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Metabolism and Target Organ Damage

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Mechanism-driven therapy for diabetic cardiovascular disease

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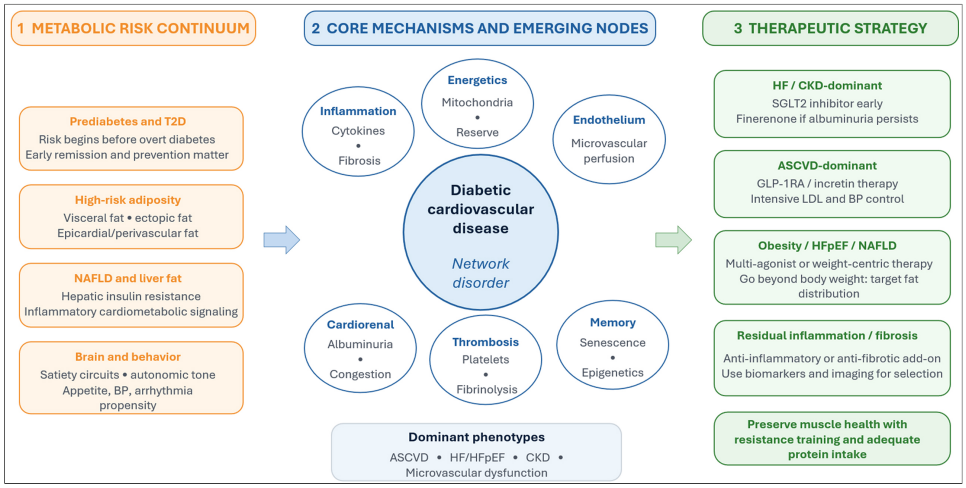

DIABETIC CARDIOVASCULAR DISEASE IS A NETWORK DISORDER, NOT A GLUCOSE-ONLY COMPLICATION

Diabetes accelerates cardiovascular (CV) target-organ damage through multiple interacting biological modules that amplify risk even when glycemia is modestly controlled[1]. These modules include (i) adipose tissue dysfunction with altered adipokine secretion and immune-cell infiltration; (ii) ectopic lipid deposition in liver, myocardium, and perivascular/epicardial fat; (iii) endothelial dysfunction with impaired nitric oxide bioavailability and heightened oxidative stress; (iv) chronic kidney disease (CKD)-mediated volume, pressure, and uremic-toxin stress; and (v) autonomic and neurohormonal activation that promotes hypertension, arrhythmias,

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and remodeling[1]. The clinical spectrum includes macrovascular disease as well as myocardial, renal, and microvascular complications, including heart failure (HF) with preserved ejection fraction (HFpEF), diabetic cardiomyopathy, CKD, and coronary microcirculatory dysfunction[1]. Importantly, cardiometabolic risk accrues even before overt diabetes; emerging evidence suggests that achieving remission of prediabetes is associated with lower subsequent cardiorenal and CV morbidity[2], reinforcing prevention and early intervention as core therapeutic strategies. Likewise, the distribution of body fat (visceral and ectopic depots) may be more relevant to risk modification than body weight alone[3].

CORE MECHANISMS AND EMERGING NODES CONNECTING METABOLISM TO CV INJURY

Core biological modules linking metabolism to diabetic cardiovascular disease (DCVD) include the following[4]. First, immune-metabolic coupling: insulin resistance and adipose stress skew innate and adaptive immune tone toward pro-inflammatory phenotypes, thereby sustaining cytokine signaling that destabilizes plaques and promotes myocardial fibrosis[5]. Second, myocardial energetics: diabetes shifts substrate use toward fatty acid oxidation, increasing the oxygen cost per ATP and reducing efficiency and metabolic flexibility; mitochondrial dysfunction and impaired ketone handling further contribute to the loss of contractile reserve[6]. Third, vascular biology: advanced glycation end products, oxidative stress, and impaired endothelial repair compromise vasomotor function and microvascular perfusion, thereby contributing to angina without obstructive coronary disease and to HFpEF[7]. Fourth, the cardiorenal axis: glomerular hyperfiltration, albuminuria, and tubuloglomerular feedback abnormalities link diabetes to sodium retention, congestion, and progressive remodeling[8]. Finally, thrombo-inflammatory signaling, platelet hyperreactivity, impaired fibrinolysis, and altered lipoprotein composition create a pro-atherothrombotic milieu[9].

An underappreciated yet increasingly actionable node is epicardial and perivascular adipose tissue[10]. In diabetes and obesity, these depots expand and shift toward a pro-inflammatory, pro-fibrotic secretome that acts locally on the coronary microcirculation and the adjacent myocardium[11]. This paracrine signaling can promote microvascular rarefaction, myocardial stiffness, and atrial remodeling, thereby providing a mechanistic link between adiposity and phenotypes such as HFpEF, microvascular angina, and atrial fibrillation[12].

