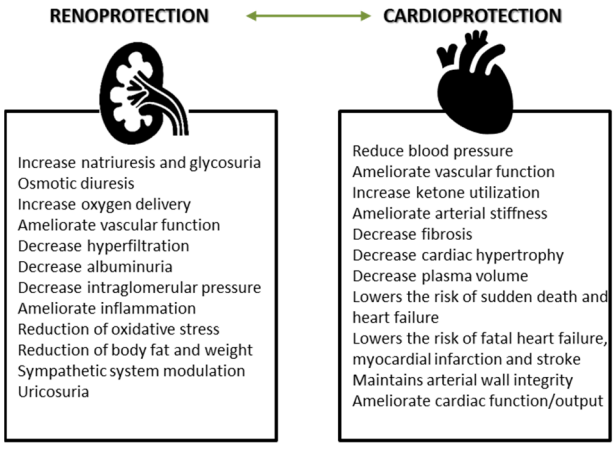

Figure 3. Cardioprotective and renoprotective effects of SGLT2 inhibitors (adapted after [100,102]).

2.2. SGLT2 Inhibitors Modulate Vascular Function

The vascular endothelium is the site of multiple pathophysiological processes in which the action of pro-inflammatory mediators induces endothelial dysfunction, vascular inflammation or vascular remodeling in all segments of the vessel wall [103–105]. The effects of SGLT2 inhibitors are also reflected in the vascular function by modulating blood pressure, reducing inflammatory status or inhibiting the sympathetic nervous system [69]. Decreasing oxidative stress and increasing circulating pro-vascular progenitor cells lead to improved vascular function (Figure 4).

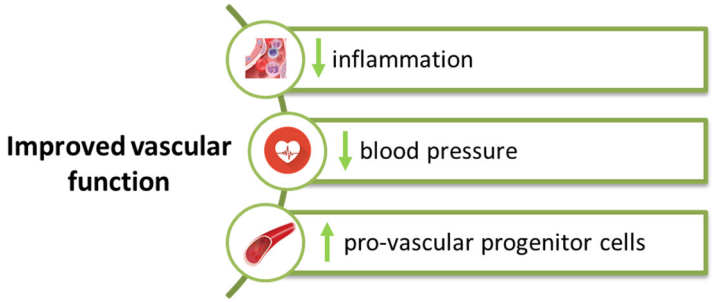

Figure 4. Effect of SGLT2 inhibitors at the vascular level.

SGLT2 inhibitors decrease arterial stiffness and vascular resistance by decreasing endothelial cell activation, stimulating direct vasorelaxation and ameliorating endothelial dysfunction or the expression of pro-atherogenic cells and molecules [69]. Heart failure is characterized by a reduced degree of chronic systemic inflammation, which leads to endothelial dysfunction. Uthman et al. [92] concluded that both empagliflozin and dapagliflozin modulate nitric oxide bioavailability by inhibiting the formation of reactive oxygen species and not by decreasing the expression of endothelial nitric oxide synthase (eNOS) or eNOS-modulated pathways at the vascular level. SGLT2 inhibitors mediate the restoration of provascular progenitor cells in patients with type 2 diabetes mellitus [69,106]. Hess et al. [107] emphasized the beneficial effect of empagliflozin in decreasing the number of pro-inflammatory M1 cells and increasing the M2 ones, with anti-inflammatory action [108].

SGLT2 inhibitors ameliorate arterial stiffness and vascular resistance by reducing blood pressure, a mechanism demonstrated in multiple clinical studies to date [109,110]. Chilton et al. [111] conducted a post hoc analysis on several trials in which patients with type 2 diabetes treated with empagliflozin were enrolled. Besides the reduction in both systolic and diastolic blood pressure ($p < 0.001$), in the pulse pressure (−2.3 mmHg) and mean arterial pressure values (−2.1 mmHg), the follow-up results showed a decrease in ambulatory arterial stiffness index values, signifying a reduction in arterial stiffness ($p = 0.059$ vs. placebo). Similar results were obtained with the administration of canagliflozin, its administration in patients with type 2 diabetes mellitus leading to an improvement in blood pressure values and arterial stiffness determinants [45,112], having thus a beneficial effect on vascular function.

2.3. SGLT2 Inhibitors and Vascular Aging—In Vitro Cell and Animal Evidence

To date, multiple in vivo and in vitro studies have been performed, demonstrating the anti-inflammatory role of SGLT2 inhibitors in coronary microvascular endothelial cells, heart or kidney. Dapagliflozin decreases the rate of inflammasome activation, thus having an anti-inflammatory and anti-fibrotic effect, independently of lowering glucose values in type 2 diabetic mice [113]. The anti-inflammatory role of dapagliflozin was also demonstrated by Gaspari et al. [114] in an in vitro study on human vascular endothelial cells stimulated with TNF-α or hyperglycemic conditions, who observed a decrease in the expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, plasminogen activator inhibitor type 1 and (nuclear factor kappa B) NFκB expression. They also highlighted the acute vaso-protective effects of dapagliflozin by inducing endothelium-independent vasorelaxation, as well as a decrease in the expression of vascular adhesion molecule with macrophage vessel wall infiltration as a result of chronic administration. Besides that, dapagliflozin mediates cardiac remodeling and attenuates cardiac fibrosis by decreasing myofibroblast infiltration in rats after myocardial infarction through a reactive oxygen and nitrogen species (RONS)/activator of transcription 3 (STAT3)-dependent pathway [115]. Li et al. [116] investigated the effect of dapagliflozin on thoracic aorta smooth muscle cells in rabbits and concluded that this SGLT2 inhibitor induces vasodilatation

independent of the endothelium by channeling the activation of voltage-dependent K^+ channels and protein kinase G signaling pathways.

