Journal of Asian-African focus in Health

ISSN: 2987-9418
Vol. 4 No. 2, 2026
Page: 15-26

The Role of SGLT2 Inhibitors and GLP-1 Receptor Agonists in Preventing Cardiovascular Complications in Type 2 Diabetes Mellitus

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Article Info

Article History:

Received June 27, 2026
Revised July 20, 2026
Accepted: August 25, 2026

Keywords:

Type 2 Diabetes Mellitus Cardiovascular Disease, SGLT2 Inhibitors, GLP-1 Receptor Agonists, Prevention of Cardiovascular Complications.

Abstract

Type 2 diabetes mellitus is one of the leading causes of morbidity and mortality associated with cardiovascular complications. Advances in antihyperglycemic therapy have demonstrated that sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists) not only improve glycemic control but also play an important role in preventing cardiovascular complications. However, evidence regarding their mechanisms of action, clinical benefits, and roles in cardiovascular prevention remains scattered across the literature. Objective of the research to review the current scientific evidence regarding the role of SGLT2 inhibitors and GLP-1 receptor agonists in preventing cardiovascular complications in patients with type 2 diabetes mellitus based on published studies. This study employed a narrative literature review using a systematic literature search approach. A literature search was conducted in the PubMed database for articles published between 2021 and 2026, following the PRISMA 2020 guidelines. A total of 15 eligible articles were included, comprising randomized controlled trials, cohort studies, observational studies, systematic reviews, meta-analyses, and post-hoc analyses. Results of the research showed that the synthesis of the included studies demonstrated that SGLT2 inhibitors consistently reduced the risk of hospitalization for heart failure, major adverse cardiovascular events (MACE), cardiovascular mortality, and the progression of chronic kidney disease. In contrast, GLP-1 receptor agonists were more effective in reducing atherosclerotic cardiovascular events through improvements in vascular function and metabolic risk factors. Several studies also suggested that combination therapy with both drug classes may provide greater cardiorenal benefits than monotherapy. SGLT2 inhibitors and GLP-1 receptor agonists have complementary roles in preventing cardiovascular complications in patients with type 2 diabetes mellitus. Therapeutic selection should be individualized according to patients' clinical characteristics and cardiovascular risk profiles to optimize cardiorenal outcomes.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia due to impaired insulin secretion, insulin action, or both (Hamzah, 2024; American Diabetes Association, 2025). Type 2 diabetes mellitus (T2DM) is the most common form and is a global health challenge due to its increasing prevalence. According to the International Diabetes Federation (IDF), in 2024, there were an estimated 589 million people with diabetes aged 20–79 years worldwide, and this number is projected to increase to 852.5 million by 2050. In addition to increasing morbidity and mortality rates, diabetes also poses a significant economic burden due to the high need for health services and the long-term complications that accompany it (Davies et al., 2022; International Diabetes Federation, 2025). Indonesia is among the

DOI: https://doi.org/10.71435/741778

countries with the highest number of people with diabetes in the world, with an estimated 20.4 million cases in 2024 and a projected increase to 28.6 million by 2050. The high proportion of undiagnosed cases indicates that diabetes remains a public health problem that requires serious attention (International Diabetes Federation, 2025).

Cardiovascular complications are a major cause of morbidity and mortality in patients with diabetes mellitus (Siam et al., 2024). Chronic hyperglycemia causes progressive damage to the vascular system through angiopathy involving both large and small blood vessels. This condition is triggered by various pathophysiological mechanisms, including the formation of advanced glycation end products (AGEs), increased oxidative stress, activation of inflammatory mediators, and endothelial dysfunction, which accelerates atherosclerosis (Joseph et al., 2022; Lindarto, 2024). Furthermore, dyslipidemia, which often accompanies diabetes mellitus, accelerates the atherosclerosis process through impaired lipid metabolism, thereby increasing the risk of various cardiovascular complications (Lindarto, 2024). These conditions make atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease the main comorbidities that significantly impact the clinical outcomes of patients with type 2 diabetes mellitus (Hidayatullah et al., 2022).