Additional emerging mechanisms likely contribute to persistent risk despite contemporary risk-factor control. Gut-immune-metabolic crosstalk, including altered bile acid signaling and microbial-derived metabolites, may amplify vascular inflammation and insulin resistance[13]. At the tissue level, cellular senescence and epigenetic metabolic memory can sustain oxidative stress and endothelial dysfunction even after glycemic improvement, supporting the rationale for earlier intervention and therapies that directly target inflammation, fibrosis, and vascular repair[14]. Nonalcoholic fatty liver disease (NAFLD) should be viewed as both a marker and mediator of high-risk adiposity, linking hepatic insulin resistance and inflammatory signaling to atherogenesis and HFpEF risk; therapies that reduce liver fat (intensive lifestyle change and incretin-based or multi-agonist pharmacotherapy) may therefore confer benefits beyond body mass index (BMI) alone[15-18]. Finally, the brain is not merely an appetite "controller" but a cardiometabolic effector organ. Central satiety circuits and autonomic pathways shape sympathetic tone, blood pressure, propensity for arrhythmias, and cardiometabolic behavior, providing an additional mechanistic lens for incretin-based therapies[19].

THERAPEUTIC STRATEGIES ALIGNED TO THE MECHANISM: WHAT HAS CHANGED?

Outcome trials have shown that mechanism-targeted cardiometabolic therapies improve hard outcomes in patients with DCVD or related high-risk cardiometabolic phenotypes. Sodium-glucose cotransporter-2 (SGLT2) inhibitors provide rapid benefits in HF and CKD. These effects likely reflect natriuresis, reduced

Table 1. Phenotype-guided mechanism-based treatment priorities in diabetic cardiovascular disease

Mechanistic driver	Dominant phenotype and clinical clues	Therapeutic priority and strategy
Cardiorenal hemodynamics and congestion	HF (including HFpEF), CKD, albuminuria, volume sensitivity	SGLT2 inhibitor early; optimize HF and hypertension therapy; consider finerenone with albuminuria[20,36]
Adiposity and immune-metabolic inflammation	Obesity, visceral or epicardial fat, NAFLD, HFpEF symptoms, atrial arrhythmia tendency	Incretin-based or multi-agonist weight-centric therapy; lifestyle with resistance training; address sleep and BP[15,16,25,39]
Atherothrombosis and endothelial dysfunction	Established ASCVD, high plaque burden, microvascular angina	Incretin therapy plus intensive LDL and BP control; antiplatelet strategy per risk; smoking cessation[21,22,41]
Fibrosis and residual inflammatory risk	Elevated hsCRP or IL-6, diabetic kidney disease, imaging fibrosis, persistent risk despite guideline therapy	Finerenone where indicated; consider anti-inflammatory approaches in selected patients; monitor biomarkers[33-36]

ASCVD: Atherosclerotic cardiovascular disease; BP: blood pressure; CKD: chronic kidney disease; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; LDL: low-density lipoprotein; NAFLD: nonalcoholic fatty liver disease; SGLT2: sodium-glucose cotransporter-2.

congestion, restoration of tubuloglomerular feedback, and improved myocardial efficiency[20]. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduce major adverse cardiovascular disease (CVD) events, primarily in atherosclerotic phenotypes, plausibly via weight loss, blood pressure reduction, improved endothelial function, and anti-inflammatory effects[21]. Oral semaglutide has been associated with a significantly lower risk of major adverse CVD events in type 2 diabetes (T2D) and atherosclerotic CVD (ASCVD), CKD, or both, without increasing the incidence of serious adverse events[22]. The recent demonstration that an oral GLP-1RA formulation can deliver CVD benefit reinforces the importance of route of administration and adherence-friendly options in shaping population-level impact, particularly in primary care settings, where injectable therapies may face barriers[23].

A practical implication is the use of phenotype-driven sequencing rather than uniform escalation [Table 1]. In HF and CKD-dominant presentations (congestion, albuminuria, declining estimated glomerular filtration rate), prioritize early SGLT2 inhibition and consider add-on non-steroidal mineralocorticoid receptor antagonism if albuminuria persists. In ASCVD-dominant disease (prior myocardial infarction or stroke, high coronary plaque burden), prioritize incretin-based therapy alongside intensive lipid and blood pressure control. In obesity-driven cardiomyopathy or HFpEF (visceral or epicardial adiposity, exercise intolerance), weight-centric incretin or multi-agonist strategies may be foundational, paired with structured exercise to preserve lean mass.

