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THE EFFECTS OF SGLT2 INHIBITORS IN CARDIOVASCULAR PROTECTION: A REVIEW OF MECHANISTIC INSIGHTS AND CLINICAL EVIDENCE

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ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, or gliflozins, represent one of the most significant pharmacological breakthroughs in modern cardiovascular and renal medicine. Originally developed as glucose-lowering agents for type 2 diabetes, these medications have demonstrated profound, life-saving cardiovascular benefits in patients, regardless of their glycemic status. This shift from a "glucocentric" to an "organoprotective" paradigm is driven by a complex array of pleiotropic mechanisms that transcend simple osmotic diuresis.

This work provides a comprehensive analysis of the multifaceted physiological pathways through which SGLT2 inhibitors exert their effects. Key mechanisms explored include the optimization of myocardial bioenergetics through ketone body utilization, the stabilization of ion exchange, the restoration of tubuloglomerular feedback, reduction of epicardial adipose tissue, microbiome management and improvement in cardiac muscle remodelling.

This review evaluates the landmark clinical evidence from pivotal trials such as EMPA-REG, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, DAPA-MODA, DAPA-CKD, CREDENCE, EMPA-KIDNEY, DAPA-MI and EMPACT-MI; exploring the SGLT2i role in patients with heart failure and chronic kidney disease. These studies have established SGLT2 inhibitors as the first class of therapy to show consistent mortality and morbidity benefits across the entire spectrum of left ventricular ejection fraction. The work also addresses recent 2024 to 2025 data regarding early implementation in the post-myocardial infarction setting and the emerging role of the gut-kidney-heart axis in modulating systemic inflammation.

Materials and Methods: The article was written based on scientific papers available on PubMed and Google Scholar

KEYWORDS

SGLT2 Inhibitors, Gliflozins, Heart Failure, CVD, Cardioprotection, Cardiovascular Benefits

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1. Introduction

Cardiovascular diseases (CVD) remain the leading cause of global mortality, despite significant advances in lipid-lowering, antihypertensive and antiplatelet therapies [1,2]. In 2022, CVDs claimed an estimated 19.8 million lives, representing approximately 32% of all global fatalities. Myocardial infarctions and strokes were responsible for 85% of these deaths. [2]. The etiology of CVD is multifactorial, ranging from environmental stressors like air pollution to behavioral factors such as physical inactivity and dietary imbalances (including excess salt, sugar, and fats) [2]. The global health burden is further exacerbated by the escalating prevalence of metabolic conditions, most notably obesity and type 2 diabetes (T2DM). With diabetes currently affecting upwards of 460 million individuals and the number being projected to increase by 25% in 2030 reaching 592 million by 2035, there is a profound pathophysiological intersection between metabolic dysfunction and cardiovascular disease [3,4,5].

While proactive glycemic management in the early stages of the disease significantly mitigates the risk of micro- and macrovascular complications - such as CVD, nephropathy, and overall mortality - conventional therapies often fall short as they rarely offer cardioprotective benefits. Many standard glucose-lowering agents, including insulin, present challenges in achieving target levels without triggering adverse effects like weight gain and hypoglycemia; furthermore, these strategies frequently fail to provide substantial cardiovascular protection [6,7,8]. This gap in cardioprotective benefits underscored the need for therapies that address the underlying pathophysiology of vascular and myocardial damage beyond simple blood glucose control.

Inhibitors of the sodium-glucose cotransporter 2 (SGLT2i) are a class of antihyperglycemic agents that include drugs such as empagliflozin, dapagliflozin, canagliflozin, ertugliflozin and sotagliflozin. These agents enhance glycemic management by decreasing the renal threshold for glucose. They function by selectively

inhibiting glucose reabsorption within the proximal convoluted tubule of the kidney, thereby promoting its excretion through urine [5,9]. Research indicates that SGLT2 inhibitors lead to substantial reductions in glycated haemoglobin (HbA1c), body mass, and systolic blood pressure while maintaining a favorable cardiovascular safety profile. These benefits are observed regardless of whether the treatment is administered as monotherapy or in conjunction with other glucose-lowering agents [10,11]. Furthermore, SGLT2 inhibitors distinguish themselves from conventional antidiabetic agents by reducing heart failure (HF) hospitalizations and enhancing renal outcomes independently of a T2D diagnosis. Notably, these benefits are achieved with a minimal side-effect profile [12,13,14,15,16]. In addition, emerging evidence from 2024 and 2025, including analyses from the EMPACT-MI and DAPA-MI trials, suggest that early initiation of SGLT2 inhibitors following acute myocardial infarction is safe and reduces the risk of early-onset heart failure, regardless of glycemic status, although their impact on cardiac mortality within such a short timeframe remains a subject of debate [17,18].

As of 2026, SGLT2 inhibitors have transitioned from auxiliary diabetic medications to a foundational pillar of cardiovascular prevention. They are now integrated into international guidelines as a core therapy for a broad spectrum of patients, regardless of glycemic status, with a safety profile characterized by negligible severe adverse effects. In this review we aim to synthesize the mechanistic insights and clinical evidence, providing an overview of the indispensable role of SGLT2 inhibitors in modern cardiovascular protection.

2. Mechanistic Insights: The Pleiotropic Nature of SGLT2i

2.1. Glucose-lowering Effects

The foundational mechanism of SGLT2 inhibitors lies in their potent ability to modulate glucose homeostasis through a non-insulin-dependent pathway. Under physiological conditions, the kidneys play a pivotal role in glucose conservation, filtering approximately 180 g of glucose daily, nearly all of which is reabsorbed into the systemic circulation. This process is primarily mediated by the Sodium-Glucose Cotransporter 2 (SGLT2) - a transporter located in the S1 and S2 segments of the proximal convoluted tubule, responsible for approximately 90% of renal glucose reabsorption [19,20,21].

In patients with type 2 diabetes (T2D), the expression and activity of SGLT2 are paradoxically upregulated, which increases the renal threshold for glucose and exacerbates hyperglycemia by preventing the excretion of excess glucose. SGLT2 inhibitors counteract this maladaptive state by selectively binding to these transporters, thereby lowering the renal threshold for glucose to approximately 70-90 mg/dL. This induces controlled glucosuria, typically ranging from 60 to 100 grams of glucose per day [22], which directly leads to a significant reduction in glycated hemoglobin levels without stimulating insulin secretion [23].

Crucially, the pharmacodynamic effect of SGLT2 inhibitors extends to individuals without diabetes [21]. In euglycemic patients, the lowering of the renal threshold for glucose still occurs, but because plasma glucose levels remain near or slightly above the new threshold, the volume of induced glucosuria is substantially lower (typically 30-50 g/day) compared to diabetic populations [22]. This "glucose-clamping" effect ensures that SGLT2 inhibitors do not trigger hypoglycemia in non-diabetic individuals, as the excretion of glucose ceases once plasma levels fall below the drug-induced threshold.

