doi.org/10.36721/PJPS.2026.39.3.REG.15014.1

Integrated approaches to preventing macrovascular complications in type 2 diabetes mellitus: Advances in secondary prevention

Fang Qian[1], Jing Dai[2] and Qian Huang[1]*

[1]Department of General Practice, The First People's Hospital of Xiaoshan District, Xiaoshan Affiliated Hospital of Wenzhou Medical University, Hangzhou, Zhejiang, China.

[2]Department of Endocrinology, Tonglu County Hospital of Traditional Chinese Medicine

Abstract: **Background**: Type 2 diabetes mellitus (T2DM) substantially increases the risk of macrovascular complications, including coronary artery disease, cerebrovascular disease and peripheral arterial disease, which collectively represent the leading causes of morbidity and mortality among affected individuals. Evidence from clinical trials has demonstrated that intensive glycemic control alone provides limited protection against macrovascular outcomes, underscoring the need for comprehensive secondary prevention strategies. **Objectives**: This review aims to synthesize recent advances in integrated secondary prevention strategies for macrovascular complications in T2DM, with emphasis on pharmacological, lifestyle and personalized approaches that extend beyond glucose lowering. **Methods**: A narrative review of the literature published between 2015 and 2025 was conducted, including randomized controlled trials, meta-analyses, major cardiovascular outcome trials and international guideline updates. Evidence was evaluated across key domains: glycemic management, lipid lowering, blood pressure control, antithrombotic therapy, lifestyle interventions, emerging pharmacotherapies, biomarkers and digital health–based risk stratification tools. **Results**: Accumulating evidence supports a multifactorial approach to secondary prevention in T2DM. Sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists consistently reduce major adverse cardiovascular events, heart failure hospitalization and renal outcomes, independent of glycemic control. Optimized lipid management with statins, PCSK9 inhibitors and icosapent ethyl, along with strict blood pressure control and selective antiplatelet therapy, further lowers atherosclerotic risk. Emerging strategies targeting inflammation, endothelial dysfunction and the gut microbiota show promise. Biomarkers such as high-sensitivity C-reactive protein, N-terminal pro-brain natriuretic peptide and cystatin C, combined with artificial intelligence–driven risk prediction models, enable improved patient stratification and individualized therapy. **Conclusion**: Secondary prevention of macrovascular complications in T2DM requires an integrated, multidisciplinary strategy combining cardioprotective pharmacotherapy, lifestyle modification and personalized risk assessment. Advances in novel therapies, biomarkers and digital health technologies offer substantial potential to further improve long-term cardiovascular outcomes in this high-risk population

Keywords: Cardiovascular disease; Macrovascular complications; Secondary prevention; Type 2 diabetes mellitus (T2DM)

Submitted on 12-08-2025 – Revised on 28-09-2025 – Accepted on 23-10-2025

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a rapidly escalating global epidemic and a major public health challenge. As of 2021, over 530 million adults were living with diabetes worldwide and this number is projected to surge to approximately 693 million by 2045, driven largely by lifestyle changes, urbanization, aging populations and genetic predisposition [IDF, WHO] (Khan *et al*, 2020; Hossain *et al*, 2024). T2DM is associated with both acute and chronic complications. Acute complications include hyperosmolar hyperglycemic state (HHS) and hypoglycemia, which can lead to severe neurological manifestations. Chronic complications are broadly categorized as microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (cardiovascular disease, stroke, peripheral arterial disease), the latter accounting for over 65% of diabetes-related deaths (Song *et al*., 2024, Huang *et al*., 2025). Macrovascular complications involve large blood vessels and include cardiovascular disease (heart attack, heart failure), cerebrovascular disease (stroke) (Khan *et al*, 2020) and peripheral arterial disease (poor circulation, ulcers, risk of amputation) illustrated in fig. 1, which account for more than 65% of diabetes-related deaths (Cade, 2008). Historically, diabetes management focused on intensive glycemic control under the assumption that lowering blood glucose would reduce cardiovascular risk. Large clinical trials, including ACCORD, ADVANCE and VADT, challenged this paradigm by showing that glycemic control alone has a limited impact on macrovascular outcomes, especially in patients with established cardiovascular disease (Papa *et al*., 2013). Consequently, a more comprehensive, multifactorial approach has become the standard of care, targeting glycemia, blood pressure, lipids, inflammation and lifestyle factors simultaneously (Monique & Brian, 2023).

**Corresponding author:* e-mail: huangqian1109@126.com

Over the past decade, novel pharmacological agents such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as cornerstone therapies for secondary prevention of macrovascular complications (Hossain *et al*., 2024). These agents confer cardiovascular benefits beyond glucose lowering, including improved endothelial function, reduced cardiac workload, natriuresis and attenuation of inflammation (Guan *et al*., 2024). Moreover, lipid and blood pressure management, anti-inflammatory therapies, lifestyle modifications and behavioural interventions have been increasingly recognized as critical components of effective secondary prevention (Davies *et al*., 2022). Technological advances, including continuous glucose monitoring (CGM), telemedicine, mobile health (mHealth) platforms and AI-driven decision support tools, are enhancing personalized care and proactive risk management (Robert *et al*., 2021). In parallel, a shift toward team-based care models and the application of precision medicine tools, including genetic and biomarker profiling, is fostering a more patient-centered and risk-adapted approach to long-term management (Sun *et al*., 2021). Despite extensive research on macrovascular complications in type 2 diabetes mellitus (T2DM), knowledge gaps remain regarding the discordance between glycemic control and cardiovascular outcomes, variability in patient responses to emerging therapies and practical barriers to implementation. The aim of this review is to critically synthesize current evidence on the pathophysiology, therapeutic strategies and translational challenges of T2DM-related macrovascular disease, highlight unresolved controversies and gaps in knowledge and provide a comprehensive perspective to guide future research and clinical practice (Song *et al*. 2024)

Pathophysiology of macrovascular complications in T2DM

The heightened risk of macrovascular complications in individuals with T2DM arises from a multifaceted network of metabolic, inflammatory and vascular disturbances (Viigimaa *et al*., 2020). Unlike microvascular complications, which are primarily linked to chronic hyperglycemia, macrovascular disease results from cumulative damage to large blood vessels influenced by diverse pathophysiological mechanisms (Huang er al.,2025). Chronic hyperglycemia leads to the formation of advanced glycation end-products (AGEs), which interact with their receptors (RAGE) on endothelial and immune cells, inducing oxidative stress and pro-inflammatory pathways that disrupt vascular function (Khan *et al*., 2020). Simultaneously, insulin resistance, a central feature of T2DM, promotes compensatory hyperinsulinemia and contributes to atherogenic dyslipidemia characterized by elevated triglycerides, low HDL cholesterol and small dense LDL particles. Insulin resistance also impairs nitric oxide (NO) production, undermining vasodilation and promoting platelet aggregation (Chawla *et al*., 2016). These metabolic imbalances precipitate endothelial dysfunction, a hallmark of diabetic macrovascular disease, whereby the protective barrier function of the endothelium is compromised, allowing for lipoprotein infiltration, leukocyte adhesion and vascular smooth muscle proliferation, all of which favour plaque formation (Roy, 2025).

Chronic low-grade inflammation further exacerbates vascular injury. Elevated circulating cytokines such as TNF-α, IL-6 and CRP amplify insulin resistance and promote atherosclerotic plaque progression and destabilization (Mansour *et al*., 2023). Dyslipidemia compounds these effects, as oxidized small dense LDL easily penetrates the arterial wall, forming foam cells (Dunn *et al*., 2025). Platelet hyperactivity and coagulopathy also contribute to a pro-thrombotic state, increasing the likelihood of thrombus formation upon plaque rupture. Hyperglycemia additionally activates the polyol and hexosamine pathways and enhances glycolysis, leading to reactive oxygen species (ROS) production, mitochondrial dysfunction, endoplasmic reticulum (ER) stress and DNA damage, all fostering a pro-inflammatory environment (Hasheminasabgorji & Jha, 2021). AGE accumulation and oxidized LDL further amplify endothelial injury, while upregulated adhesion molecules such as VCAM-1 and ICAM-1 facilitate leukocyte recruitment and vascular inflammation (Cade, 2008, Chakraborty *et al*., 2023) The loss of neurotrophic signals and the accumulation of inflammatory mediators such as TNF-α, IL-6, VCAM-1 and ICAM-1 further exacerbate vascular injury, leading to atherosclerosis and related macrovascular complications like coronary artery disease (Adare *et al*.,2024), stroke and peripheral artery disease as illustrated in fig. 2.

Recent studies highlight the cardio-renal-metabolic axis, wherein comorbidities like diabetic kidney disease (DKD) exacerbate endothelial dysfunction (Eid *et al*., 2023), fluid retention and hypertension, while heart failure can impair glucose metabolism and insulin sensitivity, creating a vicious cycle that accelerates vascular damage (Theodorakis & Nikolaou, 2025). Consequently, macrovascular complications in T2DM are multifactorial, arising from the combined effects of hyperglycemia, insulin resistance, dyslipidemia, inflammation, platelet dysfunction and cardio-renal interactions (Jha *et al*., 2024).

