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SPECIAL ARTICLE
Diabetes and metabolic disorders

Novel cardiovascular metabolic risk factor mechanisms and therapeutic opportunities

A scientific statement of the ESC Council on Basic Cardiovascular Science, the ESC Working Group on Atherosclerosis and Vascular Biology, the ESC Working Group on Cellular Biology of the Heart, the ESC Working Group on Myocardial Function, and the ESC Working Group on Cardiac Cellular Electrophysiology

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Abstract

Metabolic disorders such as obesity, type 2 diabetes, and dyslipidaemia are major drivers of cardiovascular risk and have reached epidemic levels in Western populations. Recent advances in clinical research have uncovered unexpected and often beneficial effects of pharmacological classes of metabolic drugs on cardiovascular outcomes, revealing complex interactions between metabolism and cardiac pathology. Despite their clinical efficacy, the molecular and cellular mechanisms through which many of these agents act

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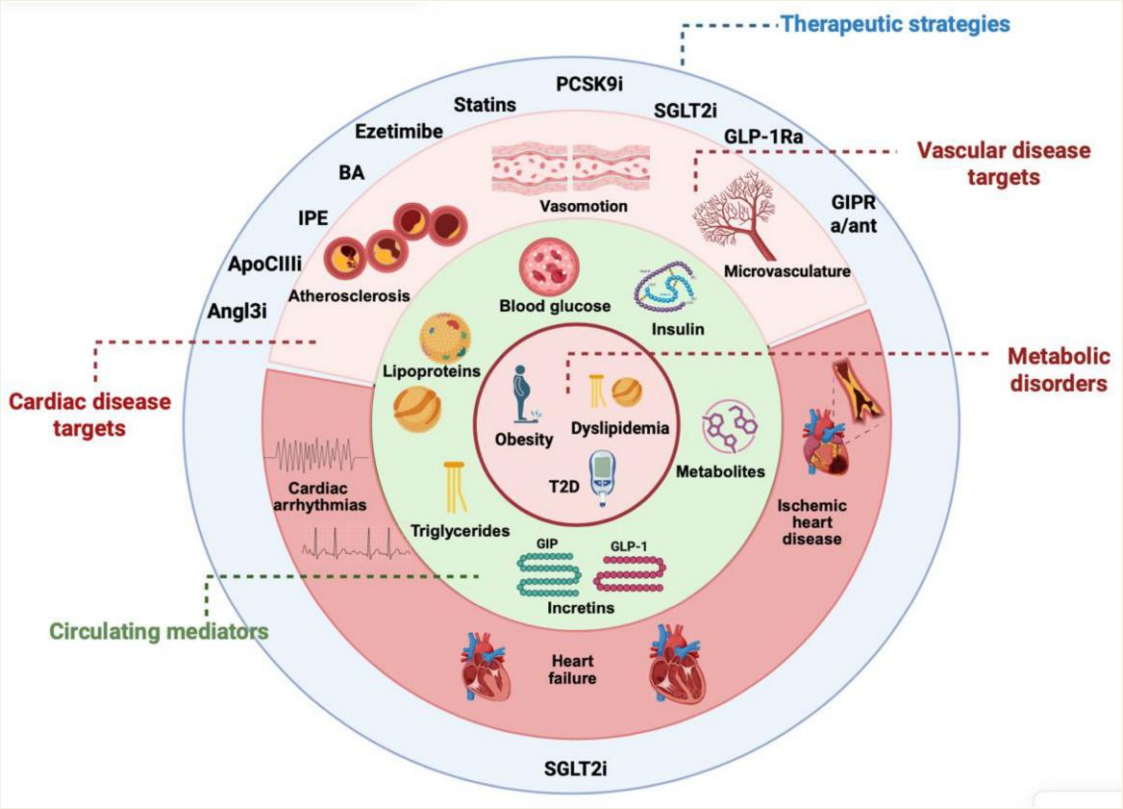
remain only partially understood. This gap in knowledge underscores the urgent need for fundamental research that not only dissects the biology of metabolic disorders and cardiovascular disease but also reveals the mechanistic basis of existing and emerging therapies, thereby enabling rational therapeutic development. This scientific statement, developed by researchers from the European Society of Cardiology (ESC) Council on Basic Cardiovascular Science and several ESC Working Groups, provides a state-of-the-art overview of the emerging molecular and cellular pathways linking metabolic abnormalities with vascular and cardiac disease. By illuminating these critical connections and unresolved questions, this article aims to catalyse innovation in the prevention and management of cardiovascular disease in the context of metabolic dysfunction and to suggest new directions for future research.

Graphical Abstract



This scientific statement seeks to delineate the mechanisms that link metabolic disorders to cardiovascular disease, and is organized around the complex interactions between obesity, type 2 diabetes (T2D), and dyslipidaemia, and four major cardiovascular conditions, including atherosclerosis, ischaemic heart disease, heart failure, and arrhythmias. Particular attention is given to circulating mediators of metabolic risk, and molecular mechanisms underlying the beneficial effects of major therapeutic strategies.