It should be emphasized that recent outcome trials (SELECT, SURPASS-CVOT, SOUL[22,24-26]) suggest that the CVD benefits of incretin-based therapies may not be fully explained by weight loss alone. Clearly, the development of incretin-based therapies has been a remarkable advance in the management of patients living with CVD-CKD-metabolic syndrome, including T2D and obesity. Because of their powerful effects on appetite and food craving, which lead to reduced food intake and substantial weight loss, the assumption is that the effects of incretins on weight loss are directly related to the reduction in CVD events observed in these recent trials. This has spurred the continued development of even more powerful incretin-based therapies that would produce greater weight loss, with the hope of generating further benefits in terms of protection against adverse CVD outcomes. However, there appears to be a mismatch between the degree of weight loss and the observed CVD benefits with incretin-based therapies. In a prespecified analysis of SELECT, the CV benefit of semaglutide appeared independent of weight loss, and the magnitude of weight reduction was similar to that achieved in Look AHEAD. However, Look AHEAD was an intensive lifestyle intervention trial conducted in adults with overweight or obesity and T2D, with distinct behavioral context and background medication dynamics, whereas SELECT and SURPASS-CVOT evaluated pharmacotherapy. Therefore, direct mechanistic comparisons should be made cautiously, because the biological pathways

engaged by weight loss and the accompanying cardiometabolic milieu may differ meaningfully across these settings. Notably, the primary Look AHEAD analysis did not show a reduction in CV events despite greater weight loss in the intervention group, whereas SELECT showed a small association between CV benefit and reduction in waist circumference, a crude anthropometric marker of abdominal-visceral adiposity[24,25,27]. In patients with T2D, the SURPASS-CVOT trial showed that, at 36 months, the magnitude of weight loss in the tirzepatide group (-11.6%) was more than twice that in the dulaglutide group (-4.8%). Despite this substantial difference in weight loss between the two treatment arms, the primary endpoint occurred in 12.2% of patients in the tirzepatide group *vs.* 13.1% in the dulaglutide group [$P = 0.003$ for hazard ratio (HR) noninferiority and $P = 0.09$ for HR superiority][26]. In patients with T2D and atherosclerotic CVD, CKD, or both, the SOUL trial showed that oral semaglutide at a target dose of 14 mg daily resulted in a 14% reduction (HR 0.86; 95% confidence interval (CI): 0.77 to 0.96; $P = 0.006$) in the primary endpoint of major adverse CVD events (a composite of death from CVD causes, nonfatal myocardial infarction, or nonfatal stroke). However, there was only an approximately 3 kg difference in body weight loss in the semaglutide group *vs.* placebo (estimated difference -2.95 kg; 95%CI: -3.18 to -2.73)[22].

Thus, weight loss alone may not be an adequate metric for fully appreciating the benefits of incretin-based therapies on inflammatory and other processes that modulate CVD risk. In HFpEF, the benefits for functional capacity and quality of life are likely mediated by treating obesity, not necessarily by HFpEF itself, and improvements in N-terminal pro-B-type natriuretic peptide levels and CVD outcomes may also be driven by the incretin pathway rather than just weight loss[28,29].

Many cardiometabolic imaging studies have shown that patients with T2D have greater visceral adipose tissue (VAT) and liver fat than individuals without T2D[17,18]. As weight loss induced by diet or physical activity/exercise can also produce a significant loss of visceral/ectopic fat way beyond what could be estimated by the magnitude of weight loss[30,31], one likely scenario in the SURPASS-CVOT trial is that the energy deficit achieved in the dulaglutide arm was sufficient to induce a substantial mobilization of VAT and of liver fat that could not be fully appreciated from the magnitude of weight loss. Imaging studies measuring these hidden fat depots have reported marked reductions in VAT and liver fat with incretin-based therapies. Dedicated cardiometabolic imaging trials with incretin-based therapies will need to be conducted to confirm this hypothesis[16,32]. With the relevance of these compounds to the management of patients with high-risk adiposity phenotypes, there is an opportunity to go beyond body weight and weight loss as clinically relevant metrics/outcomes. By measuring VAT and ectopic fat depots, as well as critical behaviors and their outcomes, we may be better positioned to understand how these revolutionary compounds work and optimize their use in clinical practice.

Next-generation incretin and weight-centric therapeutics

Dual and triple incretin agonists [e.g., glucagon-like peptide-1 (GLP-1)/glucose-dependent insulinotropic polypeptide (GIP) and GLP-1/GIP/glucagon] and potent anti-obesity pharmacotherapy shift the field toward adiposity as a treatable mechanism. Beyond weight loss, reductions in VAT and ectopic fat (hepatic steatosis and epicardial fat) may reprogram inflammatory tone and improve diastolic function. Key questions for DCVD include whether a greater reduction in adiposity yields incremental plaque stabilization, whether it modifies arrhythmia burden through autonomic and atrial remodeling, and how best to sequence incretin-based agents with SGLT2 inhibitors and guideline-directed HF therapies.