The resulting atherosclerotic process is often diffuse, rapidly progressive and affects multiple vascular territories, including coronary, cerebral and peripheral arteries, even in individuals with relatively well-controlled blood glucose levels (Dunn *et al*., 2025). The major molecular and cellular mechanisms contributing to this complex vascular pathology including chronic hyperglycemia, insulin resistance, dyslipidemia, inflammation, platelet dysfunction and endothelial injury are systematically summarized in table 1. Each of these interconnected pathways contributes to a pro-atherogenic

environment that accelerates plaque formation and increases the risk of thrombotic events (Papa *et al*., 2013)

Integrated principles and strategies in secondary prevention of macrovascular complications

Secondary prevention in T2DM targets individuals with established diabetes and/or CVD, aiming to prevent the recurrence or progression of macrovascular events such as myocardial infarction, stroke and peripheral artery disease. Effective prevention hinges on the early identification and management of both traditional (e.g., hypertension, dyslipidemia, obesity, smoking) and non-traditional risk factors (e.g., inflammation, insulin resistance, endothelial dysfunction), supported by aggressive, individualized interventions (Monique & Brian, 2023). Lifestyle modifications remain foundational, with medical nutrition therapy associated with a 7-32% reduction in all-cause and cardiovascular mortality (Lu *et al*., 2024). Dietary patterns emphasizing low saturated fat, higher fiber and monounsaturated fats contribute significantly to risk reduction. Regular physical activity, whether aerobic, resistance, or combined, has been linked to a 16–26% (Zhang *et al*., 2025) lower incidence of cardiovascular events, while sustained weight loss improves cardiometabolic health, particularly in overweight individuals with T2DM (Bermudez *et al*., 2018).Recent studies highlight that while intensive glycemic control has limited impact on macrovascular outcomes, comprehensive management of cardiovascular risk factors is crucial. Statin therapy reduces nonfatal myocardial infarction risk by up to 43% and icosapent ethyl further lowers ASCVD events by 23.3% (Guan *et al*., 2024). Blood pressure control, particularly systolic reduction, decreases cardiovascular mortality by up to 34% (Oikonomou & Khera, 2023). Additionally, antiplatelet strategies, such as low-dose aspirin or rivaroxaban-aspirin regimens, provide selective benefit in high-risk T2DM patients (Corrao *et al*., 2025).

Recent years have seen a paradigm shift toward multidrug regimens incorporating metformin with SGLT2i and GLP-1 RAs (Yu *et al*., 2016). These agents not only improve glycemic control but also significantly lower MACE, with dual or triple therapy combinations reducing cardiovascular risk by up to 83%. GLP-1 RAs and SGLT2i confer protection through mechanisms such as anti-inflammatory action, oxidative stress modulation and improvement in endothelial function (Altabas *et al*., 2023, Hrncir, 2022). A growing body of evidence supports integrated, multifactorial strategies over isolated interventions. Simultaneous management of glycemia, lipids and blood pressure yields superior vascular protection compared to sequential or single-target approaches (Muttiah & Hanafiah, 2025). Biomarker-guided therapy using lipid profiles, inflammatory markers and renal indicators further enables personalized care. Importantly, early and aggressive interventions even before clinical manifestation of macrovascular disease are associated with improved outcomes (Gebremariam *et al*., 2022). Over the past decade, trends reveal a decline in myocardial infarction and stroke among older adults with T2DM, yet rising prevalence of early heart failure and peripheral artery disease (Awal *et al*., 2020). This shift highlights the dynamic nature of macrovascular complications and the need for continuous risk factor modification from diagnosis onward (Hasheminasabgorji & Jha, 2021). Community-based and interdisciplinary care models have demonstrated success in reducing vascular events, emphasizing patient education and integrated primary care. Despite significant progress, substantial gaps persist, particularly among individuals with coexisting obesity, hypertension and dyslipidemia (Ahmadian *et al*., 2022). Ongoing research is increasingly directed toward personalized strategies using novel biomarkers, digital health platforms and telemedicine for continuous monitoring and intervention.

Established therapies with cardiovascular benefits

Over the past decade, a more holistic, multi-targeted approach has emerged in diabetes care, expanding beyond glucose control to address comprehensive cardiovascular risk management. Two major classes of glucose-lowering agents have consistently demonstrated cardiovascular protection:

- *SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin)*: The EMPA-REG OUTCOME (2015) and DECLARE-TIMI 58 (2019) trials provided early evidence of reduced MACE and hospitalization for heart failure. More recently, the EMPEROR-Preserved (2021) and EMPA-KIDNEY (2023) trials confirmed benefits in patients with both heart failure and chronic kidney disease, regardless of diabetes status (Chaiyasut *et al*., 2023).
- *GLP-1 receptor agonists (e.g., liraglutide, semaglutide)*: The LEADER (2016) and SUSTAIN-6 (2016) trials first demonstrated significant reductions in cardiovascular mortality and stroke. The REWIND trial (2019), followed by SELECT (2023) with semaglutide, further highlighted cardiovascular event reductions in obese patients, even without T2DM (Lübeck *et al*., 2025).

These agents exert cardioprotective effects through multiple mechanisms, including anti-inflammatory actions, reduction in oxidative stress and improvement in endothelial function, arterial stiffness and left ventricular remodeling (Davies *et al*., 2022).

Emerging strategies and trials

Recent research has expanded into novel pharmacologic targets and multi-omics-driven personalized medicine, including:

- *Anti-inflammatory therapies*: The CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) demonstrated reduced cardiovascular events in post-MI patients through IL-1β inhibition, showing promise for diabetic populations. Current studies like

ZEUS (2024) are evaluating ziltivekimab, an IL-6 inhibitor, in T2DM patients with atherosclerosis and chronic inflammation (Zeinali *et al*., 2020).

- *Lipid-lowering agents*: Beyond statins, inclisiran, a small interfering RNA (siRNA) that inhibits PCSK9 synthesis, has shown LDL-C reduction and cardiovascular event lowering in the ORION-4 trial (2024), especially beneficial in high-risk diabetic patients (Li *et al*., 2020)].
- *Dual pathway inhibition*: The COMPASS trial investigated low-dose rivaroxaban plus aspirin, reducing MACE in T2DM patients with peripheral artery disease. Newer trials are exploring factor XIa inhibitors for thrombosis prevention with lower bleeding risk (Einarson *et al*., 2018).

Cardiorenal-metabolic care models: Integrated care programs such as the DAPA-CARE initiative (2023) focus on early identification and coordinated management of heart, kidney and metabolic risk in T2DM using SGLT2i, RAAS blockers and tailored lifestyle plans (Gallo *et al*., 2022). Table 2 summarizes the study design, randomization, sample size, population, inclusion and exclusion criteria, interventions, primary outcomes and key findings of major clinical trials.

Technological innovations

Modern diabetes care integrates digital health tools, enhancing the precision and personalization of secondary prevention:

- Continuous glucose monitoring (CGM) and ambulatory blood pressure monitoring provide real-time data for optimizing metabolic and vascular control (Espinoza *et al*., 2022)
- Artificial intelligence (AI)-driven risk algorithms are being developed to stratify patients based on combined genomic, proteomic and clinical biomarkers for individualized therapeutic decisions (Cole & Florez, 2020).
- Wearable devices and mobile apps are increasingly used for behaviour modification, adherence tracking and early detection of cardiovascular decompensation (Cole & Florez, 2020).

Recent clinical evidence also supports the integration of anti-inflammatory agents, next-generation lipid-lowering drugs and dual pathway antithrombotic therapies into treatment algorithms for high-risk diabetic populations (Chaiyasut *et al*., 2023). Moreover, the development of digital health platforms, wearable technologies and AI-driven risk stratification tools is enabling a shift toward personalized, data-informed prevention strategies. These innovations facilitate real-time monitoring and individualized therapeutic adjustments, thereby enhancing long-term adherence and cardiovascular outcomes (Mohsen & Shah, 2025). Despite these advances, significant gaps persistparticularly in patients with coexisting obesity, hypertension and chronic kidney disease. Therefore, the future of secondary prevention lies in the adoption of integrated, interdisciplinary care models, such as those proposed in cardio-renal-metabolic (CRM) frameworks, which coordinate therapy across disease domains and clinical specialties. A concise overview of these integrated principles, emerging therapies and their cardiovascular impact is summarized in table 3.

Therapeutic strategies and emerging interventions in secondary prevention

Secondary prevention of macrovascular complications in T2DM has shifted from a glucose-centric approach to a multifaceted strategy targeting lipid abnormalities, hypertension, inflammation, thrombosis and endothelial dysfunction. This integrated approach is supported by a growing body of evidence demonstrating cardiovascular benefits independent of glycemic control (Regassa *et al*., 2021).

Pharmacological interventions

Lipid management

Statins remain the primary agents for ASCVD risk reduction (Fowler, 2008). The CARDS trial demonstrated a 37% reduction in major cardiovascular events with atorvastatin in T2DM patients without high LDL-C. The REDUCE-IT trial (Bhatt *et al*., 2019) showed that icosapent ethyl (4g/day) reduced ischemic events by 23% in statin-treated T2DM patients with high triglycerides (Cho *et al*., 2018).

Blood pressure control

Meta-analyses show that every 10-mmHg reduction in systolic BP reduces cardiovascular mortality by 20–30%. The ADVANCE trial demonstrated that perindopril–indapamide reduced macrovascular events in T2DM (Bethel *et al*., 2007).