Keywords Obesity • Metabolic disorders • Metabolism • Incretin-based therapies • Cardiovascular disease

Introduction

Cardiovascular disease (CVD) remains the leading global cause of morbidity and mortality, and its strong association with metabolic disorders is increasingly recognized as a defining feature of the contemporary epidemic of non-communicable diseases.[1] Metabolic abnormalities such as obesity, insulin resistance, type 2 diabetes (T2D), and dyslipidaemia rarely manifest in isolation; rather, they frequently co-occur in the form of the metabolic syndrome, where their combined effects exert synergistic and multiplicative risk on cardiovascular outcomes. This clustering substantially accelerates the development of atherosclerosis, ischaemic heart disease (IHD), heart failure (HF), arrhythmias, and ultimately premature death. Robust epidemiological evidence demonstrates that the presence of metabolic syndrome approximately doubles the risk of coronary heart disease and triples the risk of myocardial infarction or stroke compared with metabolically healthy individuals.[2] In recent years, Mendelian randomization analyses have provided causal evidence that genetically determined metabolic disturbances significantly increase the risk of IHD and HF, and identifying genes for metabolic disorder-related traits using genome-wide association studies.[3–5] Collectively, these data support a paradigm in which CVD is conceptualized not solely as a pathology of the heart and vasculature, but as the downstream consequence of systemic metabolic dysfunction involving the pancreas, liver, kidney, spleen, bone

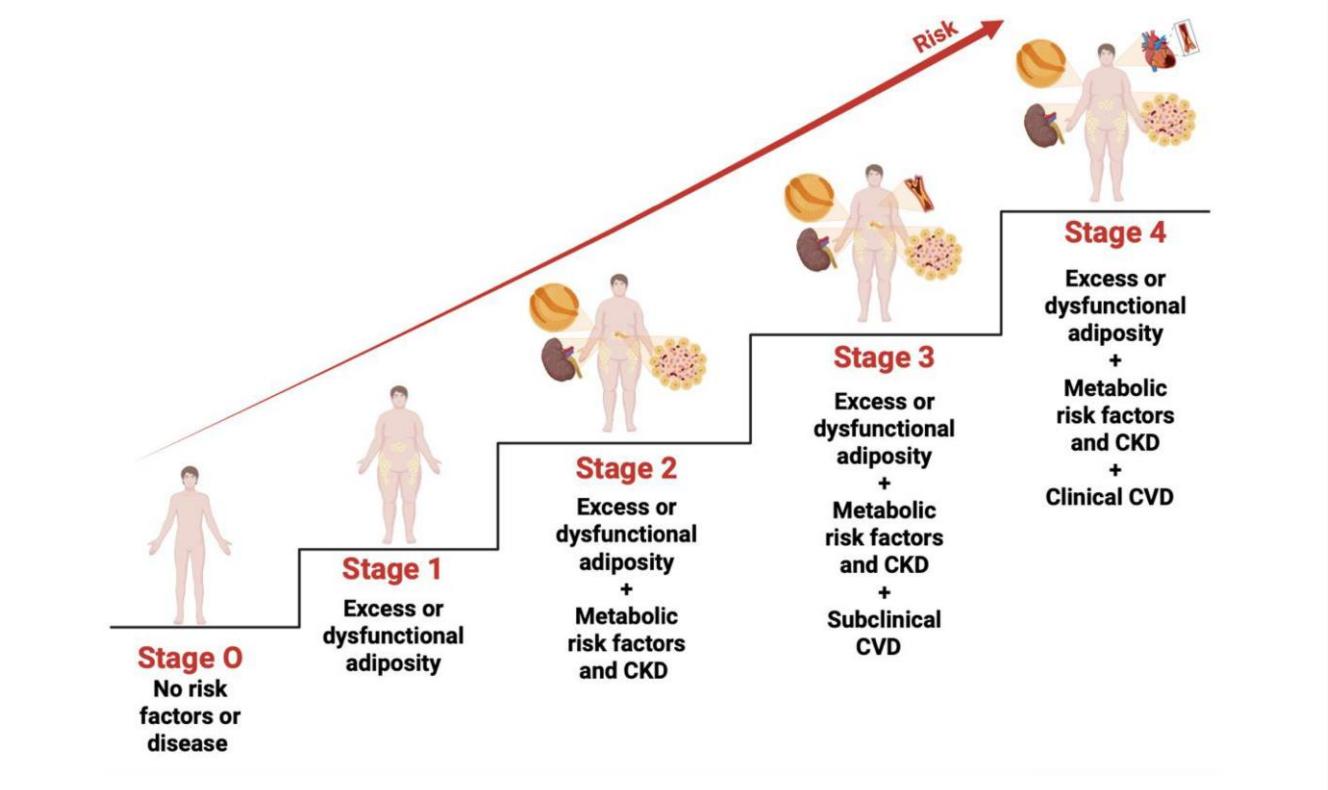


Figure 1 Stages of cardiovascular-kidney-metabolic syndrome. Schematic representation of stages 0–4 of cardiovascular-kidney-metabolic syndrome. CKD, chronic kidney disease; CVD, cardiovascular disease (created with BioRender.com)

marrow, and myocardium.[6] This integrated framework has given rise to the emerging discipline of multi-organ metabolic medicine, which now represents a central axis of contemporary preventive and therapeutic cardiology.[7]

The mechanisms that underlie the cardiovascular risk associated with metabolic disorders are multifactorial, complex, and tightly intertwined. A range of molecular perturbations, including low-grade inflammation, oxidative stress, endothelial dysfunction, insulin resistance, and disruptions in both lipid and energy metabolism, are not restricted to the myocardium but operate as systemic processes.[8] These disturbances exemplify the principle of inter-organ crosstalk wherein metabolic and inflammatory signals propagate across multiple tissues. In particular, the liver, adipose tissue, kidneys, and heart engage in bidirectional communication through secreted mediators such as cytokines, adipokines, and hepatokines, collectively shaping cardiovascular risk and disease progression.[6,9–11] The complexity of these interactions is exemplified by the cardiovascular-kidney-metabolic syndrome, a recently proposed framework that encompasses the intersection between obesity, T2D, dyslipidaemia, CVD, and chronic kidney disease (CKD) (*Figure 1*).[12,13]