Numerous cardiovascular outcome trials published over the past decade have shifted the paradigm of type 2 diabetes mellitus therapy (Davies et al., 2022; Wilding et al., 2022; Sinha, 2026). Therapeutic approaches are no longer solely oriented toward glycemic control but also directed toward reducing the risk of cardiovascular complications and providing cardiorenal benefits. Several studies have shown that SGLT2 inhibitors and GLP-1 receptor agonists can reduce major adverse cardiovascular events (MACE), the risk of hospitalization for heart failure, and slow the progression of chronic kidney disease in patients with type 2 diabetes mellitus at high cardiovascular risk (Marx et al., 2023).

Although several studies have demonstrated the benefits of SGLT2 inhibitors and GLP-1 receptor agonists in reducing the risk of cardiovascular complications in patients with type 2 diabetes mellitus, most studies have only evaluated the effectiveness of each therapy on specific cardiovascular outcomes (Li et al., 2022; Neuen et al., 2024; Colombijn et al., 2026). Consequently, few studies have comprehensively integrated the current evidence regarding the mechanisms of action, clinical benefits, and role of these two drug classes in the prevention of cardiovascular complications (McGuire et al., 2021; Patorno et al., 2022). Therefore, this article aims to review the current scientific evidence regarding the role of SGLT2 inhibitors and GLP-1 receptor agonists in the prevention of cardiovascular complications in patients with type 2 diabetes mellitus, based on published research results.

Method

Study Design

This study employed a narrative literature review using a systematic literature search approach to examine the current scientific evidence regarding the role of sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor (GLP-1 receptor) agonists in preventing cardiovascular complications among patients with type 2 diabetes mellitus (T2DM). The identification, screening, and selection of relevant literature were conducted systematically based on the PRISMA 2020 guidelines to enhance transparency and reproducibility in the literature selection process. However, because this study was designed as a narrative literature review rather than a systematic review, no formal critical appraisal or risk-of-bias assessment was performed for the included studies.

DOI: https://doi.org/10.71435/741778

Literature Search Strategy

The literature search was conducted using the PubMed database to identify relevant articles published between 2021 and 2026. The search was restricted to English-language publications involving human subjects. The search strategy employed Boolean operators (AND and OR) and consisted of three main combinations: ("Diabetes Mellitus, Type 2"[Mesh]) AND ("Cardiovascular Diseases"[Mesh]) AND ("SGLT2 inhibitor" OR "GLP-1 receptor agonist"); ("Diabetes Mellitus, Type 2"[Mesh]) AND ("SGLT2 inhibitor") AND ("Cardiovascular Diseases"[Mesh]); and ("Diabetes Mellitus, Type 2"[Mesh]) AND ("GLP-1 receptor agonist") AND ("Cardiovascular Diseases"[Mesh] OR MACE). Medical Subject Headings (MeSH) terms were incorporated into the search strategy to improve the precision and relevance of article retrieval in accordance with the research objectives.

Eligibility Criteria and Evidence Selection

The inclusion criteria comprised original studies employing randomized controlled trial (RCT), prospective or retrospective cohort, case-control, cross-sectional, and observational designs that evaluated the use of SGLT2 inhibitors and/or GLP-1 receptor agonists in relation to cardiovascular outcomes among patients with T2DM. Systematic reviews and meta-analyses were also considered as supporting references for the synthesis and interpretation of the available evidence. Eligible studies involved adult patients with T2DM who had established atherosclerotic cardiovascular disease, heart failure, peripheral arterial disease, or a high risk of cardiovascular complications. Studies were required to be available in full text and to address at least one of the following aspects: mechanism of action, clinical effectiveness, or cardiovascular outcomes associated with SGLT2 inhibitors and/or GLP-1 receptor agonists.

Studies were excluded if they were published before 2021, were not available in full text, or were published as case reports, editorials, letters to the editor, commentaries, conference abstracts without full manuscripts, or grey literature. Experimental animal and in vitro studies were also excluded. In addition, articles that did not specifically examine SGLT2 inhibitors or GLP-1 receptor agonists in relation to the prevention of cardiovascular complications in patients with T2DM were excluded from the review.