Oxidative stress and inflammation are intrinsically linked, serving as synergistic drivers of nearly all major cardiovascular pathologies. Inflammation precipitates both acute and chronic oxidative stress via signaling pathways involving cytosolic protein kinase C (PKC) and calcium, which subsequently activate reactive oxygen species (ROS) sources such as nicotinamide adenine dinucleotide phosphate oxidase (NOX) and the mitochondrial electron transport chain. Conversely, oxidative stress acts as a potent modulator of the inflammatory cascade by upregulating the NLRP3 inflammasome and NF-κB. Due to this bidirectional and convoluted relationship, the impact of SGLT2 inhibitors on these processes is examined in tandem [45].

The clinical significance of SGLT2i-induced glucose modulation extends beyond the simple attainment of glycemic targets. By lowering systemic glucose levels and reducing the time spent in hyperglycemia, these agents effectively mitigate glucotoxicity - a detrimental state characterized by the overproduction of ROS and the formation of advanced glycation end-products (AGEs) [24]. Furthermore, the continuous loss of glucose through the urine triggers a systemic metabolic shift that mimics a state of fasting or caloric restriction [25]. This caloric deficiency also activates key nutrient-sensing pathways, such as AMPK (adenosine monophosphate-activated protein kinase) and SIRT1 (sirtuin 1), which are vital for cellular repair, mitochondrial biogenesis, and the suppression of pro-inflammatory signals [24]. By improving antioxidant activity, SIRT1 alleviates oxidative stress; concurrently, AMPK acts to safeguard mitochondrial function [26,27,28]. Additionally, SIRT1 and AMPK activation triggers autophagy, which facilitates the clearance of

damaged organelles. By eliminating these major sources of oxidative stress and metabolic derangement, this pathway helps preserve the functional integrity of cardiomyocytes [29,30]. Beyond the anti-inflammatory benefits of mitigating oxidative stress, SGLT2 inhibitors have been shown to attenuate a broad spectrum of inflammatory pathways in both preclinical models and human cohorts. This pleiotropic effect includes the downregulation of the NLRP3/ASC inflammasome and a decrease in the accumulation of cardiotoxic lipids. Furthermore, SGLT2 inhibition suppresses a wide array of pro-inflammatory mediators and cytokines, notably interleukin-1β, interleukin-6, nuclear factor-kappa B, tumor necrosis factor-α and high-sensitivity CRP [41].

Consequently, even in euglycemic individuals, the mild metabolic "stress" induced by SGLT2 inhibition acts as a potent stimulus for organoprotective signaling. By transitioning the body from a state of energy storage to a state of energy utilization and cellular defense, SGLT2 inhibitors provide a robust metabolic foundation that supports the heart's resilience against ischemic and hemodynamic stress.

2.2. Hemodynamic Regulation: Diuresis and Cardiovascular Offloading

Beyond its established role in glucose recovery, the Sodium-Glucose Cotransporter 2 mediates the symport of sodium and glucose at a 1:1 molar ratio; consequently, SGLT2 inhibition directly reduces the proximal reabsorption of Na^+. Furthermore, this inhibition triggers a unique osmotic diuretic response, primarily localized in the distal nephron. Under physiological conditions, nearly all filtered glucose is reabsorbed within the proximal tubule (PT), with minimal distal delivery unless plasma glucose levels exceed the renal threshold of approximately 250 mg/dl. However, SGLT2 blockade allows unreabsorbed glucose to reach the distal segments. As water is progressively reabsorbed along the nephron, the rising luminal glucose concentration increases tubular fluid osmolality, thereby narrowing the osmotic gradient between the tubule and the interstitium. This attenuation of the osmotic driving force impairs passive water reabsorption, particularly in the collecting duct, leading to osmotic diuresis [31]. The osmotic diuresis induced by SGLT2 inhibitors (SGLT2is) is mechanistically distinct from that of conventional diuretics. While traditional agents such as thiazides, loop diuretics, and potassium-sparing compounds primarily inhibit Na^+ reabsorption, with water following as an obligatory byproduct, SGLT2is operate differently. Beyond their direct impact on proximal glucose and sodium transport, SGLT2is create an osmotic driving force that directly impairs water reuptake, subsequently leading to an indirect reduction in Na^+ reabsorption. Consequently, SGLT2is are characterized by a superior capacity for electrolyte-free water clearance compared to traditional natriuretic-driven drugs [31,32].

Unlike conventional diuretics, SGLT2is facilitate a disproportionate reduction in interstitial fluid volume compared to intravascular volume. This differential fluid partitioning is clinically transformative. By preferentially clearing fluid from the interstitial "third space" (the site of clinical edema) while maintaining relative intravascular stability, SGLT2i mitigate systemic congestion and pulmonary edema without the severe reflex activation of the sympathetic nervous system or the renin-angiotensin-aldosterone system (RAAS) typically triggered by the aggressive plasma contraction of loop diuretics [31,32]. While research involving euvolemic patients has demonstrated that SGLT2is do induce a measurable contraction of intravascular volume - evidenced by reproducible signs of hemoconcentration across major trials [33,34,35] - this effect is significantly less pronounced than their impact on the interstitium. Mathematical modeling indicates that the clearance of interstitial fluid is approximately 2-fold greater than the reduction in plasma volume [31].

This process effectively reduces cardiac preload and afterload without the detrimental effects of acute systemic volume depletion, providing a stable hemodynamic environment that supports myocardial function and prevents the progression of heart failure.

2.3. Metabolic and Bioenergetic Reprogramming of the Myocardium

Characterized by relentless contractile activity, the human heart exhibits an extraordinary metabolic demand, with a daily ATP turnover ranging from 6 to 35 kg. This function is supported by a substantial coronary blood flow of approximately 200 mL/min and a specific oxygen consumption rate of 4.3 mmol/kg/min - the highest of any organ relative to its tissue mass [36,37]. Given that the total myocardial ATP pool is so limited that it requires complete turnover approximately every 10 seconds, even a minor disruption in substrate oxidation can lead to rapid functional decline [38]. Mitochondrial oxidative metabolism accounts for approximately 95% of myocardial energy production, while the remaining 5% is derived from glycolysis and GTP formation. Under physiological conditions, the mitochondrial fuel substrate is primarily composed of free fatty acids (FFAs, 60-70%) and glucose (30%), with minor contributions from lactate, ketones, and amino acids. A hallmark of the healthy heart is its metabolic flexibility, allowing it to dynamically shift