Lipid-lowering drugs such as statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and bempedoic acid target key metabolic pathways of cholesterol synthesis and clearance, improving lipid profiles, reducing inflammation, and stabilizing atherosclerotic plaques. By modulating hepatic and cellular lipid metabolism, these agents significantly lower cardiovascular risk and major adverse events across populations.[14–16] Over the past decade, cardiovascular outcome trials mandated by regulatory agencies have provided a robust evidence base demonstrating that certain classes of glucose-lowering therapies confer significant cardiovascular benefit. Across large randomized controlled trials, sodium–glucose cotransporter 2 inhibitors (SGLT2i) consistently reduced the composite outcome of hospitalization for HF or cardiovascular death.[12,17–20] Notably, these benefits extend to individuals without T2D but with HF or CKD, emphasizing mechanisms beyond glycaemic control. Similarly, glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1Ras) have demonstrated significant reductions in major adverse cardiovascular events, particularly non-fatal stroke and myocardial infarction. The cardioprotective effects of semaglutide were independent of baseline adiposity and weight loss, suggesting benefit beyond adiposity reduction.[21] More recently, dual incretin agonists such as tirzepatide, which co-activate GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, have produced unprecedented improvements in glycaemic control and weight loss with cardiovascular benefits being non-inferior to those observed with GLP-1Ra.[22]

Despite these compelling clinical results, the precise mechanisms by which SGLT2i, GLP-1Ras, and GLP-1/GIP receptor agonists confer cardiovascular benefit remain incompletely understood. For SGLT2i, hypotheses include osmotic diuresis and natriuresis leading to preload and afterload reduction, improvements in ventricular loading conditions, modulation of myocardial energetics via increased ketone body utilization, inhibition of myocardial Na^+/H^+ exchanger activity, and anti-inflammatory and anti-fibrotic effects. For GLP-1Ras potential mechanisms encompass weight reduction, modest

blood pressure lowering, improved lipid profiles, direct anti-atherosclerotic effects on vascular endothelium, anti-inflammatory effects, and cardioprotective signalling through GLP-1 receptor (GLP-1R) expressed in the heart and vasculature.[23] The elucidation of mechanisms of action of dual incretin agonists will require further research, since the mechanistic contribution of GIP receptor (GIPR) activation remains particularly enigmatic. Importantly, the magnitude and rapidity of clinical benefits observed in clinical trials suggest improvements beyond glycaemic and weight control alone, underscoring the need for deeper mechanistic studies.

The divergence between what is demonstrated in clinical outcomes and what is explained mechanistically raises the important conceptual distinction between evidence-based and mechanism-based medicine.[24] In the case of metabolic therapies for cardiovascular protection, evidence-based medicine has outpaced mechanism-based medicine, and while the efficacy of these drugs is well established, it is still uncertain exactly how mechanistically their pleiotropic benefits are achieved.[7,25] This disconnect presents both a challenge and an opportunity. On one hand, it limits our ability to optimize therapy or to anticipate long-term safety across diverse populations. On the other hand, it invites a new era of translational investigation into myocardial metabolism, vascular biology, systemic homeostasis and genetics that could ultimately refine treatment paradigms. Addressing this knowledge gap requires a synthesis of evidence-based medicine with mechanism-based inquiry, recognizing that the goal of cardiovascular prevention lies not only in proving that interventions work, but in understanding why they work, in whom, and under what circumstances.

This scientific statement seeks to categorize and delineate the mechanisms that link metabolic disorders with cardiovascular risk. It is organized around the complex interactions between obesity, T2D, hyperlipidaemia, and four major cardiovascular conditions, including atherosclerosis, IHD, HF, and arrhythmias. Particular attention is given to how the metabolic demands of the myocardium and vasculature are altered in disease states, with an emphasis on catabolic processes, metabolic inflexibility and maladaptive shifts in substrate utilization that drive pathological processes. In addition, we critically examine the mechanisms underlying both the risks and the pleiotropic, as well as still incompletely defined, effects of therapeutic agents commonly prescribed for metabolic disorders. By integrating these perspectives, the statement synthesizes current understanding and highlights gaps in knowledge, thereby helping to identify novel directions for future research in cardiovascular and metabolic health (*Graphical Abstract*).

Cardiac metabolic flexibility in health and disease

The heart is a metabolically dynamic organ with a high and constant demand for ATP to maintain contractile function. Under physiological conditions, approximately 60%–70% of myocardial ATP derives from fatty acid oxidation (FAO), while glucose, lactate, ketone bodies, and amino acids contribute the remainder.[26] A key attribute of the heart is its ability to switch between different fuel sources, including fatty acids (FA), glucose, glucose-derived metabolites, ketones, and branched-chain amino acids to maintain adequate production of ATP and its contractile function. The choice of the major energy-providing substrate will depend on hormonal status, nutrient availability, and body needs, with balanced production and use of energy. This metabolic flexibility allows the heart to maintain energy production under various physiological and even pathological conditions. The Randle effect (also known as the glucose–FA cycle), first described by Randle *et al*. in 1963, comprises a central and tightly regulated system modulating substrate competition, where increased FAO suppresses glucose utilization.[27] This metabolic hierarchy ensures efficient energy production based on substrate availability, particularly in fasting or high-fat states. According to the Randle cycle, FAO increases acetyl-CoA and nicotinamide adenine dinucleotide reduced levels, which inhibit pyruvate dehydrogenase. This reduces pyruvate conversion to acetyl-CoA and the flux of the tricarboxylic acid cycle, thereby suppressing glucose oxidation.

