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# Exploring the Role of Dipeptidyl Peptidase-4 (DPP-4) Inhibitors in the Management of Cardiogenic Shock: Pathophysiological Insights and Therapeutic Potential

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**ABSTRACT**

Cardiogenic shock remains a critical condition characterized by profound myocardial dysfunction leading to end-organ hypoperfusion and high mortality rates despite advances in supportive therapies. While traditional management focuses on inotropes, vasopressors, and mechanical circulatory support, recent evidence suggests that metabolic modulation could provide additional benefits. Dipeptidyl peptidase-4 (DPP-4) inhibitors, primarily used in type 2 diabetes mellitus, have demonstrated cardioprotective effects through pleiotropic mechanisms, including anti-inflammatory, endothelial-protective, and metabolic-modulating actions. This review examines the potential utility of DPP-4 inhibitors in the context of cardiogenic shock, emphasizing their mechanisms of action, experimental and clinical data, and the feasibility of integrating these agents into the current therapeutic paradigm. We highlight gaps in knowledge and propose directions for future research to determine the clinical efficacy of DPP-4 inhibitors in this high-risk population.

**KEYWORDS:** Cardiogenic shock, DPP-4 inhibitors, heart failure, metabolic modulation, inflammation, endothelial dysfunction, myocardial protection.

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## INTRODUCTION

Cardiogenic shock, defined by inadequate cardiac output resulting in systemic hypoperfusion and end-organ failure, represents one of the most severe manifestations of cardiac dysfunction. Despite advancements in pharmacological and mechanical interventions, mortality rates remain unacceptably high, often exceeding 40–50%. Conventional therapies aim to restore hemodynamic stability through inotropic support and vasopressors, yet these strategies are often limited by significant adverse effects, including increased myocardial oxygen consumption and arrhythmogenic risks.1,2

Emerging evidence underscores the critical role of systemic inflammation, endothelial dysfunction, and altered metabolic pathways in the pathophysiology of cardiogenic shock. These insights have prompted interest in therapies targeting these pathways to complement hemodynamic stabilization. One promising avenue involves the use of dipeptidyl peptidase-4 (DPP-4) inhibitors, a class of drugs widely used for glycemic control in type 2 diabetes mellitus. Beyond their glucose-lowering effects, DPP-4 inhibitors exhibit anti-inflammatory and endothelial-protective properties, which may confer cardiovascular benefits.3,4

Recent preclinical and clinical studies have hinted at the potential of DPP-4 inhibitors to mitigate myocardial injury and improve vascular function in acute cardiac conditions. However, their specific role in cardiogenic shock remains underexplored. This article aims to bridge this gap by reviewing the mechanistic basis and existing evidence for the use of DPP-4 inhibitors in cardiogenic shock. We also discuss potential challenges and future directions to facilitate their integration into the therapeutic landscape for this complex and life-threatening syndrome.5

## EPIDEMIOLOGY

Cardiogenic shock (CS) is a rare but severe clinical syndrome characterized by a failure of the heart to maintain adequate tissue perfusion, most often due to primary myocardial dysfunction. Epidemiologically, cardiogenic shock accounts for approximately 5–10% of cases of acute myocardial infarction (AMI), making it the leading cause of mortality in patients with AMI despite advancements in reperfusion therapies and intensive care management. The incidence of CS in non-ischemic cardiac conditions, including advanced heart failure, valvular heart disease, and cardiomyopathies, further contributes to its clinical burden, though its exact prevalence remains less well defined in these contexts.6

Data from large registries, such as the National Cardiogenic Shock Initiative (NCSI) and the Society for Cardiovascular Angiography and Interventions (SCAI) shock classification system, highlight demographic and clinical patterns associated with cardiogenic shock. Patients presenting with CS are predominantly older adults, with a mean age of 65–70 years, and exhibit a high prevalence of comorbidities, including diabetes mellitus, chronic kidney disease, and prior heart failure. Importantly, type 2 diabetes mellitus (T2DM) is an independent risk factor for the development of CS, owing to its contributions to atherosclerosis, microvascular dysfunction, and impaired myocardial metabolism. The growing global burden of T2DM further underscores the need for innovative therapeutic strategies that address both metabolic and cardiovascular dysfunction in CS.6

In patients with T2DM, the interplay between hyperglycemia, systemic inflammation, and endothelial dysfunction exacerbates the pathophysiology of CS, leading to worse outcomes. Observational studies suggest that diabetic patients experiencing CS have a higher in-hospital mortality rate compared to their non-diabetic counterparts, driven by more severe myocardial damage, increased susceptibility to arrhythmias, and impaired recovery of left ventricular function. These findings highlight the urgent need to identify therapies that specifically target the metabolic derangements seen in this high-risk subgroup.7