Inflammation, fibrosis, and vascular repair as explicit targets

Diabetes-related CV injury exhibits a prominent inflammatory-fibrotic signature[33]. Clinical proof of concept for anti-inflammatory risk reduction in atherosclerosis [e.g., interleukin (IL)-1β pathway inhibition or low-dose colchicine strategies] raises the possibility of targeted use in ASCVD-dominant DCVD with

residual inflammatory risk despite optimal lipid lowering[34,35]. In parallel, non-steroidal mineralocorticoid receptor antagonism with finerenone reduces cardiorenal events in T2D with CKD and albuminuria, supporting a broader anti-fibrotic paradigm[33,36]. Future directions include identifying biomarkers [e.g., high-sensitivity C-reactive protein (hsCRP), IL-6, albuminuria, imaging of epicardial fat or myocardial fibrosis] to guide patient matching to anti-inflammatory or anti-fibrotic intensification. From a practical standpoint, anti-inflammatory intensification is most defensible in ASCVD-dominant DCVD with evidence of residual inflammatory risk (e.g., persistently elevated hsCRP despite optimized lipid lowering) and recurrent events or high plaque burden, while anti-fibrotic intensification is most actionable in T2D with CKD and albuminuria (where finerenone is indicated) and in HFpEF/structural heart disease phenotypes where imaging or biomarkers suggest a fibrotic substrate. These phenotype cues can help avoid indiscriminate add-on therapy while trials refine precision selection.

Combination therapy, implementation, and precision cardiometabolic care

The highest-risk patients rarely have isolated disease. They typically present with overlapping ASCVD, HF, and CKD. A mechanistically rational combination therapy, including SGLT2 inhibition to improve cardiorenal hemodynamics, incretin-based therapy to reduce adiposity and inflammation, and aggressive lipid and blood pressure control, should be considered the default rather than the exception, unless limited by tolerability or other factors such as cost. The field now requires implementation science: simplifying algorithms, integrating multidisciplinary care, and assessing real-world adherence. Precision approaches may arise from (i) phenotyping (ASCVD-dominant *vs*. HF/CKD-dominant); (ii) biomarker stratification (inflammatory risk, albuminuria); and (iii) imaging-enabled evaluation of visceral/epicardial fat, plaque features, and myocardial fibrosis. Ultimately, the goal is to align therapy to the mechanism, delivering earlier and more durable prevention of diabetic target-organ damage.

Key implementation barriers include therapeutic inertia, fragmented cardiology-endocrinology-nephrology workflows, injection aversion, and payer-driven step therapy. Actionable solutions include simple phenotype-based algorithms embedded in electronic health records, pharmacist- or nurse-led initiation and monitoring pathways, shared cardiometabolic clinics, and structured follow-up focused on tolerability, renal function, and volume status. Certainly, strategies are needed to improve adherence, as 1-year discontinuation rates are 65% among those without T2D and 46% among those with T2D[37].

Finally, although these therapies produce marked reductions in adiposity, they may also be accompanied by reductions in lean mass. In a small study (SEMALEAN), semaglutide was associated with improved handgrip strength despite reductions in lean mass; however, this observation requires confirmation in larger, more diverse cohorts[38]. Therefore, future studies should systematically assess comprehensive muscle health (quantity, quality, and function) and physical function during incretin-based and weight-loss pharmacotherapy. As potent weight-loss pharmacotherapies continue to expand, treatment programs should incorporate resistance training and adequate protein intake to mitigate the risk of sarcopenia and functional decline[39,40].

Ultimately, DCVD should be managed through earlier, phenotype-guided, mechanism-based prevention and combination therapy rather than stepwise glucose-centric escalation after target-organ damage is established.

DECLARATIONS

Authors' contributions

Contributed equally to the conception, drafting, revision, and final approval of the manuscript: Sanchis-Gomar F, Lavie CJ, Carbone S, Neeland IJ

Read and approved the final manuscript: Sanchis-Gomar F, Lavie CJ, Carbone S, Neeland IJ

Availability of data and materials

Not applicable.

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During the preparation of this manuscript, the AI tool ChatGPT (OpenAI, GPT-5.2, accessed 2026-04-28) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Lavie CJ is an Editorial Board Member of the journal *Metabolism and Target Organ Damage*. Lavie CJ was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision-making. The other authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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