Obesity, insulin resistance and dyslipidaemia result in increased circulating free FA levels, and uptake into cardiomyocytes. This results in the chronic activation of the Randle cycle, favouring FAO over glucose oxidation. This shift reduces metabolic flexibility, and could lead to less efficient ATP generation, increases reactive oxygen species production, promotes accumulation of toxic lipid intermediates and lipotoxicity and impairs glucose oxidation and utilization even when it would be advantageous, for example, during ischaemia, increasing vulnerability to ischaemia-reperfusion injury or in HF.[28,29]

Metabolic remodelling in cardiovascular diseases: mechanisms and therapeutic targets

Metabolic risk and its modulation in atherosclerosis

Atherosclerosis is a multifactorial process that can be initiated and sustained by metabolic dysregulation.[30–32] Metabolic disorders such as obesity, T2D, and dyslipidaemia induce a wide-ranging disturbance in systemic metabolic homeostasis, extending far beyond abnormalities in glucose metabolism or body weight control. Instead, they affect lipid handling, inflammatory signalling, endothelial function, and immune cell metabolism, thereby creating a chronic pro-atherogenic environment that accelerates vascular injury and plaque formation.[33–36]

Diabetes and obesity in atherosclerosis

Obesity and T2D induce endothelial dysfunction, a key contributor to insulin resistance in tissues involved in glucose and lipid metabolism, preceding and promoting atherosclerosis. High oxidative stress and reduced vasoactive substances bioavailability, e.g. nitric oxide $(NO)^2$, are regarded as a primary defect that link obesity, insulin resistance to endothelial dysfunction and atherosclerosis.[37,38]

Current T2D treatments including SGLT2i, and activators of pathways downstream from incretin hormones GLP-1 and GIP have distinct functions converging on glucose metabolism.[39] Previously, intensive glucose *per se* was demonstrated to reduce cardiovascular and microvascular endpoints.[40] However, GLP-1Ras[33] or SGLT2i[41] have additional benefits in reducing

cardiovascular mortality, morbidity, and risk factors compared to glucose management without those agents. These benefits are particularly notable in high-risk patients with T2D, as previous glucose-lowering strategies, mainly insulin, thiazolidinediones or sulphonylurea, showed limited benefits.[42–44] These benefits can be attributed at least partially to glucose lowering;[42,45] however, it is likely that GLP-1Ras and SGLT2i have pleiotropic effects that extend beyond glucose lowering, including improvements in blood pressure and plasma lipid levels.[46–51] This possibility was brought into sharp relief by the SELECT trial which found that the GLP-1Ra semaglutide reduces overall cardiovascular mortality, non-fatal myocardial infarction or non-fatal stroke in patients with preexisting CVD and overweight or obesity, but without established T2D.[52,53] Recent randomized clinical trials reveal that dual-agonists targeting the GIPR and GLP-1R show superior efficacy compared to semaglutide in reducing glycated haemoglobin and body weight, in people living with T2D.[54] Notably, within the SURMOUNT clinical trial programme of overweight and obese people without T2D, the dual GLP-1/GIP receptor agonist tirzepatide demonstrated pronounced and sustainable effects on weight loss.[55,56] Recently the SURPASS-CVOT trial (ClinicalTrials.gov: NCT06779929)[57] demonstrated non-inferiority of tirzepatide compared to dulaglutide for major adverse cardiovascular events in people with T2D.

The pleiotropic effects of GLP-1Ra and SGLT2i extend to the enhancement of endothelial cell function by restoring NO bioavailability and increasing circulating levels of endothelial progenitor cells with enhanced angiogenic activity.[58–63] Moreover, these drugs reduce systemic low-grade inflammation and oxidative stress,[64] blunt vascular smooth muscle proliferation and enhance atherosclerotic plaque stability.[65–69]

A peculiarity of both GLP-1Ras and SGLT2i is the beneficial modulation of the imbalances between energy intake and expenditure, leading to body weight loss effects, which are key in dysmetabolic conditions and obesity. GLP-1Ra-dependent body weight loss is associated with central hypothalamic effects influencing satiety, ingestion as well as peripheral mechanisms such as the slowing of gastric emptying, modulation of nutrient absorption and utilization.[70,71] SGLT2i induce a 'starvation-mimicking' effect, hypothesized to result from glucose loss through urine,[72] estimated at approximately 200 kcal/day. This promotes systemic metabolic reprogramming, leading to the production of ketone bodies as alternative energy substrates.[73,74] Overall, these findings have changed our understanding of the pathophysiology of CVD, suggesting that SGLT2i, GLP-1Ras have pleiotropic actions beyond glycaemic control (*Figure 2*).

