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LETTER TO THE EDITOR

Sodium-dependent glucose transporter 2 inhibitors: Transforming diabetic cardiomyopathy management

Chun-Han Cheng, Wen-Rui Hao, Tzu-Hurng Cheng

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Abstract

This article addresses the substantial findings of a study on sodium-dependent glucose transporter 2 inhibitors (SGLT2is) and their effects on myocardial function in patients with type 2 diabetes and asymptomatic heart failure. The editorial explores the broader implications of the study findings for clinical practice, thus highlighting the pivotal role of SGLT2is in improving cardiac function, reducing oxidative stress, and attenuating inflammation. It emphasizes the importance of early intervention with SGLT2is in preventing the progression of diabetic cardiomyopathy; hence, these inhibitors have the potential to transform the management of asymptomatic heart failure in patients with diabetes.

Key Words: Sodium-dependent glucose transporter 2 inhibitors; Diabetic cardiomyopathy; Asymptomatic heart failure; Cardiac function; Type 2 diabetes

Core Tip: This article emphasizes the clinical importance of sodium-dependent glucose transporter 2 inhibitors (SGLT2is) in managing myocardial function for patients with type 2 diabetes and asymptomatic heart failure. By improving cardiac function, reducing oxidative stress, and lowering inflammation, SGLT2is present a promising therapeutic strategy. Early intervention with SGLT2is can prevent the progression of diabetic cardiomyopathy, highlighting their transformative potential in the treatment of asymptomatic heart failure in patients with diabetes.

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TO THE EDITOR

Sodium-dependent glucose transporter 2 inhibitors (SGLT2is) have proven effective in managing type 2 diabetes by improving glycemic control. However, emerging research highlights their broader cardiovascular benefits. Recent studies, such as one by Grubić Rotkvić *et al*[1], demonstrate the positive impact of SGLT2is on myocardial function in patients with type 2 diabetes and asymptomatic heart failure[1]. This editorial examines these findings within the growing field of cardiovascular care advancements, emphasizing how SGLT2is's cardioprotective properties extend beyond glucose regulation. A key takeaway is that SGLT2is play a crucial role in slowing the progression of heart failure in diabetic patients, signaling a shift toward early intervention strategies. This is particularly significant for addressing diabetic cardiomyopathy, a condition characterized by structural and functional changes in the myocardium due to diabetes. The study by Grubić Rotkvić *et al*[1] reveals that SGLT2is can improve myocardial function in patients with asymptomatic heart failure[1], aligning with broader evidence from studies like those by Matthews *et al*[2], which show that SGLT2is benefit both heart and kidney health, even in non-diabetic patients[2]. Further evidence supporting the cardiovascular benefits of SGLT2is comes from a network meta-analysis by Lv *et al*[3], which highlights a reduced risk of new-onset atrial fibrillation compared to other hypoglycemic agents[3]. Understanding the mechanisms behind these effects is critical. Xie *et al*[4] discuss the clinical potential of SGLT2is to induce autophagy, a process that may slow atherosclerosis progression, a key concern in diabetic cardiomyopathy[4]. Autophagy is essential for cellular homeostasis, making this mechanism particularly relevant for long-term cardiovascular health. In addition to their heart-protective properties, SGLT2is also offer renal benefits, which are closely tied to cardiovascular health. For instance, Zhang *et al*[5] found that SGLT2is reduce renal lipid deposition and improve renal oxygenation in newly diagnosed diabetic patients [5]. These findings highlight the holistic benefits of SGLT2is, which simultaneously address cardiovascular and renal complications associated with type 2 diabetes. Overall, the study by Grubić Rotkvić *et al*[1] adds to the growing body of evidence supporting the use of SGLT2is in comprehensive cardiovascular care for diabetic patients[1]. By prioritizing early intervention and leveraging the multifaceted benefits of SGLT2is, healthcare providers can better manage diabetic cardiomyopathy and related complications. This research underscores the evolving role of SGLT2is, not only in controlling blood glucose but also in improving cardiovascular outcomes, offering new insights into the management of type 2 diabetes and its associated risks.