In a recent study conducted by Hodrea et al. [64], the group of investigators demonstrated that dapagliflozin ameliorates cardiac inflammation induced by diabetes mellitus similarly to the effect observed in type 2 diabetic rodent models by Aragón-Herrera et al. [117] or Ye et al. [118]. The anti-inflammatory and anti-fibrotic effect of dapagliflozin was also evidenced in the study proposed by the last mentioned investigators, dapagliflozin administration leading to decreased inflammasome activation and decreased levels of IL-1β [118].

In a similar preclinical study, empagliflozin improved cell viability and stimulated ATP replenishment in endothelial cells previously exposed to hypoxia-reoxygenation injury [92,119]. Lin et al. [120] highlighted the beneficial effect of empagliflozin in ameliorating cardiovascular injury, preventing cardiac remodeling and ameliorating vascular dysfunction or cognitive decline in obese and type 2 diabetic mice, raising the hypothesis of its administration in cases with diabetic macrovascular disease and associated cognitive decline. Empagliflozin has a major impact on microvascular complications associated with diabetes mellitus. It preserves the microvascular barrier integrity and associated homeostasis through the enhancement of eNOS phosphorylation and vasorelaxation endothelium-dependent, which leads to an improvement in microvessel density and perfusion [121–123]. Based on the idea that hyperglycemia contributes to arterial stiffness, Aroor et al. [124] studied the effects of empagliflozin administration in type 2 diabetic female mice and concluded that its administration is associated with an improvement in the renal microvasculature stiffening measured using the renal resistivity index ($p = 0.003$). These findings are supported by pre-existing data in the literature that increases in the degree of cortical tissue periarterial and tubulointerstitial fibrosis, alongside aortic stiffness, lead to renal vascular stiffness and albuminuria in patients with diabetes mellitus [125,126]. Aragón-Herrera et al. [117] demonstrated the cardioprotective role of empagliflozin by ameliorating cardiac metabolome and lipidome through regulation of cellular energy homeostasis AMP-activated protein kinase and stimulating autophagy at the cardiac level while decreasing the cardiac mRNA levels of pro-inflammatory molecules.

Empagliflozin, dapagliflozin and canagliflozin inhibit in vitro the progression of arterial atherosclerotic lesions related to vascular aging by blocking cell proliferation and migration of VSMC. The effect of canagliflozin is dose-dependent, but in the case of the other two representatives, it has been demonstrated that an extremely high concentration is required for a moderate decrease in VSMC processes [127,128]. In vitro administration of canagliflozin is also associated with the reduction in pro-inflammatory agents such as TNF receptor 1, IL-6, matrix metalloproteinase 7 and fibronectin 1 [129,130].

Most clinical studies documented canagliflozin as the only SGLT2 inhibitor that activates AMP-activated protein kinase (AMPK) [131] and inhibits pro-inflammatory status by decreasing the concentration of chemokines and cytokines without interfering with IL-1β signaling pathways [132]. In a recent study, Cai et al. [133] emphasized the protective role of empagliflozin in mitochondrial metabolism through the activation of the AMPKα1/UNC-51-like kinase (ULK1)/FUN14 domain containing 1 (FUNDC1)/mitophagy pathway both in intro and in vivo [134–136]. In addition to acting at the level of mitochondrial metabolism, empagliflozin alleviates microvascular dysfunction by mediating the interaction between cardiac microvascular endothelial cells and cardiac myocytes [137,138]. In a similar study, Soares et al. [139] concluded that empagliflozin reduces arterial stiffness in aged mice by increasing the activation of eNOS and downregulating pathways involved in the synthesis of reactive oxygen species.

Ipragliflozin is another representative of the SGLT2 inhibitor class, less known than the main representatives presented above, but with a similar effect on endothelial function proven in multiple in vitro studies [52]. Salim et al. [140] conducted a study on the impact of ipragliflozin on endothelial cells in diabetic mice and demonstrated its active role in preventing endothelial dysfunction by decreasing the expression of reactive oxygen species

or pro-inflammatory molecules such as monocyte chemotactic protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1).