Antiplatelet therapy

The COMPASS trial reported a 24% reduction in major cardiovascular events with low-dose rivaroxaban (2.5 mg BID) plus aspirin in patients with stable ASCVD, including those with diabetes. However, benefits must be weighed against bleeding risk, especially in primary prevention settings (Ahmad *et al*., 2021, An *et al*., 2021).

Glucose-lowering therapies with CV benefits

- SGLT2 inhibitors: The EMPA-REG OUTCOME trial showed a 38% reduction in cardiovascular death with empagliflozin. The DAPA-HF trial confirmed dapagliflozin's benefits in heart failure patients, including diabetics (Du *et al*., 2009).
- GLP-1 receptor agonists: LEADER trial reported a 13% reduction in MACE with liraglutide. More recently, the REWIND trial with dulaglutide showed benefits even in low-risk diabetic populations (Lopaschuk & Verma, 2020).

Emerging therapies

- The CANTOS trial using canakinumab, an IL-1β inhibitor, showed reduced recurrent cardiovascular events independent of lipid levels, highlighting the role of inflammation (Zeinali *et al*., 2020).

- Inclisiran, a PCSK9 siRNA, demonstrated LDL-C reduction of >50% with twice-yearly dosing in the ORION trials, with ongoing studies evaluating CV outcome benefits (e.g., VICTORION-2P) (Chan & Chan, 2023).

Lifestyle and behavioral interventions

The Look AHEAD study found that intensive lifestyle intervention improved glycemic control, blood pressure and lipid profiles, though not significantly MACE rates. However, benefits in weight loss, quality of life and secondary cardiovascular risk factors were consistent (Mitsis *et al*., 2024).

Recent updates

- A 2023 meta-analysis (JAMA Network Open) confirmed the effectiveness of Mediterranean and DASH diets in lowering systolic BP (−5.5 mmHg), LDL-C and fasting glucose in T2DM (Pi-Sunyer, 2014).
- The DiRECT study newly diagnosed T2DM patients showed diabetes remission and improved cardiovascular risk markers with structured weight loss (Yehuda *et al*., 2023).

Integrated and technological approaches

Team-based care models and use of digital tools (e.g., continuous glucose monitoring, mobile-based BP and lipid monitoring) improve adherence and outcomes (Wing, 2022). A 2022 systematic review (Lancet Digital Health) reported that digital interventions reduced HbA1c by 0.4% and improved BP control in T2DM (Maida *et al*., 2025). Ongoing studies, such as PROTECT-T2D, are evaluating AI-guided interventions for real-time cardiovascular risk assessment and behavior modification in diabetic populations (Moschonis *et al*., 2023).

Ongoing and landmark trials

- ***EMPA-KIDNEY (2023)*****:** In the EMPA-KIDNEY (2024) trial, empagliflozin significantly reduced the risk of kidney disease progression in a broad range of CKD patients, including those with non-diabetic causes. The relative benefits were consistent across different primary kidney disease etiologies, supporting the inclusion of SGLT2 inhibitors as part of standard care to reduce the risk of kidney failure in CKD (Overgaard *et al*., 2024).

- ***SELECT (2025)*****:** A large-scale cardiovascular outcomes trial, SELECT, evaluated semaglutide in over 17,000 adults with overweight or obesity and established atherosclerotic cardiovascular disease (ASCVD), but without diabetes (EMPA-KIDNEY trial, 2024). The trial demonstrated that semaglutide significantly reduced major cardiovascular events and also showed beneficial effects on kidney health. In this low kidney-risk population, semaglutide was associated with a reduction in albuminuria and a slower decline in kidney function. Additionally, in a separate smaller trial involving approximately 100 individuals with overweight or obesity and albuminuric chronic kidney disease (CKD), semaglutide reduced albuminuria by around 50%, highlighting its potential renoprotective effects in high-risk populations (Weng *et al*., 2020).

Flow trial

Ongoing study on semaglutide for renal outcomes with CV endpoints in T2DM. Patients with type 2 diabetes and chronic kidney disease (CKD) face a significantly elevated risk of kidney failure, cardiovascular events and mortality (Neuen *et al*., 2025). The impact of semaglutide on these risks had remained uncertain until recently. Emerging evidence now shows that semaglutide significantly reduces the risk of clinically important kidney outcomes, including progression of kidney disease as well as death from cardiovascular causes, in this high-risk population. These findings support the potential role of semaglutide in improving both renal and cardiovascular outcomes in patients with type 2 diabetes and CKD (Tantigegn *et al*., 2023). Table 4 provides a summary of recent and ongoing landmark clinical trials that have shaped the current therapeutic landscape for macrovascular risk reduction in T2DM patients.

Future directions

Precision medicine via integration of multi-omics, genetic profiling and microbiome analysis may allow individualized secondary prevention strategies (Wang *et al*., 2022). Early-stage studies suggest gut microbiota modulation influences systemic inflammation and atherosclerosis. Anti-inflammatory therapies, endothelial repair agents and dual pathway inhibitors (e.g., FXI inhibitors like asundexian in PACIFIC-AMI) are under evaluation (Kosiborod *et al*., 2018).

Recent advances and future directions in the prevention of macrovascular complications in T2DM

Recent advancements in the prevention of macrovascular complications in T2DM have been driven by the convergence of molecular research, pharmacological innovation and precision medicine (Haile & Timerga, 2020). Beyond traditional risk factor control, recent studies emphasize early identification of high-risk individuals through multi-omic profiling (genomics, proteomics, metabolomics), machine learning-based risk prediction models and biomarker discovery (Allesøe *et al*., 2023).

Emerging therapeutic targets

Targeting inflammation and endothelial dysfunction is now at the forefront. The CANTOS trial demonstrated that IL-1β inhibition with canakinumab reduced major cardiovascular events in patients with prior myocardial infarction, including those with T2DM (Tian *et al*., 2025) TNF-α blockers and novel agents targeting vascular adhesion molecules are under evaluation for their potential to mitigate atherosclerotic progression in diabetic individuals (Astrup *et al*., 2020).

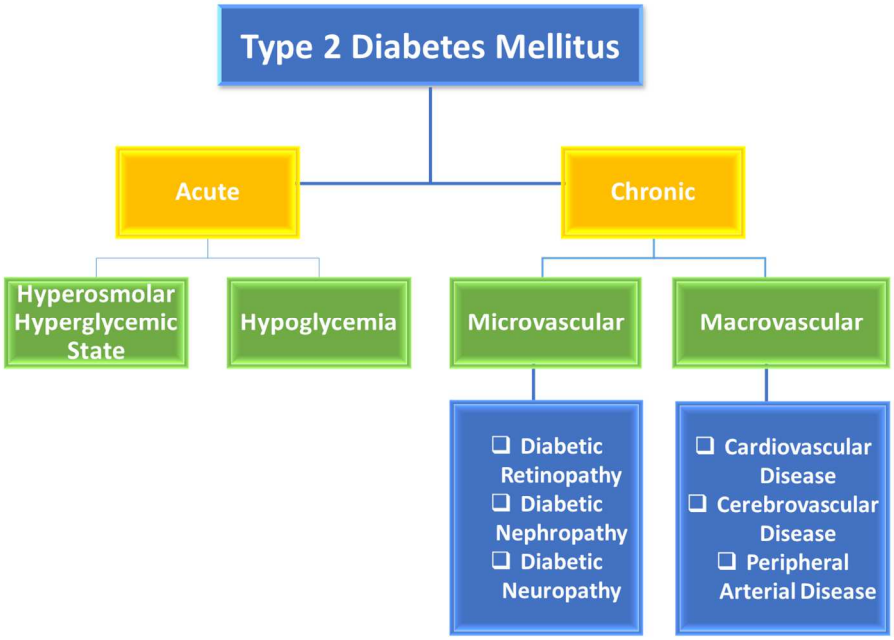

Fig. 1: Classification of complications in type 2 diabetes mellitus**.** This diagram categorizes the complications of type 2 diabetes mellitus into acute and chronic types. Acute complications include hyperosmolar hyperglycemic state and hypoglycemia. Chronic complications are further divided into microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (cardiovascular, cerebrovascular, and peripheral arterial disease) types.