Mechanisms of action

SGLT2is are primarily recognized for their ability to reduce glucose reabsorption in the kidneys, thereby lowering blood sugar levels. However, their benefits extend well beyond glycemic control, particularly in the cardiovascular system. In patients with type 2 diabetes and asymptomatic heart failure, SGLT2is have been shown to enhance myocardial function through several interrelated mechanisms. One key mechanism is the reduction of oxidative stress, a major contributor to cardiac dysfunction in diabetes. SGLT2is inhibit the activity of NADPH oxidase, a key enzyme in the production of reactive oxygen species (ROS)[4]. By decreasing ROS generation, SGLT2is help preserve mitochondrial function and protect cellular integrity. This reduction in oxidative stress is crucial for maintaining the health of myocardial cells, especially in diabetic cardiomyopathy, where oxidative damage drives cardiac dysfunction. Studies have demonstrated that SGLT2is mitigate oxidative damage, improving cardiac outcomes in diabetic patients with heart failure[1]. Inflammation is another critical factor in the progression of heart failure and cardiovascular diseases. SGLT2is reduce inflammatory markers such as C-reactive protein (CRP) and interleukin-6, both of which play key roles in cardiovascular health [5]. By decreasing systemic inflammation, these inhibitors help slow the progression of heart failure. This anti-inflammatory effect improves both renal and cardiac outcomes, further supporting their cardioprotective role. In addition to these effects, SGLT2is enhance endothelial function, which is essential for maintaining vascular health. Improved endothelial function promotes better myocardial perfusion and reduces cardiac workload. Enhanced vascular function has been observed in patients treated with SGLT2is, with better myocardial outcomes, particularly in heart failure contexts[1,2]. Another important mechanism is the promotion of autophagy, a cellular process that clears damaged cells and prevents atherosclerosis progression. By inducing autophagy, SGLT2is reduce plaque formation in the vasculature and protect myocardial function[6]. This process not only prevents further oxidative damage but also improves the myocardium's ability to cope with metabolic stress, ultimately enhancing cardiac outcomes. SGLT2is also benefit myocardial energetics by promoting a metabolic shift from glucose to fatty acids and ketone bodies as energy sources.

This shift is particularly beneficial in heart failure, where the heart's energy demand often exceeds its supply. Ketone bodies, produced during periods of low glucose availability, provide a more efficient energy source for the failing heart, requiring less oxygen for ATP production compared to glucose or fatty acids. SGLT2is enhance the expression of enzymes involved in ketone body metabolism, facilitating this shift and improving cardiac efficiency[4]. By optimizing energy use, SGLT2is reduce metabolic stress on the heart, alleviating its workload and improving overall function. Finally, the renal benefits of SGLT2is indirectly contribute to cardiovascular health. These drugs reduce renal lipid deposition and improve renal oxygenation, which alleviates the burden on the heart. Improved renal function lowers blood pressure and reduces the risk of heart failure progression[5], further contributing to their cardioprotective effects. In sum, the cardioprotective mechanisms of SGLT2 inhibitors in patients with type 2 diabetes and asymptomatic heart failure are multifaceted. These drugs reduce oxidative stress and inflammation, enhance endothelial function, promote autophagy, optimize myocardial energetics, and improve renal function. Together, these mechanisms form a comprehensive cardioprotective profile[1,2].

Clinical implications

The findings have significant implications for clinical practice, particularly in the management of diabetic cardiomyopathy. SGLT2is have demonstrated promise not only in improving glycemic control but also in offering cardioprotective benefits. These drugs extend their effects beyond glucose regulation, reducing cardiovascular complications in both diabetic and non-diabetic individuals, as noted in recent research[2]. This dual action provides a critical opportunity for early intervention, especially in patients with type 2 diabetes and asymptomatic heart failure. Supporting this, evidence suggests that early use of SGLT2is can prevent the progression from asymptomatic to symptomatic heart failure, reducing the onset of conditions such as atrial fibrillation[3]. Given the high incidence of diabetic cardiomyopathy in type 2 diabetes, as highlighted in recent studies[7], early integration of SGLT2is into treatment regimens could substantially lower the long-term burden of heart failure. The cardioprotective mechanisms of these inhibitors are multifaceted, impacting several biological pathways. Research has shown that SGLT2is enhance myocardial energy metabolism, reduce myocardial fibrosis, and decrease inflammation and oxidative stress, as seen in studies on myocardial function and ventricular remodeling[6,8]. These actions collectively improve left ventricular function and mitigate adverse ventricular remodeling following acute myocardial infarction, suggesting that SGLT2is can not only halt but potentially reverse early-stage cardiac damage. Furthermore, clinical evidence demonstrates that SGLT2is improve cardiac function in diabetic patients, reducing the risk of progression to more advanced heart failure[1]. This aligns with findings showing that SGLT2is improve cardiac oxygenation and myocardial function, both crucial for preventing adverse outcomes in diabetic cardiomyopathy[5]. Also, the reduction of inflammation, as indicated in studies of inflammation and cardiovascular health, emphasizes the broad therapeutic potential of these drugs[9]. From a clinical perspective, incorporating SGLT2is into treatment protocols could significantly improve patient outcomes. By addressing both metabolic and cardiovascular factors in type 2 diabetes, this comprehensive approach leads to better long-term outcomes and reduces the incidence of heart failure. The research underscores the transformative potential of SGLT2is in managing diabetic cardiomyopathy, emphasizing the importance of early intervention in preventing disease progression.