Tirzepatide, a GLP1/GIP dual receptor agonist, has beneficial cardiovascular effects, even if the role of GIP in CVD and the mechanisms in weight regulation have not yet been fully elucidated. Activation of GIPR signalling attenuates,[75] while its loss exacerbates,[76] aortic inflammation and atherosclerosis. Treatment with acyl-GIP reduced dyslipidaemia and atherogenesis in male *Ldlr*$^{-/-}$ mice by directly modulating lipid metabolism in adipocytes, independent of weight loss.[77] However, the role of GIP in the cardio-reno-metabolic framework needs further elucidation, particularly in relation to weight loss. Indeed, a human monoclonal antibody anti-human GIPR with two GLP-1 analogue agonist peptides, exhibited effective reduction in body weight and good glycaemic control with a GIPR antagonistic effect.[78] GIPR agonism and antagonism decrease body weight via different mechanisms active in the central nervous system. GIPR agonism decreases body weight and food intake via GIPR signalling in gabaergic neurons,[79] while GIPR antagonism, unlike agonism, appears to depend on the activation of the receptor in different brain regions.[80] However, other data suggest that continuous stimulation of GIPR desensitizes GIPR activity, finally leading to GIPR antagonism.[80] Interestingly, GIPR expression in vascular endothelial cells allows GIP to exert vasodilatory effects on the microvasculature of the pancreas, heart, and skeletal muscle, enhancing blood flow and endothelial function. These findings underscore the intricate relationship between metabolism and multi-organ crosstalk, paving the way for a deeper understanding of the cardiovascular and metabolic actions of GIP and GLP-1.

Recently, novel effects of dual agonists on neurobiology have also been described. In male and female adults with overweight/obesity and without diabetes receiving tirzepatide or placebo in a 6-week phase 1 study, the tirzepatide-treated group showed early reduction of food intake, potentially by impacting ingestive behaviour as suggested by the reduced activity shown by magnetic resonance imaging in brain implicated in the regulation of food intake.[81] Understanding the pleiotropic mechanisms that underpin the impact of dual GLP-1/GIP receptor agonism or GLP-1R agonism/GIPR antagonism in various organ systems, particularly the brain, is needed for their effective and safe use and for the development of future incretin-based therapies.

Dyslipidaemia and atherosclerosis

Plasma lipid and lipoprotein abnormalities are also key drivers of atherosclerosis and a cardinal feature of metabolic syndrome.[8] Classically, atherosclerosis is associated with elevated plasma levels of low-density lipoprotein cholesterol (LDL-C). Hypercholesterolaemia is controlled using statins or bempedoic acid which decrease cholesterol biosynthesis, ezetimibe which inhibits cholesterol absorption and by inhibitors of PCSK9,[82] a protein which promotes the degradation of hepatic low-density lipoprotein receptor, by preventing its recycling to the cell surface.[82] These drugs lead to a dramatic decrease of the incidence of cardiovascular events, an effect that is largely dependent on the extent of LDL-C reduction. These findings set the stage for investigating several additional therapeutic approaches to control elevated LDL-C levels in patients at very high or at extreme cardiovascular risk.[82]

Moreover, recent epidemiological and Mendelian randomization studies demonstrated that all classes of apolipoprotein B-containing lipoproteins including triglyceride (TG)-rich lipoproteins, and lipoprotein (a) [Lp(a)] are strongly associated with atherosclerotic CVD[83] and confer an additional risk beyond that related to LDL particles. Similarly to LDL, also TG-rich lipoproteins may enter the arterial intima where they remain trapped and undergo lipolysis by endothelial, or macrophage lipoprotein lipase (LPL) with the resultant release of free FAs and monoacylglycerols which contribute to foam cell formation and low-grade inflammation.[84] Within TG-lowering drugs, high doses of the omega-3 FA icosapent ethyl caused substantial declines in TG levels, but also reduced cardiovascular events compared to placebo.[85] Interestingly, the beneficial cardiovascular effects of icosapent ethyl (eicosapentaenoic acid ethyl ester)

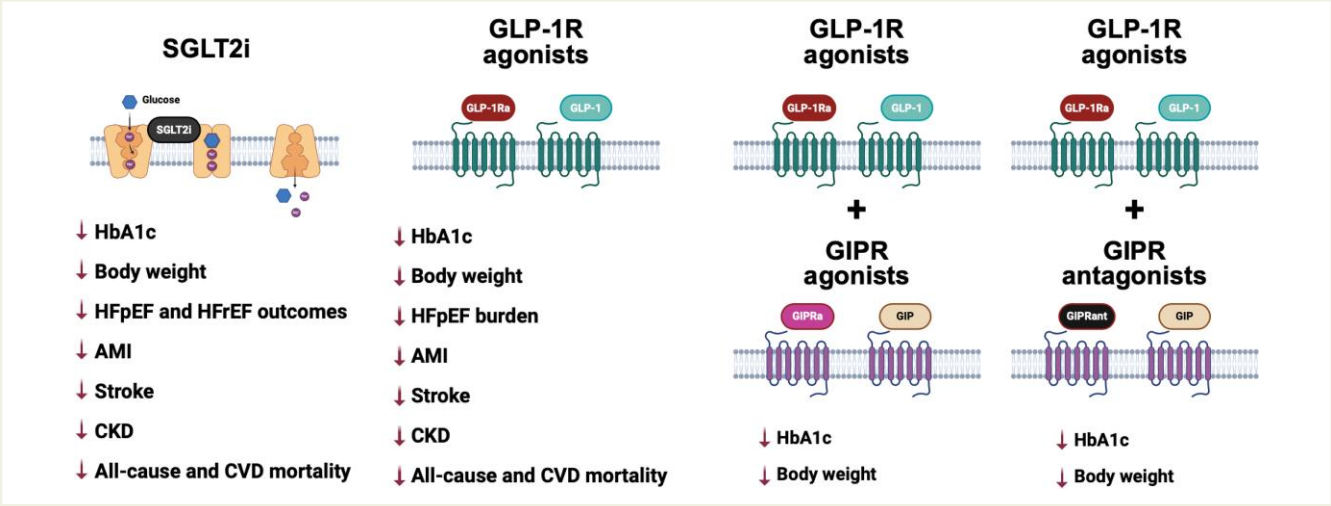


Figure 2 Pleiotropic effects of SGLT2i and GLP-1R agonists, alone and in combination with GIPR agonists or antagonists. Red downward arrows represent reduction of the respective events. AMI, acute myocardial infarction; CKD, chronic kidney disease; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; GIP, glucose-dependent insulinotropic polypeptide; GIPR, glucose-dependent insulinotropic polypeptide receptor; GIPRant, glucose-dependent insulinotropic polypeptide receptor antagonist; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GLP-1Ra, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor (created with BioRender.com)