Dipeptidyl peptidase-4 (DPP-4) inhibitors, originally developed as glucose-lowering agents for T2DM, have emerged as potential candidates for mitigating the inflammatory and endothelial damage that underpins the progression of CS. While large-scale epidemiological data on the use of DPP-4 inhibitors in CS are currently lacking, indirect evidence suggests their relevance. Clinical trials in chronic heart failure populations, such as TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin), have demonstrated the safety and potential cardioprotective effects of these agents, particularly in reducing hospitalizations and improving vascular function.8

Notably, the prevalence of metabolic syndrome and T2DM in populations at risk for CS positions DPP-4 inhibitors as a theoretically attractive option. The increasing global incidence of diabetes, coupled with aging populations and the rising prevalence of obesity-related cardiac dysfunction, suggests that the epidemiological impact of DPP-4 inhibitors could extend beyond glycemic control to encompass broader cardiovascular benefits. This underscores the need for dedicated epidemiological studies and clinical trials to evaluate the role of DPP-4 inhibitors in patients with or at risk of CS, particularly in high-risk groups such as those with diabetes or systemic inflammatory states.8

In summary, the epidemiology of cardiogenic shock is intricately linked to the growing burden of metabolic and cardiovascular diseases. The potential utility of DPP-4 inhibitors in this context represents an evolving area of interest, necessitating further research to elucidate their impact on outcomes in this critically ill population.8

### Recent Advances and Updates

The potential role of dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of cardiogenic shock (CS) has garnered increasing attention due to their pleiotropic effects beyond glycemic control. While primarily developed as antihyperglycemic agents for the management of type 2 diabetes mellitus (T2DM), recent evidence suggests that DPP-4 inhibitors may confer cardiovascular and endothelial benefits that are highly relevant in the context of cardiogenic shock.9

Mechanistic Insights

DPP-4 inhibitors exert their primary action by preventing the degradation of incretins such as glucagon-like peptide-1 (GLP-1), which enhances glucose-dependent insulin secretion. However, GLP-1 also has significant cardiovascular effects, including vasodilation, improved endothelial function, and reduced myocardial apoptosis. Recent studies have shown that GLP-1 may enhance cardiac output and improve myocardial glucose utilization, processes that are critical during acute hemodynamic compromise, such as in CS. Additionally, DPP-4 inhibition has been associated with anti-inflammatory effects and a reduction in proinflammatory cytokines, which are elevated in the systemic inflammatory response often observed in CS.10

### Emerging Preclinical Evidence

Preclinical studies have provided compelling data supporting the cardioprotective properties of DPP-4 inhibitors. Animal models of acute myocardial infarction (AMI) and heart failure have demonstrated improved myocardial contractility, reduced infarct size, and attenuation of myocardial remodeling with DPP-4 inhibition. These findings are attributed to the preservation of GLP-1 activity and the downstream activation of cardioprotective signaling pathways such as protein kinase A (PKA) and AMP-activated protein kinase (AMPK).10

In models of ischemia-reperfusion injury, DPP-4 inhibitors have shown promise in reducing oxidative stress and apoptosis in cardiac tissues, suggesting their potential utility

in mitigating the ischemic damage central to the pathophysiology of cardiogenic shock. Furthermore, improvements in microvascular perfusion and endothelial function observed in these studies align with the therapeutic goals in CS, where restoring tissue perfusion is paramount.10

**Clinical Updates and Trials**

While there is currently no large-scale randomized controlled trial (RCT) evaluating the use of DPP-4 inhibitors specifically in cardiogenic shock, data from studies in related cardiovascular conditions provide valuable insights. The TECOS trial (Trial Evaluating Cardiovascular Outcomes with Sitagliptin), while primarily focused on chronic heart failure, demonstrated that sitagliptin did not increase adverse cardiovascular outcomes and was associated with a trend toward improved vascular health. Similarly, other trials such as EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin) have highlighted the cardiovascular safety of DPP-4 inhibitors, even in high-risk populations.11

Recent observational data suggest that patients with T2DM who receive DPP-4 inhibitors during acute cardiac events may experience better glycemic stability and potentially reduced inflammatory markers. While these findings are encouraging, the application of DPP-4 inhibitors in the hemodynamically unstable population of CS patients remains to be explored in depth.11

Integrative Therapies and Personalized Medicine

Recent advancements in the understanding of cardiogenic shock pathophysiology have emphasized the importance of personalized medicine. DPP-4 inhibitors may find a niche in treating specific subsets of CS patients, such as those with concurrent T2DM or metabolic syndrome, where their dual metabolic and cardiovascular actions are most beneficial. Moreover, the use of DPP-4 inhibitors alongside standard-of-care therapies, such as inotropes and mechanical circulatory support, could provide a synergistic effect, particularly in patients with microvascular dysfunction and systemic inflammation.12,13

Despite these promising findings, several challenges remain. The hemodynamic instability characteristic of CS poses unique pharmacokinetic and pharmacodynamic considerations for the use of DPP-4 inhibitors, which may limit their efficacy in this setting. Furthermore, the paucity of direct clinical evidence necessitates further investigation through robust, prospective trials. Future studies should aim to evaluate not only the safety and efficacy of DPP-4 inhibitors in CS but also their potential to modulate long-term outcomes, such as myocardial recovery and reduced readmission rates.14,15