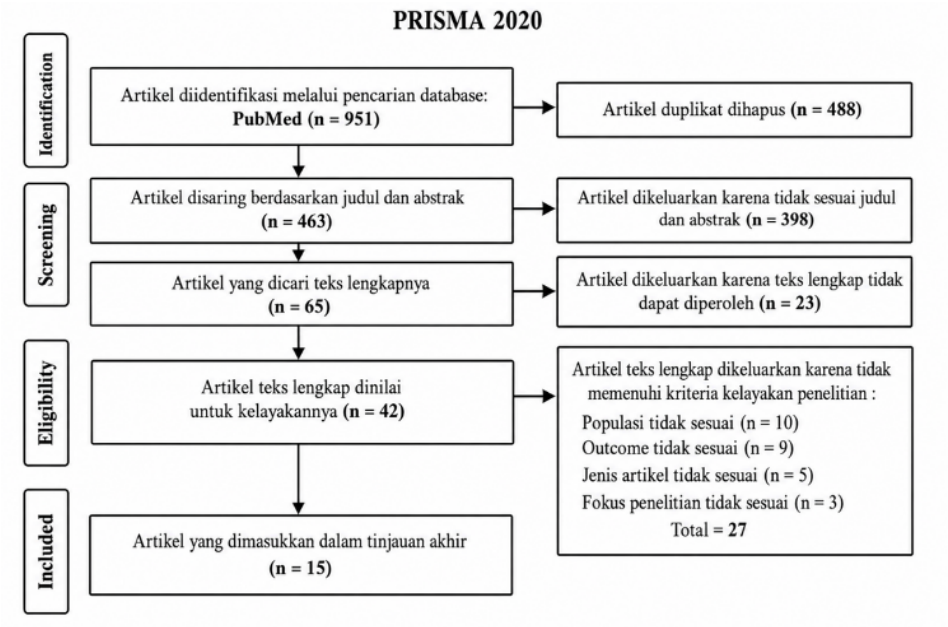

Figure 1. PRISMA 2020 Data Analysis Techniques

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Result and Discussion

Based on the literature selection process according to the 2020 PRISMA guidelines, 15 articles met the inclusion criteria, consisting of 12 primary studies and 3 secondary studies published between 2021 and 2026. The characteristics of the primary and secondary studies are presented in Tables 1 and 2.

Table 1. Characteristics of Primary Studies in Humans

Author (Year)	Research Design	Population	Drug Exposure/Dose	Outcome	Key Findings
Thirunavukarasu et al. (2021)	Longitudinal prospective cohort	18 type 2 DM patients	Empagliflozin 10 mg for 12 weeks	Cardiac function, myocardial metabolism, NT-proBNP	Empagliflozin improves myocardial metabolism, improves left ventricular function, and lowers NT-proBNP.
Sørensen et al. (2025)	National cohort-based target emulation trial	25,753 type 2 DM patients	GLP-1 receptor agonists vs. DPP-4 inhibitors	3P-MACE, mortality, heart failure	Continuous use of GLP-1 RAs reduces the risk of MACE, mortality, and heart failure compared to DPP-4 inhibitors.
Takahashi et al. (2024)	Nested retrospective case-control study	11,209 patients with type 2 diabetes	SGLT2 inhibitors	Heart failure hospitalizations	Long-term use of SGLT2 inhibitors reduces the risk of hospitalization for heart failure, and the benefits increase with the duration of therapy.
Nakai et al. (2022)	Propensity score-matched retrospective cohort	Heart failure patients with type 2 diabetes	SGLT2 inhibitors vs DPP-4 inhibitors	Mortality and heart failure hospitalizations	SGLT2 inhibitors reduce mortality and hospitalization for heart failure compared to DPP-4 inhibitors.
Kaku et al. (2022)	Post-hoc analysis of the EMPA-REG OUTCOME RCT	7,020 type 2 DM patients with ASCVD	Empagliflozin 10/25 mg	MACE, hospitalization, mortality	Empagliflozin consistently reduced cardiovascular events and hospitalizations in both Asian and non-Asian populations.
Wang et al. (2023)	Database-based retrospective cohort	313,396 type 2 DM patients	SGLT2 inhibitors	Cardiovascular disease, heart failure, stroke, myocardial infarction	SGLT2 inhibitors are associated with a lower risk of cardiovascular disease compared to other second-