extended beyond triglyceride level reduction, suggesting additional cardiovascular benefits of this class. Indeed, icosapent ethyl also promotes plaque stabilization in patients with documented coronary atherosclerosis likely by modulating inflammation, oxidative stress, and endothelial function.[86] Given the critical role of TG-rich lipoproteins in atherogenesis and the persistent cardiovascular risk despite optimal LDL-C levels, new drugs that reduce TG-rich lipoprotein metabolism are currently being developed including antisense oligonucleotides (ASO),[14] small interfering RNAs (siRNA) and antibodies[87] targeting apolipoprotein C-III (ApoC-III) (a LPL inhibitor) and angiopoietin-like 3 protein (another player in TG-rich lipoprotein catabolism).[82] In this regard, a recent study in hypertriglyceridaemic mice demonstrated an effective reduction in atherosclerosis burden upon ApoC-III ASO administration when lipid lowering was achieved.[87]

Another atherogenic particle is Lp(a), a LDL-like particle present in human plasma, in which a large plasminogen-like glycoprotein apolipoprotein(a) [apo(a)] is bound to apolipoprotein B100 (apoB100).[88] Lp(a) atherogenicity has been linked to its ability to bind and transport oxidized phospholipids, exert antifibrinolytic effects, and modulate smooth muscle cell proliferation.[89] Also, the diacylglycerol and lysophosphatidic acid associated with Lp(a) promote cytokine production in monocytes and drive trans-endothelial migration of monocytes.[90] So far, the use of novel Lp(a)-RNA-targeting agents including ASOs and siRNAs sharply reduced Lp(a) plasma levels.[91] More recently, disruptors of the binding of apo(a) with apoB100 were successfully tested in humans,[82] yet, the impact of Lp(a) lowering strategies cardiovascular outcomes is still currently under investigation[88] and the results of cardiovascular outcome trials with Lp(a) lowering therapies are awaited with great interest. The results from different multiomics studies are expanding our knowledge of lipid and lipoprotein metabolism and contributing to the identification of novel targets to improve the control of lipids and lipoprotein metabolism.

Metabolic risk and its modulation in ischaemic heart disease

Persistent metabolic imbalance alters substrate utilization in cardiomyocytes, enhances oxidative stress, and promotes vascular inflammation and endothelial impairment, contributing to the development of IHD. Disruption of cardiac energy metabolism, characterized by impaired mitochondrial function and reduced metabolic flexibility, further compromises myocardial efficiency and increase vulnerability to ischaemic events and myocardial injury.[26]

Diabetes, obesity, and myocardial ischaemia

Glucose pathway regulators have emerged as a key factor in myocardial responses to ischaemia. Intriguingly, the SGLT2i empagliflozin reduced infarct size in global *Sglt2* knockout mice,[92] indicating the protection was through an off-target effect. Consistently, Andreadou's group showed that some SGLT2i (empagliflozin, dapagliflozin) reduced infarct size in healthy non-diabetic mice,[92] confirming a degree of independence of SGLT2i from glycaemic control. At the clinical level, the EMMY trial was the first to investigate an SGLT2i in patients with acute myocardial infarction (AMI). When administered within 72 h of percutaneous coronary intervention for the acute event, empagliflozin significantly improved left ventricular ejection fraction, end-systolic and end-diastolic volumes.[93] However, dedicated cardiovascular outcome trials for empagliflozin[94] and dapagliflozin[95] in AMI patients did not show a significant reduction in the composite of hospitalization for HF or all-cause/

cardiovascular death. Thus, further research is needed to elucidate the potential benefits of these drugs in myocardial ischaemia, and the mechanisms underlying these effects.

Pre-clinical studies suggest that treatment with metformin, a first-line treatment for T2D,[96] or glucagon-like peptide-2[97] can reduce myocardial ischaemia-reperfusion injury indirectly by affecting gut microbiota. These findings pave the way for exploring the potential role of probiotics in cardioprotection.

Dyslipidaemia and myocardial ischaemia

Lipid-lowering therapies have been linked to cardioprotection in ischaemic hearts.[98] Atorvastatin was one of the first drug administered in the setting of AMI and limited cardiac damage, improved heart function and mitigated adverse cardiac remodelling in dyslipidaemic pigs.[99–102] These findings led to a wide use of statins in AMI patients. PCSK9 inhibitors also offer cardioprotective effects,[103,104] Consistently, PCSK9 inhibition 4 days post-AMI reduced infarct size, improved cardiac function, mitigated mitochondrial damage, and attenuated inflammation. It also reduced fibrosis and enhanced ventricular function by suppressing fibroblast-to-myofibroblast trans-differentiation[105] Yet, PCSK9 deficiency was associated with metabolic alterations in the heart potentially affecting cardiac function in experimental models and in humans.[106] These findings suggest a nuanced interaction between PCSK9 inhibition and cardioprotection, warranting further clinical investigation and mechanistic studies.