between energy sources in response to changes in workload, hormonal status, tissue perfusion, and substrate availability [36,37]. During the fasting state, the myocardium primarily relies on free fatty acids as its favored oxidative substrate. Conversely, in the fed state, elevated levels of insulin and glucose drive a metabolic shift toward glucose oxidation while concurrently suppressing FFA utilization. During intense physical exertion, rising lactate levels establish it as a primary metabolic substrate for the heart. Similarly, ketone bodies only provide a meaningful contribution to myocardial energetics when their circulating concentrations are elevated -such as during starvation - as their cellular uptake is strictly concentration-dependent. In response to hypoxia or increased workload, the myocardium shifts from lipid to carbohydrate oxidation; in these states, glucose becomes the preferred fuel because anaerobic glycolysis can generate ATP independently of oxygen. Furthermore, glucose is a more oxygen-efficient substrate than free fatty acids, offering a superior ATP yield per oxygen atom consumed (a higher P/O ratio) during oxidative phosphorylation; this value denotes the number of ATP molecules generated for every oxygen atom consumed during the process of oxidative phosphorylation [36,37,38]. FFAs as a substrate generate more ATP than glucose, but at the effect of higher oxygen consumption. Consequently, regardless of the baseline level of left ventricular (LV) function, a metabolic shift favoring fatty acids over glucose - common in states of insulin resistance and diabetes - diminishes myocardial efficiency and elevates the risk of heart failure development.

In the state of chronic heart failure, myocardial energy metabolism undergoes a detrimental transformation, resulting in the loss of its inherent "metabolic flexibility". While a healthy heart relies primarily on the mitochondrial oxidation of free fatty acids and, to a lesser degree, on the oxidation of glucose, the failing myocardium becomes increasingly energy-starved and metabolically more dependent on ketone production. This metabolic profile, however, remains highly dynamic and can shift significantly depending on substrate availability and hormonal status [38,39]. By inducing a fasting-like state characterized by increased fatty acid oxidation and systemic ketogenesis and shifting fuel utilization away from lipids and glucose, SGLT2 inhibitors (SGLT2i) counteract the energetic crisis faced by the failing heart. Since ketones are energetically more superior fuel source, it has been suggested that SGLT2i exert their cardiovascular benefits by promoting more efficient myocardial bioenergetics and restoring cellular energy balance [37,38,39,40,41].

While early models of the "Thrifty Substrate" hypothesis that suggests ketones provide more ATP per oxygen consumed than glucose or fatty acids, were largely theoretical, recent clinical evidence has provided robust validation. Notably, the EMPA-TROPISM trial utilized cardiac magnetic resonance to demonstrate a fundamental shift in myocardial fuel preference from glucose to ketone bodies in patients with non-diabetic heart failure [42]. This is further supported by positron emission tomography (PET) studies which quantified a direct, linear increase in myocardial ketone uptake following SGLT2 inhibition [43]. Perhaps most convincingly, metabolic profiling of blood from the coronary sinus confirmed that the failing human heart actively extracts these circulating ketones to restore energetic homeostasis, bypassing the dysfunctional glucose oxidation pathways characteristic of heart failure [44].

2.4. Ion Homeostasis: NHE-1 Inhibition and Sodium/Calcium Handling

Beyond systemic hemodynamic and metabolic shifts, SGLT2 inhibitors (SGLT2i) exert direct cardioprotective effects at the cellular level by modulating ion homeostasis. A pivotal mechanism in this regard is the potent inhibition of the Sodium-Hydrogen Exchanger 1 (NHE-1), an isoform predominantly expressed in the myocardium and vascular smooth muscle [45].

A significant off-target mechanism of SGLT2 inhibitors involves their high-affinity interaction with the NHE-1 within cardiomyocytes. In the context of heart failure, the maladaptive upregulation of NHE-1 leads to intracellular Na^+ and Ca^{2+} overload, a key factor in the progression of cardiomyopathy. By inhibiting NHE-1, SGLT2is reduce cytosolic levels of these ions while simultaneously augmenting mitochondrial Ca^{2+}. This ionic rebalancing potentially optimizes excitation-contraction coupling and mitigates the mitochondrial production of reactive oxygen species (ROS) [41]. A further molecular characteristic of heart failure is the pathological upregulation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). This elevation triggers excessive Ca^{2+} leakage from the sarcoplasmic reticulum, ultimately driving contractile impairment. Empagliflozin has demonstrated the capacity to attenuate this CaMKII-driven SR Ca^{2+} leak in both murine and human cardiomyocytes. Given that CaMKII also mediates pathways of myocardial hypertrophy, ventricular dilation, and apoptosis, its inhibition represents a significant avenue for SGLT2i-induced cardioprotection [41,46].

In addition, it has been hypothesized that SGLT2 inhibitors facilitate natriuresis by suppressing NHE-3 activity within the proximal tubule. Given that NHE-3 - a key mediator of tubular sodium reuptake - is typically

upregulated in heart failure, its inhibition may be instrumental in restoring systemic sodium homeostasis and alleviating cardiac dysfunction. Consequently, the dual inhibition of cardiac NHE-1 and renal NHE-3 represents a potential unified cardio-renal mechanism through which these agents exert their preventive and therapeutic effects in heart failure.

2.5 Improvement in LV Remodeling

Myocardial remodeling is defined as a group of molecular, cellular, and interstitial changes that manifest clinically as changes in the size, shape, and function of the heart after injury or chronic stress. In the context of heart failure, pathological remodeling typically involves ventricular dilatation, eccentric hypertrophy, and the replacement of functional kardiomyocytes with fibrous tissue. SGLT2 inhibitors have emerged as potent agents capable of inducing "reverse remodeling" - a process where the heart partially or fully recovers its original geometry and contractile efficiency. Left ventricular mass (LVM) serves as a robust and independent prognostic marker for major cardiovascular outcomes, including myocardial infarction, heart failure, and total mortality. Furthermore, the extent of LVM regression achieved through pharmacological or surgical means has been demonstrated to parallel the magnitude of cardiovascular risk reduction [47].

Landmark clinical trials such as DAPA-HF have established that SGLT2 inhibitors significantly reduce mortality, with survival curves typically diverging after several months of therapy. This delayed benefit suggests a capacity to induce favorable long-term cardiac remodeling - a therapeutic hallmark shared with other foundational HFrEF therapies, including beta-blockers, mineralocorticoid receptor antagonists, and renin-angiotensin-aldosterone system inhibitors or neprilysin inhibitors [41,48].