Broader implications for cardiovascular care

The use of SGLT2is in patients with type 2 diabetes and asymptomatic heart failure offers significant public health and economic benefits, extending beyond individual patient outcomes. These medications have been shown to reduce the incidence and severity of heart failure, leading to fewer hospitalizations and decreased healthcare costs. Positive effects on myocardial function further support their inclusion in treatment guidelines for this population[1]. A key aspect of the broader cardiovascular impact of SGLT2is is their ability to prevent new-onset atrial fibrillation[3], a serious and costly complication associated with diabetes. By reducing the incidence of atrial fibrillation, SGLT2is not only improve patient outcomes but also alleviate the financial burden on healthcare systems, which must manage the high costs of arrhythmia-related complications. The pharmacoeconomic benefits of SGLT2is are especially evident in the context of heart failure. By slowing its progression, these medications reduce the frequency of acute cardiovascular events, translating into fewer hospital admissions and decreased reliance on costly interventions such as mechanical circulatory support or heart transplants. Preventing advanced heart failure and mitigating complications such as myocardial infarction lead to substantial long-term savings. Improved cardiac oxygenation and myocardial function are critical to preventing severe cardiac deterioration, as evidenced by studies showing that SGLT2is improve these key factors[5]. Mechanistically, SGLT2is offer benefits by enhancing myocardial energy metabolism, reducing fibrosis, and attenuating inflammation and oxidative stress, all of which contribute to their pharmacoeconomic advantages[6,8]. These actions not only improve left ventricular function but also promote broader cardiovascular health in diabetic patients, making SGLT2is a cost-effective addition to diabetes management. From a healthcare systems perspective, incorporating SGLT2is into treatment regimens has the potential to significantly lower costs associated with managing diabetic cardiomyopathy and related cardiovascular diseases. Research has highlighted the inflammation-reducing properties of SGLT2is, which further support their potential to reduce recurrent hospitalizations and the need for intensive medical interventions[9]. This aligns with the growing emphasis on preventive care, where early intervention can substantially reduce long-term healthcare expenditures. Largely, integrating SGLT2is into the treatment strategies for diabetic patients offers dual advantages: Improved clinical outcomes and reduced healthcare costs. Recent findings advocate for a paradigm shift in care, emphasizing the pharmacoeconomic impact of these inhibitors in managing both metabolic and cardiovascular health. By addressing not only glycemic control but also cardiovascular complications, SGLT2is provide a cost-effective and comprehensive approach to improving the quality of life for diabetic patients while alleviating financial strain on healthcare systems.