Table 1: Key Pathophysiological mechanisms leading to macrovascular complications in T2DM

S. No.	Pathway	Key mediators	Effect on vasculature	Key organs	References
1.	Chronic hyperglycemia	Polyol pathway, AGEs, ROS	Oxidative stress, endothelial injury, vascular inflammation	Heart, Brain, Peripheral vessels	(Sun *et al*., 2021)
2.	Insulin resistance	↓ NO, ↑ endothelin-1, dyslipidemia	Endothelial dysfunction, impaired vasodilation, plaque development	Heart, Brain, Peripheral vessels	(Viigimaa *et al*., 2020, González-Rivas *et al*., 2023)
3.	Inflammation	TNF-α, IL-6, CRP, NF-κB activation	Leukocyte adhesion, foam cell formation, plaque destabilization	Heart, Brain, Peripheral vessels	(Chawla *et al*., 2016)
4.	Coagulopathy & Platelet activation	↑ PAI-1, fibrinogen, thromboxane A2, P-selectin	Enhanced thrombosis, impaired fibrinolysis	Heart (MI), Brain (Stroke), Peripheral arteries	(Roy, 2025)
5.	Dyslipidemia	↑ Triglycerides, ↓ HDL, ↑ small dense LDL, oxLDL	Lipid infiltration, foam cell formation, vascular lipotoxicity	Coronary arteries, Cerebral vessels, Peripheral arteries	(Viigimaa *et al*., 2020, Chawla *et al*., 2016)
6.	Mitochondrial/ER stress	ROS, unfolded protein response (UPR), apoptosis-inducing factor (AIF)	Vascular apoptosis, endothelial cell death	Heart, Brain, Peripheral vasculature	(Roy, 2025)
7.	Cardio-renal-metabolic axis	Uremic toxins, RAAS activation, fluid overload, cardiac dysfunction	Accelerated atherosclerosis, vascular stiffness, systemic inflammation	Heart, Kidney, Vascular system	(Mansour *et al*., 2023)

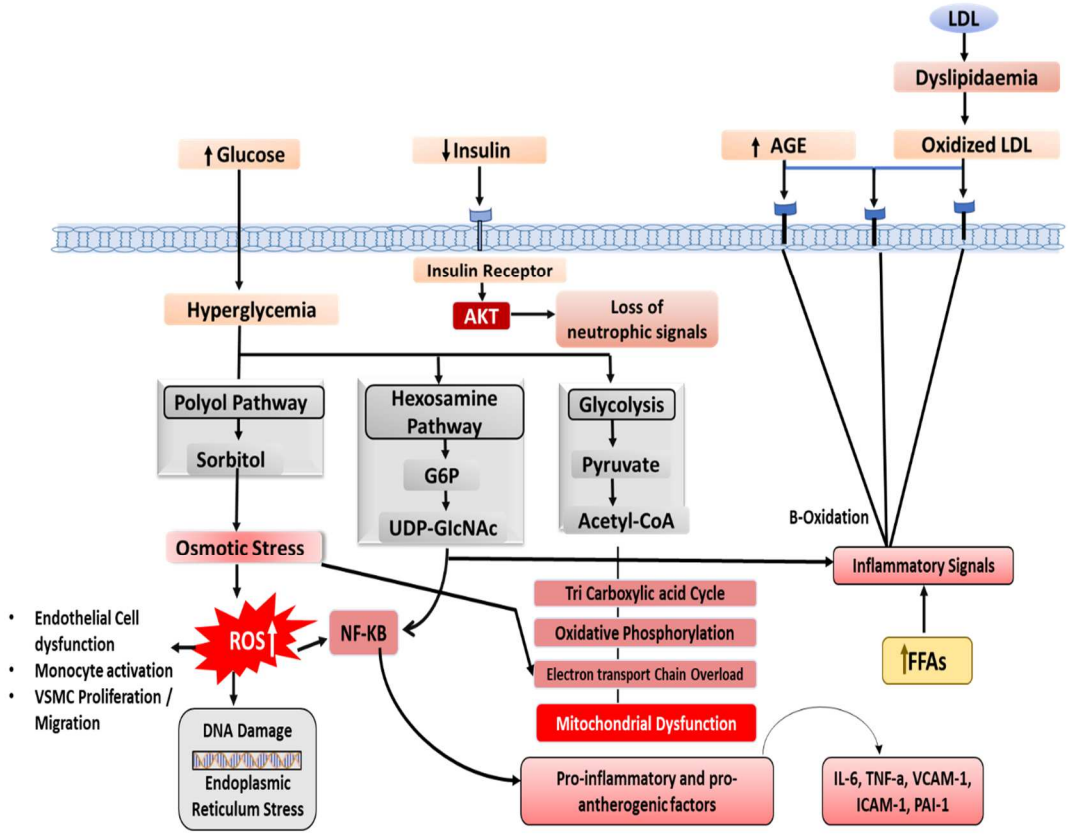

Fig. 2: Pathophysiological mechanisms of macrovascular complications in type 2 diabetes mellitus.
The figure 2 illustrates the key molecular pathways leading to vascular complications in T2DM. Chronic hyperglycemia and insulin resistance activate multiple biochemical pathways such as the polyol pathway, hexosamine pathway, and glycolysis, resulting in oxidative stress, mitochondrial dysfunction, and chronic inflammation. These events contribute to endothelial dysfunction and vascular damage. Dyslipidemia, particularly oxidized LDL and advanced glycation end products (AGEs), further intensifies vascular inflammation, promoting atherosclerosis and macrovascular complications.

Personalized medicine and AI

Machine learning algorithms are increasingly used to predict macrovascular complications by integrating EHRs, lifestyle data and continuous glucose monitoring (CGM) outputs (Baumblatt *et al*., 2024). These tools can stratify patients based on predicted cardiovascular risk and guide individualized therapy, as shown in the DISCOVER study and the UK Biobank–based predictive models (Wang *et al*., 2023).

Regenerative and cell-based therapies

Experimental studies are exploring the use of endothelial progenitor cells (EPCs) to restore vascular integrity in T2DM. Early-phase trials indicate potential in promoting neovascularization and reversing ischemic damage, offering hope for long-term vascular repair (Parker *et al*., 2024, Wilcox *et al*., 2020).

Gut microbiota and metabolic health

Recent research has linked dysbiosis in gut microbiota with systemic inflammation and vascular dysfunction. Probiotic and prebiotic interventions are being investigated to reduce low-grade inflammation and improve endothelial function, as seen in pilot studies such as the MetaCardis project (Zhang *et al*., 2025). In conclusion, a shift toward integrative, individualized strategies combining pharmacological, molecular and digital tools is shaping the future of secondary prevention in macrovascular complications of T2DM (Vlacho *et al*., 2024). These multifaceted advancements are summarized in Table 5, which highlights recent clinical trials and technological innovations that represent a shift toward mechanistic, microbiome-focused and AI-assisted strategies in the secondary prevention of macrovascular complications in T2DM (Andreas & Stefan, 2020).

Biomarkers and risk stratification in macrovascular complications of T2DM

In the era of precision medicine, the identification and validation of reliable biomarkers are critical to enhancing risk stratification and guiding individualized therapy in patients with T2DM at risk of macrovascular complications (Di Giacomo-Barbagallo *et al*., 2025). Traditional markers such as HbA1c and LDL-C, while informative, are insufficient to capture the complex, multifactorial pathophysiology underlying atherosclerotic cardiovascular disease (ASCVD) in diabetes (Sibbing *et al*., 2024).

Table 2: Summary of key clinical trials evaluating interventions for macrovascular complications in type 2 diabetes mellitus.

Trial name / Year	Study design	Randomization	Sample size	Population / inclusion criteria	Exclusion criteria	Intervention	Primary outcome	Key findings	Reporting guidelines / statistical notes	References
EMPA-REG OUTCOME, 2015	Multicenter, randomized, double-blind, placebo-controlled	Yes	7,020	T2DM with established CVD	Type 1 diabetes, recent CV events	Empagliflozin 10 or 25 mg vs placebo	Major adverse cardiovascular events (MACE)	Reduced CV death, HF hospitalization	Followed CONSORT, intention-to-treat analysis	(Robert *et al*., 2021)
CANVAS Program, 2017	Multicenter, randomized, double-blind, placebo-controlled	Yes	10,142	T2DM with high CV risk	eGFR <30 mL/min/1.73 m²	Canagliflozin 100 or 300 mg vs placebo	MACE	Reduced CV events, renal benefit	CONSORT-adherent, pre-specified subgroups	(Sun *et al*., 2021)
DECLARE-TIMI 58, 2019	Randomized, double-blind, placebo-controlled	Yes	17,160	T2DM, multiple CV risk factors	Type 1 diabetes, recent HF hospitalization	Dapagliflozin 10 mg vs placebo	MACE, CV death/HF hospitalization	Reduced HF hospitalization, neutral MACE	Intention-to-treat, per-protocol analyses	(Viigimaa *et al*., 2020)
LEADER, 2016	Randomized, double-blind, placebo-controlled	Yes	9,340	T2DM with high CV risk	History of pancreatitis, severe renal impairment	Liraglutide vs placebo	MACE	Reduced CV events and all-cause mortality	CONSORT-compliant, ITT analysis	(Chawla *et al*., 2016)
SUSTAIN-6, 2016	Randomized, double-blind, placebo-controlled	Yes	3,297	T2DM with high CV risk	Severe renal/hepatic impairment	Semaglutide vs placebo	MACE	Reduced nonfatal stroke, CV events	ITT population, pre-specified safety endpoints	(Roy, 2025)
REWIND, 2019	Randomized, double-blind, placebo-controlled	Yes	9,901	T2DM, aged ≥50, CV risk factors	History of severe pancreatitis, uncontrolled hypertension	Dulaglutide vs placebo	MACE	Significant reduction in CV events	Followed CONSORT, ITT analysis	(Mansour *et al*., 2023)
CANTOS, 2017	Randomized, double-blind, placebo-controlled	Yes	10,061	History of MI, elevated hsCRP	Active infection, immunosuppression	Canakinumab 50/150/300 mg vs placebo	Nonfatal MI, stroke, CV death	Reduced CV events independent of lipid lowering	Rigorous statistical adjustment, ITT	(Dunn *et al*., 2025)

Table 2: Secondary prevention strategies in T2DM and their impact on cardiovascular risk