DOI: https://doi.org/10.71435/741778

					line antidiabetic therapies.
Zehra et al. (2026)	Target trial emulation	137,232 type 2 DM patients	Canagliflozin, dapagliflozin, empagliflozin	MACE, mortality	Empagliflozin was slightly superior to canagliflozin, while all SGLT2 inhibitors showed comparable cardiovascular efficacy.
Nguyen et al. (2025)	Post-hoc pooled analysis of the CANVAS and CREDENCE RCTs	14,543 type 2 diabetes patients	Canagliflozin	MACE, mortality, safety	Canagliflozin provides consistent cardiovascular benefits in both frail and non-frail patients without increasing significant side effects.
Guo et al. (2025)	Kohort retrospektif propensity score-matched	Type 2 diabetes patients with high HbA1c variability	SGLT2 inhibitors vs. DPP-4 inhibitors	HbA1c variability, cardiovascular and renal outcomes	SGLT2 inhibitors reduce HbA1c variability and improve cardiovascular and renal outcomes compared to DPP-4 inhibitors.
Sun et al. (2022)	Kohort propensity score-matched	29,309 type 2 diabetes patients	Early initiation of SGLT2 inhibitors	MACE	Early initiation of SGLT2 inhibitors reduces the risk of MACE in type 2 DM patients with or at risk of ASCVD.
Neves et al. (2023)	Post hoc analysis of RCTs and meta-analysis at the trial level	13,538 type 2 diabetes patients	GLP-1 RA with or without an SGLT2 inhibitor	MACE, heart failure hospitalization	GLP-1 RA still provides cardiovascular benefits despite the use of SGLT2 inhibitors and has the potential to provide additional benefits when combined.
Patorno et al. (2022)	Retrospective propensity score-matched cohort (EMPRISE)	39,072 type 2 DM patients	Empagliflozin vs. DPP-4 inhibitors	Heart failure hospitalization, mortality, safety	Empagliflozin reduces the risk of heart failure hospitalization and mortality with a good safety profile in routine clinical practice.

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Table 2. Characteristics of Systematic Review and Meta-Analysis

Author (Year)	Article Type	Focus	Main Conclusion
Ahmed et al. (2025)	Systematic Review dan Meta-analysis RCT	Comparison of SGLT2 inhibitors and GLP-1 RAs against MACE	GLP-1 RAs provided greater reductions in MACE, while SGLT2 inhibitors were superior in preventing heart failure and kidney outcomes.
Colombijn et al. (2025)	Systematic Review dan Meta-analysis	Combination of SGLT2 inhibitors and GLP-1 RAs	The combination of an SGLT2 inhibitor and a GLP-1 RA reduced the risk of MACE, mortality, heart failure hospitalizations, and kidney outcomes compared to monotherapy.
Kongmalai et al. (2023)	Systematic Review dan Network Meta-analysis	Comparison of the effectiveness of each SGLT2 inhibitor	All SGLT2 inhibitors provided cardiovascular benefits, with canagliflozin demonstrating greater relative efficacy for several heart failure outcomes.

Mechanisms and Clinical Benefits of SGLT2 Inhibitors

Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) are a class of antihyperglycemic drugs that work by inhibiting glucose reabsorption in the proximal renal tubule, thereby increasing glucose excretion in the urine. In addition to improving glycemic control, this mechanism increases natriuresis and osmotic diuresis, contributing to reduced intravascular volume, cardiac preload, and afterload. Several studies have shown that the benefits of SGLT2 inhibitors extend beyond blood glucose-lowering effects through pleiotropic mechanisms such as improved myocardial metabolism, reduced oxidative stress and inflammation, and inhibition of myocardial fibrosis. These effects result in protection of the cardiovascular system and kidneys, and SGLT2 inhibitors are now considered a therapy with significant cardiorenal benefits in patients with type 2 diabetes mellitus (Marx et al., 2023; Ahmed et al., 2026).