Cardiac fibrosis is recognized as a terminal pathophysiological endpoint in the progression of heart failure. This process is characterized by extensive structural remodeling driven by the deposition of extracellular matrix (ECM) proteins by cardiac fibroblasts, which ultimately impairs ventricular compliance and accelerates cardiac decompensation. Recent experimental evidence in post-myocardial infarction rat models suggests that dapagliflozin exerts significant antifibrotic effects by inhibiting myofibroblast differentiation and enhancing M2 macrophage activation. Furthermore, in vitro studies using human cardiac fibroblasts have shown that empagliflozin attenuates TGF-β1-induced activation and limits cell-mediated extracellular matrix remodelling, as evidenced by reduced collagen fiber alignment. Empagliflozin also suppresses the expression of key pro-fibrotic markers, such as type I collagen, α-smooth muscle actin, connective tissue growth factor (CTGF), and matrix metalloproteinase 2. These findings support the hypothesis that SGLT2 inhibitors exert direct, glucose-independent effects on fibroblast phenotype and function, addressing a central driver of heart failure [25,41].

In addition, the EMPA-HEART CardioLink-6 trial (2019) provided a significant signal, utilizing cardiac magnetic resonance (CMR) to demonstrate a measurable reduction in left ventricular mass index (LVMI) in patients with type 2 diabetes and stable coronary artery disease. This was subsequently expanded by the landmark EMPA-TROPISM (ATLAS) trial (2021), which served as a pivotal proof-of-concept by demonstrating that empagliflozin induces significant structural improvements, including reductions in left ventricular end-diastolic (LVEDV) and end-systolic volumes (LVESV) in patients with HFrEF regardless of their glycemic status. Finally, the DAPA-MOD trial (2023) further solidified these findings as a robust class effect, confirming that dapagliflozin also facilitates favorable structural and metabolic changes in the failing myocardium. Collectively, these trials transform the theoretical framework of mechanical unloading into a clinically validated reality, proving that SGLT2 inhibitors provide a direct, tangible benefit to the architectural integrity and functional capacity of the heart [47,49,50].

2.6. Depletion of Both Epicardial and Extra-epicardial Visceral Adipose Tissue Depots

Clinical evidence indicates that several SGLT2 inhibitors effectively reduce epicardial adipose tissue (EAT) - a metabolically highly active endocrine tissue known to secrete pro-inflammatory and profibrotic cytokines [41,51,52,53,54]. Due to a shared microcirculation and the absence of a fascial interface between EAT and the myocardium, these adipokines exert a direct, deleterious paracrine effect on cardiac tissue. Beyond these local benefits, SGLT2is also attenuate systemic visceral and subcutaneous adiposity [55]. Furthermore, preclinical models suggest that these agents modulate adipose-driven inflammation by favoring a shift from pro-inflammatory M-1 to anti-inflammatory M-2 macrophage polarization [41,56].

2.7. Improvements in The Cardio-renal Axis

Initial clinical skepticism surrounding SGLT2 inhibitors focused on potential nephrological and urological complications, specifically an increased incidence of genitourinary infections and the risk of exacerbating acute kidney injury. Furthermore, the transient decline in glomerular filtration rate (GFR), alongside sustained reductions in plasma volume and blood pressure, was initially viewed with apprehension. However, robust evidence from landmark cardiovascular outcome trials (CVOTs) and real-world data has since redefined these agents, demonstrating their profound capacity to attenuate the progression of cardiovascular disease and provide long-term nephroprotection [57]. Evidence from major CVOTs in T2DM such as EMPA-REG, CREDENCE and DAPA-CKD populations reveals that SGLT2 inhibition preserves renal function more effectively than placebo [15,33,57,58]. This nephroprotective effect is characterized by a stabilized eGFR profile over time and a significant mitigation of albumin excretion, indicating a potent antiproteinuric benefit of these agents [57]. The DAPA-CKD and EMPA-KIDNEY trials results have provided evidence that these nephroprotective benefits are equally potent in patients without type 2 diabetes [14,15].

The transient reduction in eGFR observed upon initiation of SGLT2 inhibition is likely a hemodynamic phenomenon driven by afferent arteriolar vasoconstriction via the tubuloglomerular feedback (TGF) mechanism. Under physiological conditions, SGLT2 mediates approximately 5% of renal NaCl reabsorption. However, hyperglycemia triggers a significant upregulation of SGLT1 and SGLT2 (by 20% and 36%, respectively), increasing their combined contribution to NaCl reuptake to roughly 14%. This proximal hyper-reabsorption diminishes NaCl delivery to the macula densa. According to the tubular hypothesis, the juxtaglomerular apparatus misinterprets this low NaCl signal as systemic hypovolemia, triggering a maladaptive vasodilation of the afferent arteriole and subsequent glomerular hyperfiltration. SGLT2 inhibitors reverse this process by restoring distal NaCl delivery, which reactivates TGF, increases afferent arteriolar tone, and successfully mitigates detrimental hyperfiltration. This "resets" the TGF, normalizes intraglomerular pressure, and stabilizes the eGFR in the long term, protecting both the kidney and the heart from the consequences of chronic renal decline [59,60].

Beyond hemodynamics, SGLT2 inhibitors provide a "metabolic rest" for the proximal tubule. The active reabsorption of glucose and sodium is a highly energy-intensive process requiring significant ATP production. In heart failure, these cells often operate at a metabolic ceiling, leading to localized hypoxia and mitochondrial stress. By inhibiting SGLT2, gliflozins reduce the workload of the renal cortex. This process is known as an "oxygen sparing effect" which alleviates chronic hypoxia and protects tubular cells from oxidative damage and apoptosis [60,61].

In heart failure, a decline in renal function often leads to "diuretic resistance", forcing clinicians to use higher doses of loop diuretics, which further strain the kidneys [62]. By stabilizing eGFR and enhancing natriuresis, SGLT2 inhibitors break this vicious cycle. The preservation of kidney function provides a stabilization for kidneys which allows for more effective fluid management and reduces the diuretic resistance, preventing the pulmonary and systemic congestion characteristic of heart failure [60]. Furthermore, a protected kidney sends fewer sympathetic distress signals to the central nervous system, leading to a systemic downregulation of the sympathetic nervous system and the RAAS. This reduction in neurohormonal stress directly mitigates the pro-fibrotic and pro-arrhythmic pressure on the myocardium, effectively breaking the vicious cycle of the cardiorenal syndrome [61].

2.8. Cardiovascular Protection via the Gut-Kidney-Heart Axis

While the direct renal and hemodynamic effects of SGLT2 inhibitors are well-established, emerging evidence suggests a more complex, multi-organ regulatory role involving the gastrointestinal tract.

The gut microbiome represents a central metabolic hub that modulates systemic immune responses and influences the early stages of heart and kidney disease. Disruptions in microbial composition facilitate the release of microbial-derived metabolites that signal to distal organs [63,64]. This intricate inter-organ crosstalk forms the foundation of the gut-heart and gut-kidney axes, linking intestinal health directly to cardiorenal function[63].