2.4. SGLT2 Inhibitors and Vascular Aging—Clinical Evidence

SGLT2 inhibitors have been shown to be beneficial in numerous clinical trials involving patients with type 2 diabetes [52]. Santiago et al. [141] investigated the effect of dapagliflozin on arterial stiffness by measuring the velocity of the carotid-femoral pulse at 6 and 12 months from enrollment in 32 diabetic patients. At the follow-up, significant decreases in the velocity of the carotid-femoral pulse were observed, but without significant correlations between these values and blood pressure, blood glucose or weight. In a similar study, Bosch et al. [142] demonstrated an improvement in vascular parameters (central systolic blood pressure, central pulse pressure and reflected wave amplitude, all with statistically significant value) associated with arterial stiffness secondary to empagliflozin administration due to its combined anti-inflammatory mechanism.

The concomitant administration of empagliflozin and linagliptin compared to metformin and linagliptin resulted in decreased central blood pressure ($p = 0.009$) and pulse wave velocity ($p = 0.043$) values, suggestive of significant improvement in vascular function [143]. Another clinical trial conducted by Bekki et al. [144] emphasized that switching DPP-4 inhibitors to tofogliflozin was associated with an improvement in arterial stiffness in type 2 diabetic patients as a result of improved liver function. The cardio-ankle vascular index (CAVI) was used to assess arterial stiffness. The 6-month follow-up showed improvement in both CAVI and liver parameters (aspartate transaminase, γ-glutamyl transferase and AGEs), suggesting that serum levels of AGEs may be used to identify patients with improved vascular function after treatment with tofogliflozin. The benefic effect of tofogliflozin on arterial stiffens has been demonstrated by Katakami et al. [145], who evaluated the impact of the SGLT2 inhibitor on the brachial-ankle pulse wave velocity in diabetic patients without known CVD. Tofogliflozin decreased the progression of arterial stiffening processes compared to conventional treatment ($p < 0.005$), including after adjustment for cardiovascular risk factors. Unfortunately, the same group of investigators did not obtain the same results in the analysis of carotid lesions, with no significant changes in carotid intima-media thickness after administration of tofogliflozin [146].

3. Early Vascular Aging (EVA) vs. Supernormal Vascular Aging (SUPERNOVA)—From "Inflammaging" to SGLT2 Inhibitors

Vascular age is a concept used for estimating the cardiovascular risk at a certain age [147]. Early vascular aging (EVA) and supernormal vascular aging are two extreme vascular ageing phenotypes. EVA or arterial stiffness is a concept mentioned in the literature for the first time in 2008 [148] and includes premature changes in the structure and function of the arteries due to the action of cardiovascular risk factors, environmental factors, genetic predisposition or fetal programming [149,150]. On the other hand, supernormal vascular aging is defined as abnormally low arterial stiffness [151]. Although arterial stiffening is a physiological consequence of aging, there are studies in the literature on subgroups that attest to the lack of age-related increases in blood pressure, atherosclerotic lesions or vascular stiffening [152–154]. Laurent et al. [151] defined SUPERNOVA as subjects with still elastic arteries and a large discrepancy between chronological and vascular age despite exposure to the factors mentioned before.

Between these two entities, EVA and SUPERNOVA are patients with healthy vascular aging interpreted as low blood pressure and pulse wave velocity over 50 years old [155]. Bruno et al. [148] demonstrated that estimation of the age difference between the vascular and chronological one might be a useful clinical tool for identifying patients with SUPERNOVA phenotype. Individuals with a vascular age at least 6 years younger than their chronological age are associated with a 40% lower risk of cardiovascular events compared to subjects with a normal vascular age despite the prevalence of cardiovascular risk factors. Various pathophysiological mechanisms underlying EVA are incrimi-

nated such as shorter telomere length, modulating endothelial cell activity or nitric oxide bioavailability [156–158].

Inflammation serves as a precursor for EVA besides atherothrombosis and diabetes mellitus [159]. Vascular aging and diabetes mellitus are linked by the inflammatory status, with common risk factors, which allows the observation of an integrated approach in terms of prevention and primary interventions [160,161]. "Inflammaging" is a term usually used to describe the chronic low-degree inflammatory status associated with aging [161]. Similarly to "metaflammation" [162], the concepts behind these two terms are based on the modulation of the inflammatory process, one of the main pillars associated with both the onset and progression of diabetes and ageing [163]. Drug treatment with SGLT2 inhibitors can reduce AVA by increasing glucosuria and lowering blood pressure [164].

SGLT2 inhibitors, exercise training, healthy lifestyle attitudes and caloric restriction provide a protective, anti-inflammatory role that promotes normal vascular aging and also decreases the risk of CVD development and progression in patients with diabetes mellitus [165].

4. Conclusions

SGLT2 inhibitors are the latest class of antidiabetic medication with cardioprotective and renoprotective effects. SGLT2 inhibitors improve vascular function by increasing the bioavailability of nitric oxide in the endothelium and modulating the proliferation, migration, survival and senescence of endothelial cells. Their antioxidant and anti-inflammatory effect slow the arterial stiffening process in diabetic patients.

Author Contributions: C.A.A. and D.T.M.M. contributed equally to this work; C.A.A. and O.M. wrote the paper; R.A. and M.R. helped revise the language and review editing; F.M. selected the figures and revised the final script. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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