The cardioprotective effects of SGLT2 inhibitors result from the interaction of several interrelated physiological mechanisms. Natriuresis and osmotic diuresis reduce congestion and decrease cardiac workload, while shifting energy substrate utilization toward ketone bodies improves myocardial metabolic efficiency. In addition, reduced inflammation, oxidative stress, and myocardial remodeling contribute to improved cardiac structure and function. The findings of Thirunavukarasu et al., which demonstrated improved left ventricular function accompanied by reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels after empagliflozin administration, further strengthen the evidence that the cardioprotective benefits of SGLT2

DOI: https://doi.org/10.71435/741778

inhibitors are not solely related to glycemic control but also through direct effects on the myocardium and cardiovascular system (Marx, et al., 2023; Neves et al., 2023). The consistency of these benefits has been demonstrated in various clinical trials, cohort studies, real-world evidence-based research, and meta-analyses. The EMPA-REG OUTCOME analysis demonstrated that empagliflozin reduced major adverse cardiovascular events (MACE), cardiovascular mortality, and the risk of hospitalization due to heart failure in patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. These results are consistent with studies by Wang et al. (2023), Takahashi et al. (2024), Nakai et al. (2022) and the EMPRISE study, which consistently demonstrated a reduced risk of heart failure, mortality, and cardiovascular outcomes across various patient populations. Furthermore, studies by Guo et al., Nguyen et al., and Sun et al. demonstrated that the benefits of SGLT2 inhibitors also include improved metabolic outcomes, kidney protection, and a reduced risk of MACE, while a meta-analysis by Kongmalai et al. confirmed that these benefits are consistent across all classes of SGLT2 inhibitors, although the effectiveness of each agent on specific outcomes may vary (McGuire et al., 2021; Patorno et al., 2022).

Based on the synthesis of various scientific evidence, the benefits of SGLT2 inhibitors are no longer viewed solely because of blood glucose control, but rather as the result of an integration of hemodynamic, metabolic, anti-inflammatory, and nephroprotective effects that collectively reduce the risk of cardiovascular complications. The consistency of results across various study designs reinforces the role of SGLT2 inhibitors as primary therapy in the prevention of cardiovascular complications in patients with type 2 diabetes mellitus, particularly in individuals with heart failure, chronic kidney disease, or high cardiovascular risk. Thus, the use of SGLT2 inhibitors not only contributes to disease control but also becomes an important part of a long-term cardiorenal protection strategy.

Mechanisms and Clinical Benefits of GLP-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists) are a class of incretin hormone-based antihyperglycemic drugs that work by activating the GLP-1 receptor, thereby increasing insulin secretion in a glucose-dependent manner, suppressing glucagon secretion, delaying gastric emptying, and increasing satiety. In addition to improving glycemic control, this therapy also contributes to weight loss, blood pressure reduction, and lipid profile improvement. Several studies have shown that the benefits of GLP-1 receptor agonists extend beyond glycemic control to include protective effects on the cardiovascular system, including improved endothelial function, reduced vascular inflammation, reduced oxidative stress, and inhibition of atherosclerosis progression, thus contributing to a reduced risk of cardiovascular complications in patients with type 2 diabetes mellitus (Marx et al., 2023; Ahmed et al., 2026).

The cardioprotective effects of GLP-1 receptor agonists are the result of the interaction of various interrelated biological mechanisms. GLP-1 receptor activation increases nitric oxide production, thereby improving endothelial function and vasodilation, while reducing chronic inflammation, which plays a role in inhibiting atherosclerotic plaque formation. Furthermore, weight loss and improved insulin resistance contribute to the reduction of various cardiovascular risk factors. This combination of mechanisms explains why GLP-1 receptor agonists provide a more prominent benefit in preventing atherosclerotic cardiovascular complications than blood glucose control alone (Marx et al., 2023; Ahmed et al., 2026).