S. No.	Intervention	Mechanism of benefit	Cardiovascular impact	Key trials/Notes	References
1.	Lifestyle modification	Weight loss, reduced inflammation, improved insulin sensitivity	↓ Cardiovascular mortality (7–32%), ↓ MACE by 16–26%	Look AHEAD, DPP	(Lu *et al*., 2024)
2.	Statins	LDL-C reduction, plaque stabilization	↓ MI (up to 43%), ↓ stroke risk	HPS, CARDS	(Engelen *et al*., 2022)
3.	Icosapent ethyl	Triglyceride lowering, anti-inflammatory	↓ ASCVD events by 23.3%	REDUCE-IT	(Bermúdez *et al*., 2018)
4.	Antihypertensives (ACEi/ARB, CCB, Thiazides)	BP lowering, improved endothelial function	↓ CV mortality by 25–34%	ADVANCE, UKPDS	(Bermúdez *et al*., 2018, (Oikonomou & Khera, 2023)
5.	SGLT2 inhibitors	Natriuresis, ↓ preload/afterload, ↓ inflammation, renal protection	↓ HF hospitalization, ↓ renal failure, ↓ all-cause mortality	EMPA-REG, DECLARE, EMPEROR-Preserved, EMPA-KIDNEY	(Corrao *et al*., 2025)
6.	GLP-1 RAs	↓ Appetite, ↑ insulin, ↓ glucagon, ↓ inflammation	↓ CV death, ↓ stroke, ↓ non-fatal MI	LEADER, SUSTAIN-6, REWIND, SELECT	(Yu *et al*., 2016)
7.	Antiplatelet therapy	Inhibition of platelet aggregation, ↓ thrombosis	↓ MACE in high-risk patients	COMPASS, ASCEND	
8.	Multidrug therapy (Metformin + SGLT2i + GLP-1)	Multiple cardiometabolic targets (glucose, BP, lipids, inflammation)	↓ CV events by up to 83%	Real-world data, ongoing trials	(Corrao *et al*., 2025)
9.	Biomarker-guided therapy	Precision medicine using hsCRP, IL-6, NT-proBNP, etc.	Enables individualized care	Emerging strategy	
10.	Integrated care models	Team-based, interdisciplinary, telehealth-driven	↓ Hospitalization, improved adherence and long-term outcomes	DAPA-CARE, community-based trials	(Yu *et al*., 2016, Altabas *et al*., 2023)

As such, novel biochemical and molecular biomarkers are gaining prominence for their potential to reflect inflammation, endothelial dysfunction, oxidative stress, lipid abnormalities, myocardial strain and renal impairment all of which contribute to vascular injury (Rangaswami *et al*., 2020). Emerging biomarkers like high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) reflect systemic inflammation and are predictive of atherosclerotic burden and plaque instability (Kesavadev *et al*., 2021). Natriuretic peptides (BNP, NT-proBNP), traditionally used in heart failure, have now shown value in predicting cardiovascular events in diabetic patients even without overt heart failure (Klonoff *et al*., 2023). Additionally, markers of renal dysfunction such as urinary albumin-to-creatinine ratio (uACR) and cystatin C are strongly associated with increased cardiovascular risk, underscoring the cardio-renal link (Jyotsna *et al*., 2023). Table 6 summarizes key biomarkers relevant for macrovascular risk assessment in T2DM, their pathophysiological significance and potential clinical applications (Wolde *et al*., 2018). Integrating these markers into routine clinical practice possibly through multimarker panels or AI-driven algorithms may enable earlier identification of high-risk individuals and timely initiation of preventive strategies (Liu *et al*., 2025).

Table 3: Recent and ongoing clinical trials in macrovascular risk reduction in T2DM

S. No.	Trial name	Intervention	Objective	Findings	References
1.	CANTOS	Canakinumab (anti-IL-1β monoclonal antibody)	Reduce inflammation-mediated CV events	15% reduction in MACE in post-MI patients incl. T2DM	(Perkovic *et al*., 2024)
2.	REDUCE-IT	Icosapent ethyl (EPA derivative)	Lower triglyceride-related ASCVD risk	25% reduction in primary endpoints	(Ridker *et al*., 2017)
3.	EMPA-KIDNEY	Empagliflozin (SGLT2 inhibitor)	Renal and cardiovascular outcomes	Demonstrated CV and renal benefits	(Bhatt *et al*., 2019)
4.	SELECT	Semaglutide (GLP-1 RA) in overweight patients	Cardiovascular outcomes in obese/T2DM	Ongoing – early results show risk reduction	(Herrington *et al*., 2023)
5.	SURPASS-CVOT	Tirzepatide (dual GIP/GLP-1 RA)	Cardiovascular safety in high-risk T2DM	Ongoing – expected 6.completion 2026	(Deanfield *et al*., 2024)
6.	REVIVED-BCIS2	PCI vs optimal medical therapy	Evaluate PCI in ischemic cardiomyopathy	Showed no survival benefit vs medical therapy	(Nicholls *et al*., 2024)
7.	MetaCardis Project	Gut microbiota modulation via probiotics	Assess impact on systemic inflammation and CV health	Early data suggest microbiota–vascular interaction	(Ryan *et al*., 2025)

Table 4: Recent advances in the secondary prevention of macrovascular complications in T2DM, highlighting mechanistic, microbiome-based and AI-driven strategies.

S. No.	Study	Intervention	Primary findings	Relevance to macrovascular prevention	References
1.	Dulaglutide + Metformin RCT (2022)	Combination therapy in T2DM patients	↑ Endothelial progenitor cells ($CD34^+CD133^+KDR^+$), improved arterial elasticity (↓ baPWV), ↓ IL-6, TNF-α, AGEs; ↑ NO levels	Suggests a mechanism for CV benefit via vascular repair and reduced inflammation	(Vlacho *et al*., 2024)
2.	Linagliptin Add-on (DPP-4 inhibitor) RCT (2020)	Linagliptin added to metformin ± insulin in T2DM + CKD	Improved endothelial function (measured by FMD) and mobilization of EPCs	Supports DPP-4 inhibitor role in endothelial restoration and vascular health	(Sartore *et al*., 2023)
3.	Probiotic Supplementation Trial (2022)	Probiotics (L. acidophilus, L. plantarum) for 6 weeks in T2DM	↓ Systolic/diastolic BP, ↓ atherogenic index (log TG/HDL-C), ↓ Framingham risk score	Preliminary evidence of CVD risk amelioration via gut modulation	(Berberich & Hegele, 2021)
4.	Probiotic (B. breve) RCT (2023)	Bifidobacterium breve supplementation, 12 weeks	↓ HbA1c, LDL, TG; altered microbiome composition	Indicates lipid/glycemic improvement through microbiome intervention	(Forzano *et al*., 2023)
5.	ECG-DiaNet deep learning model (2025)	AI model combining ECG + clinical data to predict T2DM risk	AUROC 0.845 vs. CRF-only 0.821; improved reclassification (NRI, IDI)	Demonstrates early prediction potential-preclinical risk stratification	(Wang *et al*., 2022)
6.	AdaCVD (LLM-based CVD risk predictor) (2025)	Multimodal large language model for CVD risk using heterogeneous data	Outperformed conventional risk scores across diverse subgroups	Enhances precision risk assessment and preventive planning	(Verma *et al*., 2020)
7.	Synbiotic + miRNA protocol (2020–ongoing)	Synbiotic supplementation with gut microbiome & miRNA monitoring	Proposed track of TNF-α, miR-126, miR-146a changes in T2DM	Potential early biomarkers and mechanistic insight into vascular inflammation	(Everett et al., 2020)

Table 5: Key biomarkers for risk stratification in T2DM-associated macrovascular complications

S. No.	Biomarker	Pathophysiological role	Clinical utility	Remarks	References
1.	hs-CRP	Marker of systemic inflammation	Predicts ASCVD risk, plaque instability	High levels linked to MACE	(Eid *et al*., 2023)
2.	IL-6, TNF-α	Pro-inflammatory cytokines	Early indicators of vascular inflammation	Targets for anti-inflammatory therapies	(Eid *et al*., 2023, (Theodorakis & Nikolaou, 2025)
3.	NT-proBNP, BNP	Indicators of myocardial wall stress	Predicts HF, CV mortality, even in asymptomatic patients	Guide for GLP-1 RA/SGLT2i therapy	(Jha *et al*., 2024)
4.	Lipoprotein(a)	Pro-atherogenic lipid particle	Associated with premature atherosclerosis	Genetic testing under consideration	(González-Rivas *et al*., 2023)
5.	Cystatin C	Marker of renal filtration	Better than creatinine in CV risk prediction	Useful in elderly diabetic populations	(González-Rivas *et al*., 2023)
6.	uACR	Microalbuminuria indicator	Reflects endothelial dysfunction, renal microvascular disease	Strong independent predictor of ASCVD	(Jha *et al*., 2024)
7.	Oxidized LDL	Marker of lipid oxidation and foam cell formation	Indicates active atherogenesis	Not yet standardized in routine care	(Eid *et al*., 2023)
8.	Galectin-3	Fibrosis and inflammation	Predicts HF progression, vascular stiffness	Under investigation	(Tsushima & Galloway, 2025)
9.	sICAM-1, VCAM-1	Endothelial activation markers	Linked to early atherosclerosis and plaque vulnerability	Emerging use in clinical trials	(Tsushima & Galloway, 2025)

Knowledge gaps, controversies and translational challenges

Despite advances in managing macrovascular complications in T2DM, several gaps and controversies remain. Intensive glycemic control does not consistently reduce cardiovascular events, as shown in ACCORD, ADVANCE and VADT trials, highlighting the multifactorial nature of disease beyond hyperglycemia. The mechanisms and long-term benefits of anti-inflammatory therapies, SGLT2 inhibitors and GLP-1 receptor agonists in diverse populations remain incompletely understood (Ettehad *et al*., 2016).