Initially, gut dysbiosis compromises the structural integrity of the intestinal barrier, characterized by the downregulation of tight junction proteins (TJPs) and essential mucin components such as MUC2. This impairment leads to heightened intestinal permeability - a phenomenon frequently termed “leaky gut”, which facilitates the systemic translocation of deleterious metabolites, including lipopolysaccharide (LPS) and trimethylamine-N-oxide (TMAO), into the bloodstream [63]. Following their translocation into the systemic circulation, gut-derived metabolites exacerbate renal impairment by triggering inflammatory cascades,

oxidative stress, and progressive tissue fibrosis. Chronic kidney disease is typically characterized by compromised intestinal barrier integrity, systemic inflammation, and a depletion of protective short-chain fatty acids (SCFAs). Furthermore, the reduction in renal clearance facilitates the sequestration of protein-bound uremic toxins, which exert direct toxic effects on both the renal and cardiovascular systems; they also worsen gut dysbiosis and barrier dysfunction, creating a vicious cycle [63,65,66]. The promotion of inflammatory signals affects the heart, leading to fibrosis and structural remodeling [67]. This vicious cycle also amplifies kidney injury, ultimately leading to the progression of CKD, which is by itself a major risk factor for cardiovascular events [63]. Altogether, the interplay between the gut, kidneys, and heart creates a reciprocal feedback loop of metabolic and inflammatory toxicity. This hierarchy of insult, originating with dysbiosis and progressing through toxin accumulation and systemic inflammation serves as a central driver of synchronized structural and functional organ damage.

Preclinical investigations suggest that SGLT2 inhibitors exert a regulatory influence on the gut microbiome by augmenting the abundance of short-chain fatty acid (SCFA)-producing genera while simultaneously curtailing pathogenic populations. These microbial shifts are associated with increased butyrate synthesis and diminished systemic lipopolysaccharide (LPS) concentrations, ultimately leading to a substantial attenuation of the inflammatory burden [68,69]. Clinical data in human cohorts substantiate these observations. In patients with type 2 diabetes, an 8-week course of dapagliflozin therapy was shown to markedly augment the abundance of butyrate-producing commensals. This shift in the microbial landscape was accompanied by a significant decline in both systemic C-reactive protein (CRP) and fecal lipopolysaccharide (LPS) concentrations, indicating a dual benefit on gut health and systemic inflammation. In addition to their role in microbial modulation, SGLT2 inhibitors enhance the structural integrity of the intestinal barrier by upregulating tight junction proteins within the gut epithelium. This fortification limits the systemic translocation of LPS and other endotoxins, thereby mitigating chronic inflammation and offering a novel pathway for cardiovascular protection [63].

In summary, within the gut-heart and kidney-heart axes, SGLT2 inhibitors exert pleiotropic effects by modulating the intestinal microbiome and enhancing both renal and metabolic profiles. These integrated actions collectively lower the systemic toxin burden and dampen chronic inflammation, thereby providing an indirect but potent defense against adverse cardiac remodeling and functional decline.

3. Clinical Evidence of SGLT2 Inhibitors' Cardiovascular Benefits

Building upon the theoretical foundations and physiological mechanisms established in the previous chapter, this section evaluates the clinical evidence derived from major randomized controlled trials. These landmark studies provide the empirical proof that the discussed molecular and hemodynamic shifts translate into significant reductions in mortality and morbidity across diverse patient populations.

While the cardiovascular efficacy of empagliflozin was initially a subject of clinical uncertainty, the pioneering EMPA-REG OUTCOME trial in 2015 was one of the first major studies to demonstrate its capacity to significantly reduce adverse outcomes in high-risk patients. This landmark study paved the way for subsequent large-scale trials that have since firmly established SGLT2 inhibition as a cornerstone of cardioprotection [33]. Study participants were randomized to receive either 10 mg or 25 mg of empagliflozin once daily, or a matching placebo. The primary composite endpoint - defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke - was evaluated by comparing the pooled empagliflozin cohorts against the placebo group. Additionally, a key secondary composite outcome was assessed, extending the primary metrics to include hospitalizations for unstable angina [33].

The results of the EMPA-REG trial were exceedingly promising. Empagliflozin treatment over 3.1 years led to a significant 14% reduction in the primary major adverse cardiovascular events (MACE) endpoint. Interestingly, this benefit was not mediated by a reduction in ischemic events (MI or stroke), but rather by significant improvements in hemodynamic and survival outcomes:

CV Death: 38% relative risk reduction (3.7% vs 5.9%), HF Hospitalization: 35% relative risk reduction (2.7% vs 4.1%). All-cause Mortality: 32% relative risk reduction (5.7% vs 8.3%). Despite these gains, the key secondary outcome did not achieve superiority. The safety profile was consistent with the SGLT2i class, showing an increased rate of genital infections but no significant rise in other adverse clinical events [33].

Patients with high-risk type 2 diabetes receiving empagliflozin experienced significantly fewer primary cardiovascular events and lower all-cause mortality than those on placebo. This landmark conclusion solidified the role of empagliflozin as a foundational therapy for improving long-term outcomes in this vulnerable population.

3.1. SGLT2 Inhibitors in the treatment of Heart Failure with Reduced Ejection Fraction

3.1.1 The DAPA-HF Trial

The DAPA-HF trial sought to provide definitive data on the efficacy of SGLT2 inhibitors in a broad population with reduced ejection fraction, purposefully including both diabetic and non-diabetic cohorts to determine if the benefits transcended glycemic control.

In this Phase 3, placebo-controlled trial, 4,744 patients with NYHA class II-IV heart failure and a reduced ejection fraction (LVEF<40%) were randomized to receive either 10 mg of dapagliflozin once daily or a matching placebo, as an adjunct to guideline-recommended therapy. The primary composite outcome was defined as cardiovascular death or worsening heart failure, the latter comprising hospitalizations or urgent visits requiring intravenous pharmacological intervention [12].

During a median follow-up of 18.2 months, dapagliflozin significantly attenuated the risk of the primary composite outcome, which occurred in 16.3% of the treatment group compared to 21.2% in the placebo arm (HR = 0.74; 95% CI: 0.65-0.85; P < 0.001). This overall benefit was underpinned by a 30% reduction in worsening heart failure events (HR = 0.70) and an 18% decrease in cardiovascular mortality (HR = 0.82). Notably, the drug also provided a 17% survival benefit regarding all-cause mortality (HR = 0.83). A pivotal observation was that these cardioprotective effects were consistent regardless of the presence of type 2 diabetes. Furthermore, dapagliflozin was well-tolerated, with no significant differences in the incidence of volume depletion, renal impairment, or hypoglycemia compared to placebo [12].

In summary, the trial established that among patients with HFrEF, dapagliflozin treatment significantly reduces the risk of worsening heart failure and cardiovascular mortality. Crucially, these benefits were independent of the patient's baseline glycemic status, demonstrating equal efficacy in those with and without type 2 diabetes.