Metabolic risk and its modulation in heart failure

Metabolic dysregulation represents a central pathophysiologic axis in HF across the ejection fraction spectrum. Metabolic substrate inflexibility and nutrient overload exhibit distinct pathophysiologic signatures in HF with preserved ejection fraction (HFpEF) from that with reduced ejection fraction (HFrEF). In HFpEF, obesity, insulin resistance, and systemic inflammation lead to chronic nutrient excess and impaired substrate switching between FA and glucose oxidation. This promotes myocardial lipid accumulation, mitochondrial dysfunction, and oxidative stress, contributing to diastolic stiffness and concentric remodelling.[28,107,108] In contrast to HFpEF, HFrEF primarily arises from loss of contractile mass and systolic dysfunction, and is metabolically characterized by energy starvation, catabolic remodelling, and reduced mitochondrial oxidative capacity. Downregulation of FAO and reliance on less efficient glycolysis result in an energy-depleted myocardium with impaired ATP generation and contractile performance.[26,109] Thus, while HFpEF reflects metabolic excess and nutrient toxicity, HFrEF represents metabolic insufficiency and energetic failure. Understanding these mechanisms provides the foundation for targeted metabolic therapies.

Diabetes and obesity in heart failure with preserved ejection fraction

Obesity and T2D profoundly shape the HFpEF phenotype through intertwined haemodynamic and metabolic mechanisms.[36,110] These conditions act synergistically to impose haemodynamic overload, metabolic inflexibility, and mitochondrial dysfunction, shaping a distinct metabolic HFpEF phenotype. Excess adiposity elevates leptin and adipokines, stimulating aldosterone secretion and sympathetic–renin–angiotensin activation, which promote sodium retention, plasma volume expansion, and elevated filling pressures.[111–114] This haemodynamic overload drives hypertrophic remodelling and mechano-energetic uncoupling, whereby ATP consumption exceeds mechanical output.[115–117] At the cellular level, mitochondrial lipid accumulation, incomplete FAO, and impaired Ca^{2+} uptake compromise oxidative phosphorylation and NAD^{+}-dependent metabolism, reducing energetic reserve.[118–121] Experimental models confirm that obesity alone rarely induces HFpEF, but its combination with hypertension, simulated by high-fat diet and NO synthase inhibition, reproduces key human features.[115] Furthermore, mouse strains carrying a missense variant in the *Nnt* locus display delayed HFpEF progression, implicating nicotinamide nucleotide transhydrogenase and redox imbalance in disease pathogenesis.[118]

In T2D, chronic hyperglycaemia and insulin resistance exacerbate these disturbances, promoting excess FAO, mitochondrial redox stress, and accumulation of lipotoxic intermediates.[26,107] Enhanced O-linked β-N-acetylglucosamine modification and advanced glycation of contractile and calcium-handling proteins impair relaxation and diastolic function.[122,123] Reverse activation of nicotinamide nucleotide transhydrogenase depletes NADPH, weakening antioxidant defences and elevating reactive oxygen species.[116] Concomitant microvascular rarefaction and reduced NO signalling further increase myocardial stiffness.[124] These haemodynamic, metabolic, and redox derangements define a heart that is energetically taxed, mechanically constrained, and unable to meet physiological demand; hallmarks of the diabetic–obese HFpEF phenotype.

Over the past decade, the remarkable outcome benefits of SGLT2i independent of diabetes status and extending to HFpEF, have re-emphasized the therapeutic potential of correcting metabolic derangements.[115,116] These agents now represent cornerstone therapy in HFpEF after consistent reductions in HF hospitalizations and cardiovascular mortality.[125,126] In line with this notion, SGLT2i improve cardiovascular and renal outcomes in patients with HF and CKD with and without T2D.[12,17–20] Moreover, T2D may also promote the development of cardiac hypertrophy, diastolic, and systolic dysfunction, a condition often termed diabetic cardiomyopathy.[105]

SGLT2i act primarily by inhibiting renal glucose and sodium reuptake, modestly reducing blood glucose and altering insulin-glucagon balance, which can stimulate hepatic ketogenesis. Early hypotheses linked these hormonal shifts to greater cardiac ketone utilization; however, subsequent studies revealed only minor increases in circulating ketones and no consistent enhancement of myocardial ketone oxidation, arguing against this as the dominant mechanism.[115,116] Instead, evidence suggests that SGLT2i directly reprogram myocardial metabolism, shifting substrate use away from glycolysis towards FAO and thereby reducing glycolysis-oxidation mismatch, acidosis, and toxic metabolite accumulation while restoring autophagy and mitochondrial function. Additional direct cardiac actions include enhanced mitochondrial Ca^{2+} uptake, activation of AMPK–sirtuin–autophagy pathways, and reduction of oxidative stress and inflammation. The contribution of intracellular sodium lowering remains debated, but preclinical evidence supports improved ionic and energetic homeostasis.[115,116]