Translating trial evidence into practice faces barriers such as high costs, patient adherence, healthcare system readiness and differences between real-world outcomes and RCT(Chalmers *et al*., 2023)s. Advanced omics diagnostics and AI-driven predictive models, though promising, pose challenges including data privacy, cost-effectiveness and regulatory hurdles. Addressing these gaps is essential to develop practical, personalized strategies for the secondary prevention of macrovascular complications in T2DM (Du *et al*., 2009).

CONCLUSION

Macrovascular complications continue to pose a significant challenge in the long-term management of T2DM, being the leading contributors to morbidity and mortality. While tight glycemic control remains foundational for preventing microvascular events, its impact on macrovascular outcomes is limited. This underscores the importance of a more comprehensive and integrative approach in secondary prevention. Recent advancements have reshaped the therapeutic landscape. Cardioprotective agents like SGLT2 inhibitors and GLP-1 receptor agonists have demonstrated benefits that extend beyond glucose regulation, reducing the incidence of MACE, heart failure hospitalizations and renal outcomes. Concurrently, optimized lipid-lowering strategies using statins, PCSK9 inhibitors and icosapent ethyl, alongside targeted blood pressure control and selective antiplatelet therapy, have significantly reduced atherosclerotic risks.

Innovative approaches targeting chronic inflammation (e.g., IL-1β blockade, TNF-α inhibition) and endothelial dysfunction are gaining ground in clinical trials and may soon augment the preventive armamentarium. Moreover, individualized risk stratification using biomarkers, imaging modalities and AI-driven predictive tools promises to tailor interventions more precisely in the near future. The integration of biomarkers such as hs-CRP, NT-proBNP, cystatin C and IL-6 enables earlier identification of high-risk individuals and supports a precision medicine framework. Their use in multimodal risk models could transform secondary prevention into a more targeted and

proactive approach. In conclusion, secondary prevention of macrovascular complications in T2DM demands a multifactorial and proactive strategy that integrates metabolic, cardiovascular and inflammatory control. Future research should emphasize personalized medicine, early intervention and the development of combinatorial therapies to effectively reduce cardiovascular burden and enhance patient outcomes.

Acknowledgment
None

Author's contribution
Fang Qian, Qian Huang: Developed and planned the study, interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions.
Fang Qian, Qian Huang, Jing Dai: Participated in collecting, assessing and interpreting the Data. Made significant contributions to Data interpretation and manuscript preparation.

Funding
None

Data availability statement
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical approval
Not applicable.

Conflict of interest
The authors declare that they have no financial conflicts of interest.

REFERENCES

Adare AF, Tiyare FT and Marine BT (2024). Time to development of macrovascular complications and its predictors among type 2 diabetes mellitus patients at Jimma University Medical Center. *BMC Endocr Disord*., **24**(1): 252.

Ahmad MS, Alslamah T, Alannaz SM, Shaik RA, Ahmad RK, Yusuf M, Khan M and Ghimire A (2021). Prevalence of micro- and macro-vascular complications and their risk factors in type 2 diabetes in the Saudi Arabian population: An analysis from SHIS. *Eur Rev Med Pharmacol Sci*., **25**(12): 4308–4316.

Fatemeh Ahmadian, Elham Razmpoosh, Hanieh-Sadat Ejtahed, Maryam Javadi, Parvin Mirmiran and Fereidoun Azizi (2022). Effects of probiotic supplementation on major cardiovascular-related parameters in patients with type 2 diabetes mellitus: A secondary-data analysis of a randomized double-blind controlled trial. *Diabetol Metab Syndr*., **14**(1): 52.

Pedersen O, Hansen T, Dermitzakis E, Franks PW, Schwenk JM, Adamski J, McCarthy MI, Pearson E, Banasik K, Rasmussen S and Brunak S (2023). Discovery of drug–omics associations in type 2 diabetes with generative deep-learning models. *Nat Biotechnol*., **41**(3): 399–408.

Altabas V, Marinković Radošević J, Špoljarec L, Uremović S, Bulum T (2023). Impact of modern anti-diabetic treatment on endothelial progenitor cells. *Biomedicines*, **11**(11): 3051.

An J, Nichols GA, Qian L, Munis MA, Harrison TN, Li Z, Wei R, Weiss T, Rajpathak S and Reynolds K (2021). Prevalence and incidence of microvascular and macrovascular complications over 15 years among patients with incident type 2 diabetes. *BMJ Open Diabetes Res Care*., **9**(1): e001952.

Andreas D and Stefan C (2020). Revisiting pharmacology of oxidative stress and endothelial dysfunction in cardiovascular disease: Evidence for redox-based therapies. *Free Radic Biol Med*., **157**: 15–37.

Astrup A, Magkos F, Bier DM and others (2020). Saturated fats and health: A reassessment and proposal for food-based recommendations: JACC State-of-the-Art Review. *J Am Coll Cardiol*., **76**(7): 844–857.

Awal HB, Nandula SR, Domingues CC, Dore FJ, Kundu N, Brichacek B, Fakhri M, Elzarki A, Ahmadi N, Safai S, Fosso M, Amdur RL and Sen S (2020). Linagliptin compared with placebo improves $CD34^+$ endothelial progenitor cells in type 2 diabetes subjects with chronic kidney disease taking metformin and/or insulin: A randomized controlled trial. *Cardiovasc Diabetol*., **19**(1): 72.

Baumblatt J, Lee R and Patel S (2024). Prevalence of total, diagnosed and undiagnosed diabetes in adults: United States, August 2021–August 2023. *MMWR Morb Mortal Wkly Rep*., **73**: 2024.

Berberich AJ and Hegele RA (2021). A modern approach to dyslipidemia. *Endocr Rev*., **43**(4): 611–653.

Bermúdez V, Rojas-Quintero J and Velasco M (2018). The quest for immunotherapy in atherosclerosis: CANTOS study, interleukin-1β and vascular inflammation. *J Thorac Dis*., **10**(1): 64–69.

Bethel MA, Sloan FA, Belsky D and Feinglos MN (2007). Longitudinal incidence and prevalence of adverse outcomes of diabetes mellitus in elderly patients. *Arch Intern Med*., **167**(9): 921–927.

Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC and Ballantyne CM (2019). Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*., **380**(1): 11–22.

Cade WT (2008). Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther*., **88**(11): 1322–1335.

Chaiyasut C, Sivamaruthi BS, Lailerd N, Sirilun S, Thangaleela S, Khongtan S, Bharathi M, Kesika P, Saelee M, Choeisoongnern T, Fukngoen P, Peerajan S and Sittiprapaporn P (2023). Influence of Bifidobacterium breve on the glycaemic control, lipid

profile and microbiome of type 2 diabetic subjects: A preliminary randomized clinical trial. *Pharmaceuticals (Basel)*, **16**(5): 678.

Chakraborty S, Verma A, Garg R, Singh J and Verma H (2023). Cardiometabolic risk factors associated with type 2 diabetes mellitus: A mechanistic insight. *Clin Med Insights Endocrinol Diabetes*., **16**: 11795514231220780.

Chalmers J, Mourad JJ, Brzozowska-Villatte R, De Champvallins M and Mancia G (2023). Benefit of treatment based on indapamide mostly combined with perindopril on mortality and cardiovascular outcomes: A pooled analysis of four trials. *J Hypertens*, **41**(3): 508–515.

Chan JCH and Chan MCY (2023). SGLT2 inhibitors: The next blockbuster multifaceted drug? *Medicina (Kaunas)*, **59**(2): 1–9.

Chawla A, Chawla R and Jaggi S (2016). Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian J Endocrinol Metab*., **20**(4): 546–551.

Cho NH, Shaw JE and Karuranga S (2018). IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract*., **138**: 271–281.

Cole JB and Florez JC (2020). Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol*., **16**(7): 377–390.

Corrao S, Janić M, Maggio V and Rizzo M (2025). Machine learning and deep learning in diabetology: Revolutionizing diabetes care. *Front Clin Diabetes Healthc*, **6**: 1547689.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A and Buse JB (2022). Management of hyperglycaemia in type 2 diabetes, 2022: A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*, **65**(12): 1925–1966.

Deanfield J, Landmesser U and Luscher TF (2024). Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: A prespecified analysis of the SELECT trial. *Lancet*, **404**(10454): 773–786.

Di Giacomo-Barbagallo F, Andreychuk N, Scicali R, Gonzalez-Lleó A, Piro S, Masana L and Ibarretxe D (2025). Inclisiran: Reasons for a novel agent in a crowded therapeutic field. *Curr Atheroscler Rep*., **27**(1): 25.

Du X, Ninomiya T, de Galan B, Abadir E, Chalmers J, Pillai A, Woodward M, Cooper M, Harrap S, Hamet P, Poulter N, Lip GY and Patel A (2009). Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: Results of the ADVANCE study. *Eur Heart J*., **30**(9): 1128–1135.