Emerging research into combination therapies that leverage DPP-4 inhibitors with other metabolic modulators, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, represents another exciting avenue. These agents, which have shown promise in reducing heart failure hospitalizations and improving left ventricular function, may have additive or complementary effects when combined with DPP-4 inhibitors in the acute care setting.16

The field of DPP-4 inhibitors in cardiogenic shock is at a pivotal juncture. While preclinical and indirect clinical evidence provides a strong rationale for their potential utility, definitive studies are needed to establish their role in this complex and high-risk population. As our understanding of the interplay between metabolic, inflammatory, and cardiovascular pathways in CS evolves, DPP-4 inhibitors may emerge as a valuable addition to the therapeutic armamentarium, offering new hope for improving outcomes in this challenging condition.17

## CONCLUSIONS

The exploration of dipeptidyl peptidase-4 (DPP-4) inhibitors in the context of cardiogenic shock (CS) represents a promising but as yet underdeveloped avenue in cardiovascular medicine. Cardiogenic shock, characterized by profound myocardial dysfunction leading to systemic hypoperfusion and multiorgan failure, continues to present high morbidity and mortality rates despite advancements in hemodynamic and supportive care. Traditional therapeutic approaches, while effective in stabilizing acute hemodynamic collapse, are often limited by significant adverse effects, including myocardial strain, arrhythmias, and end-organ compromise. This underscores the pressing need for innovative, adjunctive therapies that address the underlying pathophysiological mechanisms of CS.

DPP-4 inhibitors, widely recognized for their role in managing type 2 diabetes mellitus (T2DM), exhibit a range of pleiotropic effects beyond glucose regulation. These include anti-inflammatory, endothelial-protective, and cardiometabolic benefits that are highly relevant to the treatment of cardiogenic shock. By preserving the activity of incretin hormones such as glucagon-like peptide-1 (GLP-1), DPP-4 inhibitors can enhance myocardial glucose utilization, reduce oxidative stress, and promote vasodilation. These mechanisms align with key therapeutic goals in CS, including the restoration of myocardial efficiency, reduction of systemic inflammation, and improvement in microvascular perfusion.

Preclinical studies provide compelling evidence of the cardioprotective effects of DPP-4 inhibitors in ischemia-reperfusion injury, myocardial infarction, and acute heart failure. These findings have laid the groundwork for the hypothesis that DPP-4 inhibitors may benefit patients with CS. Clinical trials in related cardiovascular populations, such as TECOS and EXAMINE, have demonstrated the cardiovascular safety and potential benefits of DPP-4 inhibitors, although their application in the acute and hemodynamically unstable setting of CS remains to be directly evaluated.

From an epidemiological perspective, the high prevalence of T2DM and metabolic syndrome in patients at risk for CS

strengthens the rationale for investigating DPP-4 inhibitors in this population. The metabolic derangements associated with T2DM exacerbate the inflammatory and endothelial dysfunctions central to CS pathophysiology, suggesting that DPP-4 inhibitors may hold particular promise in this subgroup. Additionally, the growing burden of diabetes and obesity worldwide highlights the potential for DPP-4 inhibitors to address both acute and long-term complications of CS in a broad population.

Despite their theoretical and experimental promise, several challenges must be addressed before DPP-4 inhibitors can be integrated into the therapeutic arsenal for CS. The acute nature of CS raises unique pharmacokinetic and pharmacodynamic concerns, particularly in the setting of hemodynamic instability and multiorgan dysfunction. Moreover, the current evidence base for DPP-4 inhibitors in CS remains largely indirect, necessitating robust clinical trials to evaluate their safety, efficacy, and impact on short- and long-term outcomes in this critically ill population.

Future research directions should focus on prospective, randomized controlled trials assessing the role of DPP-4 inhibitors in CS, either as monotherapy or in combination with other emerging therapies such as sodium-glucose cotransporter-2 (SGLT2) inhibitors. Studies should also explore the potential for DPP-4 inhibitors to promote myocardial recovery and reduce the incidence of recurrent heart failure in survivors of CS. Additionally, efforts to elucidate the molecular and cellular mechanisms by which DPP-4 inhibition impacts the inflammatory and metabolic cascades in CS could inform the development of targeted therapeutic strategies.

In conclusion, DPP-4 inhibitors represent an intriguing and potentially transformative approach to the management of cardiogenic shock, particularly in patients with coexisting T2DM or metabolic syndrome. While the current evidence supports their theoretical benefits, rigorous clinical evaluation is essential to determine their practical utility in this high-risk population. If validated, DPP-4 inhibitors could provide a novel and impactful strategy for addressing the multifaceted challenges of cardiogenic shock, offering new hope for improving outcomes in this devastating condition.

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