Future directions

The research on the cardiovascular benefits of SGLT2is has revealed promising findings, paving the way for further investigations into their long-term effects on heart function in patients with type 2 diabetes and asymptomatic heart failure[1]. While the short-term benefits of these inhibitors are well-established, future studies should focus on understanding their extended effects on myocardial function, particularly concerning the reduction of heart failure progression and hospitalizations. Additionally, there is a critical need to explore the role of SGLT2is in preventing adverse cardiac remodeling following acute myocardial infarction. Evidence suggests that SGLT2is may offer protective mechanisms that mitigate long-term deterioration of heart function post-infarction[8]. Understanding these effects could solidify the role of SGLT2is in post-infarction care protocols, potentially expanding their application in cardiovascular settings beyond diabetes management. Another important area for future research is optimizing the timing and dosage of SGLT2is treatment. Synthetic approaches have been proposed to enhance the clinical application of these inhibitors[4]. Investigating how these factors influence efficacy across different populations—such as those with varying stages of heart failure or comorbid conditions like hypertension—can refine clinical guidelines and ensure optimal use of SGLT2is among diverse patient groups. In addition to cardiovascular benefits, SGLT2is may offer neuroprotective effects, as shown in studies involving neurodegenerative disease models[10]. These findings suggest that SGLT2is could have clinically significant impacts on the nervous system for patients with both diabetes and neurodegenerative disorders. Expanding research to include these effects may uncover new therapeutic applications, extending the role of SGLT2is in multimodal care for diabetes and associated comorbidities. Exploring the effects of SGLT2is on other critical organ systems, particularly the kidneys, is vital. Studies indicate that SGLT2is can enhance renal function by reducing lipid deposition and cellular senescence[2,11]. This research aligns with efforts to address the complex metabolic dysfunctions associated with type 2 diabetes, where SGLT2is may play a key role in preventing kidney disease progression. Future studies should also examine how SGLT2is influence metabolic pathways, such as lipid metabolism and autophagy, with implications for conditions like atherosclerosis. Evidence suggests that SGLT2is can induce autophagy, providing a protective mechanism against atherosclerosis progression[6]. The observed benefits in metabolic health, including reductions in visceral fat and improvements in insulin sensitivity[12], further support the notion that SGLT2is are integral components of comprehensive diabetes management. Finally, advanced modeling techniques can help predict patient-specific pharmacokinetics and pharmacodynamics of SGLT2is. These models can assist in developing individualized treatment plans, ensuring that SGLT2is are administered in ways that maximize benefits for each patient. As more data becomes available, personalized treatment approaches incorporating these inhibitors can enhance patient care and reduce the risk of adverse outcomes. The growing body of clinical evidence underscores the need for SGLT2is to be integrated more broadly into clinical guidelines. These inhibitors not only provide glycemic control but also offer cardiovascular and systemic benefits, making them a cornerstone in managing diabetic cardiomyopathy and related comorbidities. By continuing to explore their diverse applications and optimizing their use, SGLT2is have the potential to revolutionize diabetes and cardiovascular care.

CONCLUSION

The study by Grubić Rotkvić *et al*[1] provides vigorous evidence supporting the efficacy of SGLT2is in enhancing myocardial function in patients with type 2 diabetes and asymptomatic heart failure[1]. The editorial tensions the multi-dimensional mechanisms through which SGLT2is exert their cardioprotective effects, including improvements in cardiac function and reductions in myocardial stress. The evidence highlights the potential of SGLT2is to not only improve glucose control but also mitigate cardiovascular complications associated with diabetes. Recent research corroborates and extends these findings (Table 1). For instance, Xu *et al*[6] demonstrated that empagliflozin, an SGLT2is, attenuates atherosclerosis progression through the induction of autophagy, suggesting that these agents may offer additional cardiovascular benefits beyond glycemic control[6]. Another study showed that SGLT2 inhibitors alleviate renal lipid deposition and improve renal oxygenation, highlighting their protective effects on kidney function, which is closely linked to cardiovascular health[5]. The metabolic advantages of SGLT2 inhibitors, including visceral fat reduction and improved metabolic dysfunction, have also been emphasized[12]. These findings align with other research showing reductions in inflammatory markers such as CRP associated with SGLT2 inhibitor use, reinforcing their role in managing systemic inflammation and metabolic disturbances in diabetes[9]. In terms of clinical implications, the early use of SGLT2is appears promising for preventing the progression of diabetic cardiomyopathy. The evidence suggests that incorporating these drugs early in treatment regimens could significantly impact cardiovascular outcomes by reducing the burden of heart failure and potentially slowing disease progression[3,8]. As research continues to evolve, SGLT2is may solidify their role as a cornerstone in managing cardiovascular risk in diabetes. Their comprehensive benefits, including cardioprotective, nephroprotective, and metabolic advantages, offer new avenues for improving patient outcomes and reducing the overall burden of cardiovascular disease in diabetic populations. Continued investigation will be essential to fully elucidate their mechanisms and optimize their use in clinical practice[13].

Table 1 Effects of sodium-dependent glucose transporter 2 inhibitors on cardiovascular outcomes in type 2 diabetes and associated conditions: A comparative analysis of clinical studies and mechanistic insights[1]