Dunn TJ, Tan X, Harton J, Kim S, Xie L, Gamble C and Rotroff D (2025). Macrovascular and microvascular complications in US Medicare enrollees with type 2 diabetes with and without atherosclerotic cardiovascular disease. *Diabetes Obes Metab*., **27**(8): 4137–4137.

Eid SA, Rumora AE, Beirowski B, Bennett DL, Hur J, Savelieff MG and Feldman EL (2023). New perspectives in diabetic neuropathy. *Neuron*, **111**(17): 2623–2641.

Einarson TR, Acs A, Ludwig C and Panton UH (2018). Prevalence of cardiovascular disease in type 2 diabetes: A systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovasc Diabetol*., **17**(1): 83.

Engelen SE, Robinson AJB, Zurke YX and Monaco C (2022). Therapeutic strategies targeting inflammation and immunity in atherosclerosis: How to proceed? *Nat Rev Cardiol*., **19**(8): 522–542.

Espinoza MA, Munoz N and González-Vega C (2022). Health and economic effects on patients with type 2 diabetes mellitus in the long run: Predictions for the Chilean population. *Diabetol Metab Syndr*., **14**(1): 116.

Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. (2016). Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. *Lancet*, **387**(10022): 957–967.

Everett BM, MacFadyen JG, Thuren T, Libby P, Glynn RJ and Ridker PM (2020). Inhibition of interleukin-1β and reduction in atherothrombotic cardiovascular events in the CANTOS trial. *J Am Coll Cardiol*., **76**(14): 1660–1670.

Forzano I, Wilson S, Lombardi A, Jankauskas SS, Kansakar U, Mone P, Varzideh F and Santulli GS (2023). SGLT2 inhibitors: An evidence-based update on cardiovascular implications. *Expert Opin Investig Drugs*., **32**(9): 839–847.

Fowler MJ (2008). Microvascular and macrovascular complications of diabetes. *Clin Diabetes*., **26**(2): 77-82.

Gallo G, Volpe M and Savoia C (2022). Endothelial dysfunction in hypertension: Current concepts and clinical implications. *Front Med*., **8**: 747720.

Gebremariam GT, Biratu S, Alemayehu M, Welie AG, Beyene K, Sander B and Gebretekle GB (2022). Health-related quality of life of patients with type 2 diabetes mellitus at a tertiary care hospital in Ethiopia. *PLoS One*., **17**(2): e0262960.

González-Rivas JP, Pavlovska I, Polcrova A, Nieto-Martínez R and Mechanick JI (2023). Transcultural lifestyle medicine in type 2 diabetes care: Narrative review of the literature. *Am J Lifestyle Med*., **17**(4): 518-559.

Guan H, Zhang J, Wang F, Liu P and Xu Y (2024). Advances in secondary prevention mechanisms of macrovascular complications in type 2 diabetes mellitus patients: A comprehensive review. *Eur J Med Res*., **29**(1): 152.

Haile K and Timerga A (2020). Dyslipidemia and its associated risk factors among adult type 2 diabetic patients at Jimma University Medical Center, Jimma, Southwest Ethiopia. *Diabetes Metab Syndr Obes*., **13**: 4589–4597.

Hasheminasabgorji E and Jha JC (2021). Dyslipidemia, diabetes and atherosclerosis: Role of inflammation and ROS-redox-sensitive factors. *Biomedicines*, **9**(11): 1602.

WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, Preiss D, Judge P, Mayne KJ, Ng SYA, Sammons E, Zhu D, Hill M, Stevens W, Wallendszus K, Brenner S, Cheung AK, Liu ZH, Li J, Hooi LS, Liu W, Kadowaki T, Nangaku M, Levin A, Cherney D, Maggioni AP, Pontremoli R, Deo R, Goto S, Rossello X, Tuttle KR, Steubl D, Petrini M, Massey D, Eilbracht J, Brueckmann M, Landray MJ, Baigent C and Haynes R (2023). Empagliflozin in patients with chronic kidney disease. *N Engl J Med*., **388**(2): 117–127.

Hossain MJ, Al-Mamun M and Islam MR (2024). Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused. *Health Sci Rep*., **7**(3): e2004.

Hrncir T (2022). Gut microbiota dysbiosis: Triggers, consequences, diagnostic and therapeutic options. *Microorganisms*, **10**(3): 1–12.

Huang X, Liu H, Zhang L, Wang Y and Chen J (2025). Global, regional and national burden of type 2 diabetes mellitus caused by high BMI from 1990 to 2021 and forecasts to 2045: Analysis from the Global Burden of Disease Study 2021. *Front Public Health*, **13**: 2025.

Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: Secondary analyses of the EMPA-KIDNEY trial (2024). *Lancet Diabetes Endocrinol*, **12**(1): 51–60.

Jha R, Lopez-Trevino S, Kankanamalage HR and Jha JC (2024). Diabetes and renal complications: An overview on pathophysiology, biomarkers and therapeutic interventions. *Biomedicines*, **12**(5): 1098.

Jyotsna F, Ahmed A, Kumar K, Kaur P, Chaudhary MH, Kumar S, Khan E, Khanam B, Shah SU, Varrassi G, Khatri M, Kumar S and Kakadiya KA (2023). Exploring the complex connection between diabetes and cardiovascular disease: Analyzing approaches to mitigate cardiovascular risk in patients with diabetes. *Cureus*, **15**(8): e43882.

Kesavadev J, Krishnan G and Mohan V (2021). Digital health and diabetes: Experience from India. *Ther Adv Endocrinol Metab*., **12**: 20420188211054676.

Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H and Al Kaabi J (2020). Epidemiology of type 2 diabetes – global burden of disease and forecasted trends. *J. Epidemiol. Glob. Health*, **10**(1): 107–111.

Klonoff AN, Andy Lee WA, Xu NY, Nguyen KT, DuBord A and Kerr D (2023). Six digital health technologies that will transform diabetes. *J Diabetes Sci Technol*., **17**(1): 239–249.

Kosiborod M, Gomes MB, Nicolucci A, Pocock S, Rathmann W, Shestakova MV, Watada H, Shimomura I, Chen H, Cid-Ruzafa J, Fenici P, Hammar N, Surmont F, Tang F and Khunti K (2018). Vascular complications in patients with type 2 diabetes: Prevalence and associated factors in 38 countries (the DISCOVER study program). *Cardiovasc Diabetol*., **17**(1): 1–11.

Li J, Chattopadhyay K, Xu M, Chen Y, Hu F, Chu J and Li L (2020). Prevalence and associated factors of vascular complications among inpatients with type 2 diabetes: A retrospective database study at a tertiary care department, Ningbo, China. *PLoS One*., **15**(6): e0235375.

Liu Z, Lu J, Sha W and Lei T (2025). Comprehensive treatment of diabetic endothelial dysfunction based on pathophysiological mechanism. *Front Med*., **12**: 2025.

Lopaschuk GD and Verma S (2020). Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: A state-of-the-art review. *JACC Basic Transl Sci*., **5**(6): 632–644.

Lu X, Xie Q, Pan X, Zhang R, Zhang X, Peng G, Zhang Y, Shen S and Tong N (2024). Type 2 diabetes mellitus in adults: Pathogenesis, prevention and therapy. *Signal Transduct Target Ther*., **9**(1): 262.

Frederike Lübeck, Jonas Wildberger, Frederik Träuble, Maximilian Mordig, Sergios Gatidis, Andreas Krause and Bernhard Schölkopf (2025). Adaptable cardiovascular disease risk prediction from heterogeneous data using large language models. *NPJ Digit Med*., **8**: 2025.

Lukic N, Macvanin MT, Gluvic Z, Rizzo M, Radak D, Suri JS and Isenovic ER (2023). SGLT-2 inhibitors: The next-generation treatment for type 2 diabetes mellitus. *Curr Med Chem*., **31**(30): 4781–4806.

Maida E, Caruso P, Bonavita S, Abbadessa G, Miele G, Longo M, Scappaticcio L, Ruocco E, Trojsi F, Esposito K, Lavorgna L and Maiorino MI (2025). Digital health in diabetes care: A narrative review from monitoring to the management of systemic and neurologic complications. *J Clin Med*., **14**(12): 1–15.

Mansour A, Mousa M, Abdelmannan D, Tay G, Hassoun A and Alsafar H (2023). Microvascular and macrovascular complications of type 2 diabetes mellitus: Exome wide association analyses. *Front Endocrinol*, **14**: 2023.

Mitsis A, Myrianthefs M, Sokratous S, Karmioti G, Kyriakou M, Drakomathioulakis M, Tzikas S, Kadoglou NPE, Karagiannidis E, Nasoufidou A, Fragakis N, Ziakas A and Kassimis G (2024). Emerging therapeutic targets for acute coronary syndromes: Novel advancements and future directions. *Biomedicines*, **12**(8): 1670.

Mohsen F and Shah Z (2025). Improving early prediction of type 2 diabetes mellitus with ECG-DiaNet: A multimodal neural network leveraging electrocardiogram and clinical risk factors. *Front Artif Intell*., **8**: 2025.

Monique B and Brian HA (2023). Peripheral arterial disease: A small and large vessel problem. *Am Heart J Plus Cardiol Res Pract*., **28**: 100291.

Moschonis G, Siopis G, Jung J, Eweka E, Willems R, Kwasnicka D, Asare BY, Kodithuwakku V, Verhaeghe N, Vedanthan R, Annemans L, Oldenburg B and Manios Y (2023). Effectiveness, reach, uptake and feasibility of digital health interventions for adults with type 2 diabetes: A systematic review and meta-analysis of randomised controlled trials. *Lancet Digit Health*., **5**(3): e125–e143.