3.1.2. The EMPEROR-REDUCED Trial

Following the same clinical trajectory, the EMPEROR-Reduced trial aimed to reinforce the evidence for SGLT2 inhibition in heart failure. This study was specifically designed to evaluate whether empagliflozin could yield similar benefits in a diverse group of patients with reduced ejection fraction, regardless of their diabetes status, thereby solidifying the non-glucose-dependent nature of this therapy.

In this double-blind, randomized investigation, 3,730 participants with symptomatic heart failure (NYHA class II-IV) and a reduced ejection fraction (LVEF<40%) were allocated to receive either 10 mg of empagliflozin once daily or a matching placebo. This intervention was administered alongside guideline-directed medical therapy. The primary efficacy measure was a composite of cardiovascular mortality and hospital admissions resulting from deteriorating heart failure [13].

Over a median follow-up of 16 months, the primary composite outcome occurred in 19.4% of the empagliflozin group compared to 24.7% in the placebo cohort (HR = 0.75; 95% CI: 0.65-0.86; P < 0.001). This 25% risk reduction was remarkably consistent regardless of the presence of type 2 diabetes. Furthermore, empagliflozin significantly reduced the total number of heart failure hospitalizations by 30% (HR = 0.70). A key finding was the drug's profound nephroprotective effect: the annual rate of eGFR decline was markedly attenuated in the treatment arm (-0.55 vs. -2.28 mL/min/1.73 m² year, P < 0.001), alongside a decreased risk of serious renal events. While uncomplicated genital tract infections were more frequent, the overall safety profile remained favorable [13].

In conclusion, the trial established that among patients receiving guideline-recommended therapy for heart failure, those treated with empagliflozin experienced a significantly lower risk of cardiovascular death or hospitalization. Crucially, this therapeutic benefit was independent of the presence of type 2 diabetes, reinforcing the role of SGLT2 inhibition as a metabolic and hemodynamic intervention rather than a purely antihyperglycemic one.

3.2. SGLT2 Inhibitors in the Treatment of Heart Failure with Preserved Ejection Fraction

3.2.1 The DELIVER Trial

Aiming to bridge a significant therapeutic gap, the DELIVER trial sought to determine if the clinical benefits of dapagliflozin extended to the broader spectrum of heart failure, specifically targeting those with mildly reduced or preserved ejection fraction (HFmrEF and HFpEF).

In this large-scale randomized investigation, 6,263 patients with heart failure and a left ventricular ejection fraction exceeding 40% were allocated to receive either 10 mg of dapagliflozin once daily or a matching placebo, as an adjunct to standard background therapy. The primary efficacy measure was a composite of cardiovascular mortality or worsening heart failure - the latter defined as unplanned

hospitalizations or urgent clinical encounters necessitated by heart failure-evaluated through a time-to-event framework [70].

During a median follow-up of 2.3 years, dapagliflozin demonstrated a significant 18% reduction in the primary composite endpoint, occurring in 16.4% of the treatment group compared to 19.5% in the placebo cohort (HR = 0.82; 95% CI: 0.73-0.92; P < 0.001). This overall benefit was primarily driven by a 21% lower risk of worsening heart failure events (HR = 0.79), while cardiovascular mortality also trended lower (7.4% vs. 8.3%). Notably, the drug significantly reduced both the total event rate and the symptom burden. A pivotal finding was the consistency of these effects across the LVEF spectrum, with similar outcomes observed in patients with an LVEF of 60% or more and those with lower values. Furthermore, the therapeutic impact remained uniform across all prespecified subgroups, including those without diabetes, and the safety profile was comparable to placebo [70].

Ultimately, dapagliflozin therapy was found to be superior to placebo in reducing major adverse heart failure events across the HFmrEF and HFpEF spectrum.

3.2.2. The EMPEROR-Preserved Trial

Sharing a common mission with the DELIVER study, the EMPEROR-Preserved trial was designed to investigate whether the cardioprotective properties of empagliflozin could bridge the therapeutic gap in preserved ejection fraction. By including both diabetic and non-diabetic cohorts, the trial aimed to confirm that the benefits of SGLT2 inhibitors in this population were a consistent class-wide effect that functioned independently of glucose metabolism.

In this double-blind, randomized investigation, 5,988 participants with symptomatic heart failure (NYHA class II-IV) and an ejection fraction exceeding 40% were assigned to receive either 10 mg of once-daily empagliflozin or a matching placebo. This intervention was administered as an adjunct to standard clinical care. The trial's primary efficacy measure was a composite outcome consisting of cardiovascular death or hospitalization for heart failure, evaluated through a rigorous time-to-event analysis [71].

Over a median follow-up of 26.2 months, empagliflozin demonstrated a significant 21% reduction in the primary composite outcome, occurring in 13.8% of the treatment group versus 17.1% in the placebo cohort (HR = 0.79; 95% CI: 0.69-0.90; P < 0.001). This clinical benefit was primarily driven by a 27% reduction in heart failure hospitalizations (HR = 0.73), while the efficacy remained consistent across both diabetic and non-diabetic subgroups. Furthermore, the total number of hospitalizations was significantly lower in the empagliflozin arm. Regarding safety, a higher incidence of hypotension and uncomplicated genital and urinary tract infections was observed, though the overall benefit-risk profile favored SGLT2 inhibition [71].

Empagliflozin successfully reduces the risk of cardiovascular death and heart failure hospitalizations in patients with an LVEF>40%. This protective effect is universal, appearing in both diabetic and non-diabetic patients.

3.3. SGLT2 Inhibitors Effects on Cardiac Remodelling - DAPA-MODA Trial

Despite the established clinical efficacy of dapagliflozin in heart failure, the DAPA-MODA trial sought to provide definitive evidence on whether dapagliflozin can actively modulate and reverse left atrial (LA) structural changes, offering deeper insight into its cardioprotective properties beyond simple symptom management.

The DAPA-MODA trial investigated the impact of dapagliflozin on cardiac geometry over a 6-month period in 162 patients with stable chronic heart failure. Despite receiving optimized guideline-directed medical therapy (GDMT), participants exhibited significant baseline LA dilatation (LA volume index (LAVI): 48.1 pm 22.6 mL/m²). Blinded echocardiographic analysis revealed that 180 days of dapagliflozin therapy induced substantial reverse remodeling. The primary endpoint, maximal LAVI, was significantly reduced by 6.6% (P = 0.008), driven largely by a 13.8% decrease in reservoir volume. Furthermore, favorable structural changes were observed in the left ventricle, with significant reductions in LV (Left Ventricular) mass index (-13.9%), end-diastolic volume (-8.0%), and end-systolic volume (-11.9%). These architectural improvements were mirrored by an 18.2% decline in NT-proBNP levels, although Doppler filling pressures remained unchanged [50].