Study	Objective	Key findings	Mechanistic insights	Clinical implications
Grubić Rotkvić *et al*[1]	To assess the impact of SGLT2is on myocardial function in patients with type 2 diabetes and asymptomatic heart failure	SGLT2is improve myocardial function and reduce heart failure symptoms	Enhanced myocardial metabolism and reduced cardiac stress	Potential benefits for patients with asymptomatic heart failure, suggesting a need for broader use in heart failure management
Lv *et al*[3]	To evaluate the effect of various hypoglycemic agents on the risk of new-onset atrial fibrillation	SGLT2is are associated with a lower risk of new-onset atrial fibrillation compared to other hypoglycemic agents	Reduced atrial fibrillation risk may be linked to improved glycemic control and cardiovascular stability	SGLT2is may be preferred in diabetic patients with a high risk of atrial fibrillation
Xie and Zhao[4]	To review the synthetic approaches and clinical applications of SGLT2is	SGLT2is show significant promise in managing type 2 diabetes and associated cardiovascular conditions	Inhibition of glucose reabsorption leads to improved cardiovascular outcomes and reduced oxidative stress	Highlights the growing role of SGLT2is in comprehensive diabetes care
Zeng *et al*[11]	To investigate the effects of SGLT2is on kidney senescence in an animal model	SGLT2is down-regulate latent transforming growth factor beta binding protein 2 expression, improving kidney function and reducing senescence	Modulation of renal fibrosis pathways and oxidative stress reduction	Potential benefits for preventing kidney disease progression in diabetic patients
Xu *et al*[6]	To explore the impact of empagliflozin on atherosclerosis progression	Empagliflozin attenuates atherosclerosis by inducing autophagy	Activation of autophagic pathways that counteract atherosclerotic changes	Empagliflozin may offer cardiovascular protection beyond glycemic control
Zhang *et al*[5]	To evaluate the effects of SGLT2is on renal lipid deposition and oxygenation in newly diagnosed type 2 diabetes patients	SGLT2is reduce renal lipid deposition and improve renal oxygenation levels	Enhanced renal metabolism and oxygenation may prevent renal complications	Supports the use of SGLT2is for improving renal health in diabetes
Tsukagoshi-Yamaguchi *et al*[12]	To analyze metabolomic changes associated with ipragliflozin and metformin treatment	Ipragliflozin leads to visceral fat reduction and improved metabolic profiles	Alterations in metabolite profiles associated with fat metabolism and reduction	Highlights ipragliflozin's potential in managing metabolic syndrome components in diabetes
Matthews *et al*[2]	To review the impact of SGLT2is on cardiovascular and renal outcomes irrespective of diabetes status	SGLT2is show beneficial effects on heart and kidney health even in non-diabetic populations	Cardiovascular and renal protective effects are due to mechanisms beyond glucose control	Supports broader application of SGLT2is in heart and kidney disease management
Ünal *et al*[10]	To evaluate neuroprotective effects of empagliflozin in a Parkinson's disease model	Empagliflozin shows neuroprotective effects through ketogenesis and autophagy	Involvement of ketogenesis and autophagy in mitigating neurodegenerative processes	Suggests potential for SGLT2is in neurodegenerative diseases
Chen *et al*[8]	To assess the impact of SGLT2is-pretreated macrophage transplantation on ventricular remodeling post-myocardial infarction	SGLT2is pretreatment improves ventricular remodeling and reduces adverse outcomes	Enhanced macrophage function and reduced myocardial fibrosis	Potential use of SGLT2is in post-infarction recovery strategies

[1]This table provides a comparative analysis of recent clinical studies examining the impact of sodium-dependent glucose transporter 2 inhibitors (SGLT2is) on cardiovascular outcomes in patients with type 2 diabetes and related conditions. It includes information on study objectives, key findings, mechanistic insights, and clinical implications. The findings demonstrate the benefits of SGLT2is in improving myocardial function, reducing the risk of atrial fibrillation, attenuating atherosclerosis, and enhancing renal and metabolic health. The table captures the diverse effects of these inhibitors on cardiovascular and systemic health beyond their role in glucose management. SGLT2is: Sodium-dependent glucose transporter 2 inhibitors.

FOOTNOTES

Author contributions: All authors have made significant contributions to this editorial. Cheng CH and Hao WR contributed equally as co-first authors, jointly responsible for the conceptualization and initial drafting of the manuscript. Cheng CH focused on synthesizing the literature on SGLT2 inhibitors and their impact on myocardial function, while Hao WR provided clinical insights and critically assessed the therapeutic implications for diabetic cardiomyopathy; Cheng TH supervised the overall development and progression of the editorial, offering substantial input on revisions, particularly in the discussion of molecular mechanisms and potential clinical applications; Cheng TH also provided critical guidance on refining the manuscript's structure and flow to ensure clarity and coherence. All authors contributed to the final content by revising the manuscript for intellectual content and accuracy. They have all reviewed and approved the final version, ensuring that it meets the journal's requirements.

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