The consistency of these benefits is supported by numerous clinical trials and subsequent analyses. Ahmed et al. showed that efpeglenatide significantly reduced major adverse cardiovascular events (MACE) while providing benefits for kidney outcomes without increasing serious side effects. These findings align with those of Sørensen et al., which

DOI: https://doi.org/10.71435/741778

demonstrated that semaglutide could reduce the risk of major cardiovascular events in obese patients with cardiovascular disease, including individuals without diabetes. Furthermore, a post hoc analysis by Harmony Outcomes and a meta-analysis by Neves et al. showed that the benefit of GLP-1 receptor agonists in reducing MACE remained consistent in both patients taking and not taking SGLT2 inhibitors. These results indicate that the cardioprotective effect of GLP-1 receptor agonists is consistent across patient populations and has the potential to provide additional benefit when used in combination with other therapies with different mechanisms of action (McGuire et al., 2021; Nakai et al., 2022).

Based on a synthesis of scientific evidence, GLP-1 receptor agonists provide cardiovascular benefits through the improvement of vascular function, inhibition of atherosclerosis, and control of metabolic risk factors, thereby contributing to a reduction in major adverse cardiovascular events. Although their effect on heart failure is not as pronounced as that of SGLT2 inhibitors, consistent results from various clinical trials, post-hoc analyses, and meta-analyses reinforce the role of GLP-1 receptor agonists as a key therapy for preventing cardiovascular complications in patients with type 2 diabetes mellitus, particularly in individuals with established atherosclerotic cardiovascular disease or a high risk of atherosclerosis (Marx et al., 2022; Wright et al., 2022).

Synthesis of Scientific Evidence on the Role of SGLT2 Inhibitors and GLP-1 Receptor Agonists in the Prevention of Cardiovascular Complications

A synthesis of various studies shows that SGLT2 inhibitors and GLP-1 receptor agonists have shifted the paradigm of type 2 diabetes mellitus therapy from an approach solely focused on glycemic control to a strategy focused on preventing cardiovascular complications and cardiorenal protection. Although both have been shown to reduce the risk of cardiovascular events, their benefits are not identical but rather complementary, depending on the characteristics of the desired clinical outcome. Therefore, therapy selection no longer considers only blood glucose levels but also the patient's cardiovascular risk profile and comorbidities (Marx et al., 2023; Patorno et al., 2022)

Accumulating evidence from clinical trials, cohort studies, real-world evidence, and meta-analyses indicates that SGLT2 inhibitors provide more consistent benefits in reducing the risk of hospitalization for heart failure, cardiovascular mortality, and slowing the progression of chronic kidney disease. Conversely, GLP-1 receptor agonists are more effective in reducing atherosclerotic cardiovascular events, particularly major adverse cardiovascular events (MACE), while also improving metabolic risk factors such as obesity and insulin resistance. These differences reflect the fact that both therapies have different clinical targets but contribute to the same goal: reducing the burden of cardiovascular complications in patients with type 2 diabetes mellitus (Marx et al., 2023; Patorno et al., 2022).

Several recent studies have also shown that the combination of an SGLT2 inhibitor and a GLP-1 receptor agonist have the potential to provide greater cardiorenal benefits than monotherapy through complementary mechanisms of action. Although preliminary results indicate a reduced risk of major cardiovascular events, heart failure, mortality, and improved renal outcomes, most of the evidence still comes from secondary analyses and observational studies, so randomized clinical trials with long-term follow-up are needed to confirm the efficacy and safety of combination therapy. These findings suggest that SGLT2 inhibitors and GLP-1 receptor agonists should not be viewed as substitutes for each other, but rather as therapies that can be selected or combined according to patient clinical characteristics to optimize the prevention of cardiovascular complications in type 2 diabetes mellitus (McGuire et al., 2021; Patorno et al., 2022). These findings suggest that the choice of antihyperglycemic therapy in

DOI: https://doi.org/10.71435/741778

type 2 diabetes mellitus is no longer based solely on the effectiveness of glycemic control, but also on the underlying cardiovascular risk profile. Therefore, the selection of SGLT2 inhibitors or GLP-1 receptor agonists needs to consider the patient's clinical characteristics so that the benefits of preventing cardiovascular complications can be achieved optimally.