Muttiah B and Hanafiah A (2025). Gut microbiota and cardiovascular diseases: Unraveling the role of dysbiosis and microbial metabolites. *Int J Mol Sci*., **26**(9): 4264.

Neuen BL, Yeung EK, Rangaswami J, Vaduganathan M (2025). Combination therapy as a new standard of care in diabetic and non-diabetic chronic kidney disease. *Nephrol Dial Transplant*., **40**(Suppl 1): i59–i69.

Nicholls SJ, Lincoff AM and Kastelein JJP (2024). Comparison of tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease: SURPASS-CVOT design and baseline characteristics. *Am Heart J*., **267**: 1–11.

Oikonomou EK and Khera R (2023). Machine learning in precision diabetes care and cardiovascular risk prediction. *Cardiovasc Diabetol*., **22**(1): 259.

Overgaard KS, Mohamed RA, Andersen TR, Lambrechtsen J, Egstrup K and Auscher S (2024). ProtecT-2-D trial protocol: Cardiovascular protection in patients with type 2 diabetes and established heart and/or vascular disease at a cardio-metabolic clinic-a randomized controlled trial. *Cardiovasc Diabetol*., **23**(1): 241.

Papa G, Degano C, Iurato MP, Licciardello C, Maiorana R and Finocchiaro C (2013). Macrovascular complication phenotypes in type 2 diabetic patients. *Cardiovasc Diabetol*., **12**: 20.

Parker ED, Lin J, Mahoney T, Ume N, Yang G, Gabbay RA, ElSayed NA and Bannuru RR (2024). Economic costs of diabetes in the United States in 2022. *Diabetes Care*, **47**(1): 26–43.

Perkovic V, Neal B and Mahaffey KW (2024). Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med*., **391**(2): 109–121.

Pi-Sunyer X (2014). The Look AHEAD trial: A review and discussion of its outcomes. *Curr Nutr Rep*., **3**(4): 387–391.

Rangaswami J, Tuttle KR and Vaduganathan M (2020). Cardio-renal-metabolic care models: Toward achieving effective interdisciplinary care. *Circ Cardiovasc Qual Outcomes*., **13**(11): e007264.

Regassa LD, Tola A and Ayele Y (2021). Prevalence of cardiovascular disease and associated factors among type 2 diabetes patients in selected hospitals of Harari region, Eastern Ethiopia. *Front Public Health*, **8**: 618859.

Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P and Glynn RJ (2017). Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*., **377**(12): 1119–1131.

Robert HE, Karin EB and Ira JG (2021). Cardiovascular disease in diabetes, beyond glucose. *Cell Metab*., **33**(8): 1519–1545.

Roy B (2025). Pathophysiological mechanisms of diabetes-induced macrovascular and microvascular complications: The role of oxidative stress. *Med Sci*., **13**(3): 87.

Ryan M, Westaby D and Mamas MA (2025). Medical therapy and outcomes in REVIVED-BCIS2 and STICHES: An individual patient data analysis. *Eur Heart J*., **46**(22): 2052–2062.

Sartore G, Ragazzi E, Caprino R and Lapolla A (2023). Long-term HbA1c variability and macro-/micro-vascular complications in type 2 diabetes mellitus: A meta-analysis update. *Acta Diabetol*, **60**(6): 721–738.

Sibbing D, Blaha MJ, Chawla R, Lavalle-Cobo A, Kishore A, Lanas A, Li L, Santilli F, Schnell O and Shi Z (2024). Dual-pathway inhibition with low-dose aspirin and rivaroxaban versus aspirin monotherapy in patients with coronary artery disease and peripheral artery disease: Systematic literature review and meta-analysis. *Eur Cardiol*., **19**: e01.

Song WR, Li Q, Zhang Y, Zhao J and Wang L (2024). Secondary diabetes due to different etiologies: Four case reports. *World J Clin Cases*., **12**(16): 2813–2821.

Sun B, Luo Z and Zhou J (2021). Comprehensive elaboration of glycemic variability in diabetic macrovascular and microvascular complications. *Cardiovasc Diabetol*., **20**(1): 9.

Tantigegn S, Ewunetie AA, Agazhe M, Aschale A, Gebrie M, Diress G and Alamneh BE (2023). Time to diabetic neuropathy and its predictors among adult type 2 diabetes mellitus patients in Amhara regional state comprehensive specialized hospitals, Northwest Ethiopia: A retrospective follow-up study. *PLoS One*., **18**(4): e0284120.

Theodorakis N and Nikolaou M (2025). From cardiovascular-kidney-metabolic syndrome to cardiovascular-renal-hepatic-metabolic syndrome: Proposing an expanded framework. *Biomolecules*, **15**(2): 213.

Tian X, Wang L, Zhong L, Zhang K, Ge X, Luo Z, Zhai X and Liu S (2025). Research progress and future directions in the pathophysiological mechanisms of type 2 diabetes mellitus from the perspective of precision medicine. *Front Med (Lausanne)*, **12**: 1555077.

Tsushima Y and Galloway N (2025). Glycemic targets and prevention of complications. *J Clin Endocrinol Metab*., **110**(Suppl 2): S100–S111.

Verma S, McGuire DK, Bain SC, Bhatt DL, Leiter LA, Mazer CD, Monk Fries T, Pratley RE, Rasmussen S, Vrazic H, Zinman B and Buse JB (2020). Effects of glucagon-like peptide-1 receptor agonists liraglutide and semaglutide on cardiovascular and renal outcomes across body mass index categories in type 2 diabetes: Results of the LEADER and SUSTAIN-6 trials. *Diabetes Obes Metab*., **22**(12): 2487–2492.

Viigimaa M, Sachinidis A, Toumpourleka M, Koutsampasopoulos K, Alliksoo S and Titma T (2020). Macrovascular complications of type 2 diabetes mellitus. *Curr Vasc Pharmacol*., **18**(2): 110–116.

Vlacho B, Molló Iniesta À, Gratacòs M, Mata-Cases M, Rubinat E, Berenguera A, Cos FX, Franch-Nadal J and Mauricio D (2024). Effectiveness of a multicomponent healthcare intervention on blood pressure and lipids among subjects with poorly controlled type 2 diabetes: Findings from the INTEGRA study. *Prim Care Diabetes*., **18**(4): 402–408.

Wang L, Zhao Y and Zhang W (2022). The role of the gut microbiota in health and cardiovascular diseases. *Mol Biomed*, **3**(1): 30.

Wang W, Li H and Zhang P (2023). Dietary patterns and cardiometabolic health: Clinical evidence and mechanism. *MedComm* (2020), **4**(1): e212.

Wang Y, Chen H and Zhang S (2022). Medical costs associated with diabetes complications in Medicare beneficiaries aged 65 years or older with type 2 diabetes. *Diabetes Care*, **45**(11): 2570–2576.

Weng W, Liang Y, Brett J, Hobbs T and Baeres FMM (2020). Longitudinal analysis of atherosclerotic cardiovascular disease risk and healthcare costs in newly diagnosed type 2 diabetes in a real-world setting. *J Diabetes Complications.,* **34**(5): 1–8.

Wilcox T, Buse JB and McGuire DK (2020). Diabetic agents, from metformin to SGLT2 inhibitors and GLP1 receptor agonists: JACC Focus Seminar. *J Am Coll Cardiol*., **75**(16): 1956–1974.

Wing RR (2022). Effects of intensive lifestyle intervention on all-cause mortality in older adults with type 2 diabetes and overweight/obesity: Results from the Look AHEAD study. *Diabetes Care*, **45**(5): 1252–1259.

Wolde HF, Atsedeweyen A, Jember A, Awoke T, Mequanent M, Tsegaye AT and Alemu S (2018). Predictors of vascular complications among type 2 diabetes mellitus patients at University of Gondar Referral Hospital: A retrospective follow-up study. *BMC Endocr Disord*., **18**(1): 52.

Handelsman Y, Butler J, Bakris GL, DeFronzo RA, Fonarow GC, Green JB, Grunberger G, Januzzi JL Jr, Klein S, Kushner PR, McGuire DK, Michos ED, Morales J, Pratley RE, Weir MR, Wright E and Fonseca VA (2023). Early intervention and intensive management of patients with diabetes, cardiorenal and metabolic diseases. *J Diabetes Complications*., **37**(2): 108389.

Yu CG, Zhang N, Yuan SS, Ma Y, Yang LY, Feng YM and Zhao D (2016). Endothelial progenitor cells in diabetic microvascular complications: Friends or foes? *Stem Cells Int*., **2016**: 1803989.

Zeinali F, Hosseini SA and Karimi M (2020). Effects of synbiotic supplementation on gut microbiome, serum level of TNF-α and expression of microRNA-126 and microRNA-146a in patients with type 2 diabetes mellitus: Study protocol for a double-blind controlled randomized clinical trial. *Trials*, **21**(1): 324.

Zhang Y, Li Z and Hao Y (2025). Comparative efficacy of GLP-1 RAs and SGLT-2 inhibitors in reducing cardiovascular events in type 2 diabetes according to baseline use of metformin: A systematic review and meta-analysis of randomized controlled trials. *Eur J Med Res*., **30**(1): 13.