In conclusion, the administration of dapagliflozin in clinically stable outpatients with chronic HF - already receiving optimized medical therapy - induces global reverse cardiac remodeling. This structural transformation is characterized by a significant reduction in LA volumes, the refinement of left ventricular LV geometry, and a concurrent decline in NT-proBNP concentrations, highlighting a profound systemic unloading effect.

3.4. SGLT2I in the Treatment of Myocardial Infarction

3.4.1 The DAPA-MI Trial

The DAPA-MI study evaluated the efficacy of dapagliflozin in the early post-infarction period among patients with no established history of diabetes or HF. While the trial demonstrated a significant improvement in cardiometabolic metrics with 10 mg of dapagliflozin, the researchers further assessed whether these outcomes were influenced by baseline LVEF, seeking to determine if the drug's impact varies according to the degree of initial cardiac dysfunction [18].

The primary efficacy endpoint was evaluated using a hierarchical win ratio analysis, which integrated a broad spectrum of clinical and metabolic events. This composite prioritized mortality, heart failure hospitalizations, and non-fatal myocardial infarctions, followed by the incidence of atrial fibrillation/flutter, new-onset type 2 diabetes, final NYHA functional class, and a significant body weight reduction of ≥5%. For the purpose of this sub-analysis, the cohort was stratified according to baseline systolic function, dichotomizing patients into those with an LVEF<50% or an LVEF≥50% [18].

Among the 3,751 DAPA-MI participants with available LVEF data, the majority (77.7%) presented with an LVEF<50%. The primary hierarchical composite outcome demonstrated a significant benefit for dapagliflozin across both LVEF subgroups, with a win ratio of 1.38 (95% CI:1.21–1.57; P < 0.001) in those with LVEF<50% and 1.32 (95% CI: 1.00–1.73; P = 0.048) in the ≥50% cohort. The non-significant interaction (P = 0.76) confirms that the treatment effect was consistent regardless of baseline systolic function. Furthermore, a sensitivity analysis excluding patients with severe dysfunction (LVEF<30%) yielded a consistent win ratio of 1.40, while secondary outcomes showed no significant interaction with LVEF levels [18].

The DAPA-MI trial provides compelling evidence that the cardiometabolic advantages of dapagliflozin are maintained across the entire spectrum of LVEF in patients recovering from an acute myocardial infarction. Regardless of whether systolic function was reduced or preserved, dapagliflozin outperformed placebo, establishing its role as a versatile and effective component of early post-infarction management, irrespective of heart function.

3.4.2. The DECLARE TIMI-58 Trial

A specialized subgroup analysis of the DECLARE-TIMI 58 trial stratified 17,160 patients based on their cardiovascular history, comparing 3,584 individuals with a prior myocardial infarction (MI) to 13,576 without. In the cohort with a history of myocardial infarction, dapagliflozin treatment was associated with a 16% relative risk reduction and a 2.6% absolute risk reduction in MACE. Interestingly, no significant MACE reduction was observed in patients with atherosclerotic cardiovascular disease ASCVD but no prior MI, nor in those with multiple risk factors only. Furthermore, the study demonstrated a significant decrease in both recurrent and Type 2 myocardial infarctions, highlighting a potential therapeutic niche for SGLT2 inhibitors where conventional antithrombotic strategies often underperform [72,73].

3.5. SGLT2 Inhibitors as Nephroprotective Agents

As stated in the previous chapter the profound nephroprotective properties of SGLT2 inhibitors are not merely localized benefits; they serve as a fundamental pillar of systemic cardioprotection. The preservation of the kidney’s filtering capacity directly mitigates neurohormonal stress and systemic congestion, thereby reducing the risk of cardiovascular death and heart failure.

3.5.1. The CREDENCE Trial

The researchers of CREDENCE investigators designed a trial specifically powered to provide definitive evidence on the renoprotective efficacy of canagliflozin in patients with type 2 diabetes and established chronic kidney disease.

In this double-blind, randomized trial, patients with type 2 diabetes and albuminuric chronic kidney disease were allocated to receive either 100 mg of once-daily canagliflozin or a matching placebo. Eligible participants were characterized by an eGFR of 30 to <90 mL/min/1.73 m² and significant albuminuria (UACR > 300 to 5000 mg/g), with all patients receiving stable doses of renin-angiotensin system blockade as the standard of care. The primary efficacy measure was a robust composite of hard renal and cardiovascular outcomes, including end-stage kidney disease (ESKD) - defined as the initiation of dialysis, transplantation, or a sustained eGFR < 15 - doubling of serum creatinine, or death from renal or cardiovascular causes [58].

The CREDENCE trial was terminated prematurely following a planned interim analysis, with 4,401 patients and a median follow-up of 2.62 years. Canagliflozin demonstrated a 30% relative risk reduction in the primary composite outcome compared to placebo (HR = 0.70; 95% CI: 0.59-0.82; P = 0.00001). Specifically,

the renal-specific composite (ESKD, doubling of creatinine, or renal death) was reduced by 34%, while the risk of progressing to end-stage kidney disease alone fell by 32%. Beyond renal protection, the treatment arm showed significantly lower rates of major adverse cardiovascular events (HR = 0.80) and a 39% decrease in heart failure hospitalizations (HR = 0.61). Notably, previous safety concerns were mitigated, as no significant differences were observed in amputation or fracture rates [58].

Ultimately, canagliflozin was found to be superior to placebo in altering the clinical trajectory of diabetic nephropathy. By lowering the risk of terminal renal failure and cardiovascular complications, the therapy provides a robust dual benefit for patients with type 2 diabetes mellitus and established kidney disease.

3.5.2 The DAPA-CKD Trial

In this multicenter, randomized trial, 4,304 participants with chronic kidney disease characterized by an eGFR of 25 to 75 mL/min/1.73 m² and significant albuminuria (UACR: 200 to 5000 mg/g) - were assigned to receive either 10 mg of daily dapagliflozin or a matching placebo. The trial's primary efficacy measure was a robust composite endpoint encompassing a sustained ⩾50 decline in eGFR, the onset of end-stage kidney disease, or mortality resulting from either renal or cardiovascular causes [15].

Due to overwhelming evidence of efficacy, the DAPA-CKD trial was terminated early upon the recommendation of the independent monitoring committee. Over a median of 2.4 years, dapagliflozin achieved a 39% relative risk reduction in the primary composite outcome (HR = 0.61; 95% CI: 0.51–0.72; P < 0.001), with a remarkably low number needed to treat (NNT) of 19. Specifically, the risk of a sustained ⩾50% eGFR decline, end-stage kidney disease, or renal death fell by 44%. Furthermore, dapagliflozin significantly lowered the risk of cardiovascular death or heart failure hospitalization (HR = 0.71) and, crucially, all-cause mortality (HR = 0.69). These benefits were consistently observed in patients both with and without type 2 diabetes, while the drug's established safety profile was reaffirmed [15].