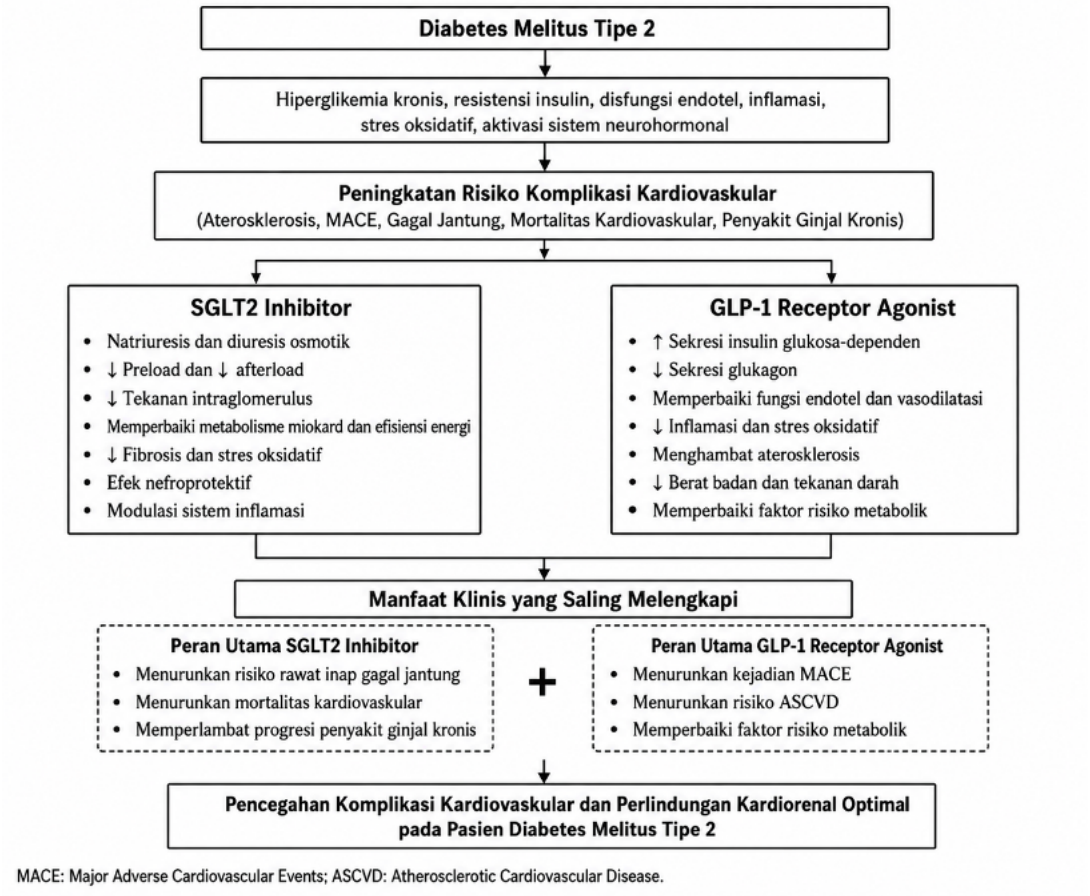

Figure 2. Conceptual scheme of the role of SGLT2 inhibitors and GLP-1 receptor agonists in preventing cardiovascular complications in patients with type 2 diabetes mellitus

Conclusion

Based on reviewed scientific evidence, SGLT2 inhibitors and GLP-1 receptor agonists are therapies that play an important role in preventing cardiovascular complications in patients with type 2 diabetes mellitus through different but complementary mechanisms. SGLT2 inhibitors provide greater benefits in preventing heart failure and cardiorenal protection, while GLP-1 receptor agonists are more effective in reducing atherosclerotic cardiovascular events. A synthesis of various studies shows that the choice of therapy needs to be tailored to the patient's clinical characteristics and cardiovascular risk to achieve optimal cardiovascular benefits.

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