In conclusion, the trial established that dapagliflozin significantly mitigates the primary composite risk of a sustained ⩾50% eGFR decline, end-stage kidney disease, and renal or cardiovascular mortality in patients with chronic kidney disease. Notably, these nephroprotective benefits were observed independently of baseline glycemic status, confirming that the drug's efficacy transcends the presence of type 2 diabetes.

3.5.3. The EMPA-KIDNEY Trial 14

The EMPA-KIDNEY trial was designed to assess the effects of treatment with empagliflozin in a group of patients with chronic kidney disease who are at risk for disease progression.

In the multicenter EMPA-KIDNEY trial, participants with chronic kidney disease were randomized to receive 10 mg of once-daily empagliflozin or a matching placebo. The inclusion criteria were intentionally broad, encompassing individuals with an eGFR between 20 and 45 mL/min/1.73 m², as well as those with an eGFR of 45 to 90 combined with significant albuminuria (UACR ⩾200 mg/g). The primary efficacy measure was a comprehensive composite of CKD progression - defined as end-stage kidney disease, a sustained eGFR<10, or a ⩾40% decline from baseline or cardiovascular mortality [14].

In the EMPA-KIDNEY trial, involving 6,609 participants over a median 2.0-year follow-up, empagliflozin demonstrated a 28% relative risk reduction in the primary composite of CKD progression or cardiovascular mortality compared to placebo (HR = 0.72; 95% CI: 0.64–0.82; P < 0.001). These results were notably consistent across diverse subgroups, irrespective of diabetes status or baseline eGFR levels. Furthermore, empagliflozin significantly reduced the rate of all-cause hospitalizations (HR = 0.86; P = 0.003). While the trial did not reach statistical significance for all-cause mortality or the composite of cardiovascular death and heart failure hospitalization, the overall safety profile remained excellent, with serious adverse events occurring at similar rates in both treatment arms [14].

In summary, the trial established that empagliflozin significantly mitigates the primary composite risk of CKD progression and cardiovascular mortality across a remarkably diverse population of patients.

4. Safety, Tolerability and Clinical Implementation

While the clinical benefits of SGLT2 inhibitors are unquestionable, their integration into routine practice requires a nuanced understanding of their safety profile and potential adverse effects. This chapter addresses the most common clinical concerns.

4.1. The "Initial Dip" in eGFR

Initiating SGLT2i therapy is characteristically associated with an initial hemodynamic dip in eGFR, typically ranging from 3 to 6 mL/min/1.73 m². This transient, functional decline reflects the restoration of tubuloglomerular feedback and a reduction in intraglomerular hypertension. Crucially, this early shift should be interpreted as a precursor to long-term renoprotection rather than an indicator of acute kidney injury (AKI), and it should not prompt the premature discontinuation of the treatment [74]. Following the initial hemodynamic shift, a partial recovery of the eGFR is typically observed by week 12. More significantly, the subsequent trajectory of renal function is markedly altered, with a substantial attenuation of the chronic eGFR slope. This stabilization reflects a durable nephroprotective effect that slows the progression of chronic kidney disease far more effectively than standard care [74].

The evidence base for SGLT2 inhibitors reveals slightly different starting points: dapagliflozin was studied down to an eGFR of 25 mL/min/1.73 m² in CKD and 30 mL/min/1.73 m² in HF populations, whereas empagliflozin trials (EMPEROR) included patients with filtration rates as low as 20 mL/min/1.73 m². From a management perspective, a key takeaway is that dapagliflozin does not need to be discontinued if a patient's eGFR falls below the 25 mL/min/1.73 m² mark, provided the therapy was successfully initiated above that threshold, although the treatment should be stopped if the patient progresses to dialysis [41].

4.2. Genital Infections and Volume Depletion

Due to the primary mechanism of inducing glycosuria (excreting approximately 70-80g of glucose per day), the risk of genital bacterial and mycotic infections is increased, particularly in women and uncircumcised men. While rarely life-threatening, these infections can impact treatment adherence. Practical management involves counseling on hygiene and, if necessary, standard antifungal therapy, rather than drug discontinuation [41,75]. Additionally, because of their mild osmotic diuretic effect, clinicians must exercise caution in elderly patients or those on high-dose loop diuretics to avoid symptomatic hypotension and volume depletion [76].

5. Conclusions

The clinical and pharmacological evolution of SGLT2 inhibitors represents one of the most significant paradigm shifts in modern cardiovascular medicine. Originally designed as glucose-lowering agents for the management of type 2 diabetes, gliflozins have fundamentally redefined the treatment of heart failure and chronic kidney disease. This transition from a "glucocentric" to an "organoprotective" model is supported by a robust framework of multifaceted mechanisms that transcend simple osmotic diuresis. As demonstrated throughout this work, the therapeutic value of these agents lies in their pleiotropic effects, including the optimization of myocardial bioenergetics through ketone body utilization, the stabilization of ion exchange, the restoration of tubuloglomerular feedback, reduction of epicardial adipose tissue, microbiome management and improvement in cardiac muscle remodelling. These pathways collectively alleviate the mechanical and metabolic stress on the cardiorenal system, providing a foundation for long-term structural and functional stability.

By mitigating intraglomerular hypertension and interrupting the pathological crosstalk within the cardiorenal syndrome, SGLT2 inhibitors protect the heart by ensuring a more resilient and efficient renal function. This systemic synergy explains why the benefits of gliflozins are observed so rapidly and across such diverse patient populations. Landmark trials mentioned in chapter 3. have provided irrefutable proof that these benefits are independent of the patient’s glycemic status or left ventricular ejection fraction. The ability of SGLT2 inhibitors to improve outcomes in heart failure solidifies their position as a revolutionary advancement in the field.

Furthermore, the integration of SGLT2 inhibitors into international guidelines as a mandatory pillar of heart failure therapy signifies a new standard of care. The scope of their application continues to expand, with recent data from the EMPACT-MI and DAPA-MI trials suggesting a vital role in early post-myocardial infarction stabilization. When combined with emerging insights into the gut-kidney-heart axis and the systemic anti-inflammatory potential of these agents, it becomes clear that SGLT2 inhibition is not merely a targeted intervention but a holistic metabolic strategy.

In conclusion, the shift toward early and widespread implementation of gliflozins marks a new era in which the prevention of organ decay is prioritized over the mere management of isolated symptoms, offering a profound improvement in both the survival and quality of life for millions of patients worldwide.

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