Recent evidence indicates that GLP-1Ras also reduce HF incidence in patients with obesity or T2D and could be particularly

useful in HFpEF through both metabolic and direct myocardial pathways.[127–129] GLP-1Ras promote substantial weight loss (~10%) through central appetite suppression while improving glycaemic control via enhanced insulin secretion and reduced glucagon release. Beyond glucose control, GLP-1Ras modulate several cardioprotective molecular cascades, overlapping with those of SGLT2i, including attenuation of oxidative stress and systemic inflammation, enhancement of NO bioavailability, and restoration of endothelial function.[130] At the myocardial level, GLP-1R activation improves mitochondrial efficiency through AMP-activated protein kinase (AMPK) and NO signalling. Upregulation of endothelial and neuronal NO synthase augments mitochondrial biogenesis and FAO, mitigating lipid accumulation and enhancing ATP generation.[131] Concurrent activation of autophagy and mitophagy pathways facilitates removal of damaged mitochondria, preserving ultrastructural integrity and limiting reactive oxygen species production. GLP-1-mediated cyclic adenosine monophosphate and protein kinase A signalling further improves calcium handling via phosphorylation of phospholamban and ryanodine receptor 2 (RyR2), contributing to diastolic relaxation and mechano-energetic coupling. Importantly, GLP-1Ras appear to exert GLP-1R-independent actions through secondary mediators such as AMPK, NO, and natriuretic peptide pathways, which converge on improved mitochondrial signalling and substrate flexibility. These pleiotropic effects may act synergistically with SGLT2i, amplifying myocardial metabolic efficiency, reducing inflammation, and restoring redox balance.

Alteration of lipid and lipoprotein metabolism and heart failure with preserved ejection fraction

In HFpEF, perturbations in lipid and lipoprotein metabolism play a significant role in the pathophysiology of the disease and patients often exhibit dyslipidaemia.[132] At the myocardial level, studies show reduced FAO and accumulation of lipid intermediates in the heart, resulting in lipotoxicity, mitochondrial dysfunction, impaired energy production and diastolic dysfunction.[133,134] Furthermore, alterations in lipoprotein receptor pathways (such as increased CD36 expression, and changes in PCSK9) may further exacerbate cardiac lipid overload and contribute to HFpEF-like phenotypes in experimental models.[106] Together, these findings suggest that disrupted lipid uptake, impaired lipid oxidation and dysfunctional lipoprotein handling contribute to the development and progression of HFpEF, making lipid metabolism a promising target for future therapeutic strategies.

Moreover, free FA receptor 4 (FFAR4), a G-protein-coupled receptor involved in FA sensing, was found to be decreased in hearts from patients with HF.[135] Studies in mice revealed that FFAR4 exerts a cardioprotective role, preventing cardiac myocyte cell death in response to oxidative stress, highlighting the signalling role of FAs in cardiac pathological conditions. Overactivation of β-adrenergic signalling, commonly observed in HF, induces adipose tissue lipolysis, while adipose tissue-specific deletion of adipose triglyceride lipase (ATGL) prevents HF induced by pressure overload. Recent investigations utilizing Atglistatin, a pharmacological inhibitor of ATGL, demonstrated its cardioprotective, anti-apoptotic, and anti-fibrotic effects in a mouse model of catecholamine-induced HF, revealing the potential of targeting adipose tissue as a potential novel therapeutic target.[136] Furthermore, the intramyocellular lipid metabolism is maladapted in patients with T2D and obesity that are also sedentary, with increased storage of unsaturated FAs and blunted FA turnover contributing to their increased cardiovascular risk.[137]

Diabetes and obesity in heart failure with reduced ejection fraction

Data from the Framingham study suggest that along with a history of AMI, T2D represents one of the strongest predictors for incident HFrEF.[138] An initial major myocardial injury, followed by remodelling processes is often at play in the pathophysiology of HFrEF, and obesity, hyperinsulinemia and T2D impact both, extracardial and cardiac mechanisms leading to left ventricular remodelling and HFrEF. For instance, an activation of the neurohumoral system including the renin–angiotensin–aldosterone system (RAAS) as well as of the sympathetic nervous system are common in insulin resistant states.[139,140] In turn, chronic RAAS activation leads to adverse effects, including peripheral vascular resistance, increased cardiac afterload or fluid overload. In addition, increased levels of angiotensin II induce cardiomyocyte hypertrophy, aldosterone to stimulate extracellular matrix synthesis and subsequently fibrosis.[141,142] On the myocellular level, T2D has been linked to increased cytoplasmatic glucose and lipid intermediates accumulation, leading to increased nutrient surplus sensing with activation of protein kinase B (Akt) and mammalian target of rapamycin complex 1 (mTORC1) and subsequently suppression of autophagy, increased oxidative stress and inflammation observed in T2D.[143,144] In contrast, recently cardiomyocyte-specific overexpression of the sirtuin 4, a mitochondrially localized stress-responsive NAD^+-dependent deacetylase, increased oxidative stress and fibrotic signalling in a mouse model of pressure overload-induced HFrEF.[145] Moreover, enhanced activity of the sodium hydrogen exchanger isoforms 1 and 3 (NHE1 and NHE3) mediated by insulin and described in T2D contributes to cardiac hypertrophy and dysfunction.[144,146,147]

After the first cardiovascular outcome trials in patients with T2D, impressive reductions in hospitalizations for HF became apparent leading to subsequent investigations of this drug class in HFrEF. SGLT2i were subsequently demonstrated to reduce the combined risk for HF hospitalization or cardiovascular death in HFrEF by relative 26% with consistent effects amongst age, sex, diabetes and baseline estimated glomerular filtration rate subgroups.[148]

A prespecified *post hoc* analysis of the SELECT trial demonstrated a 35% relative reduction in the composite HF outcome (cardiovascular death or hospitalization or urgent hospital visit for HF) with semaglutide 2.4 mg for the 1347 people of the subgroup with established HFrEF at baseline.[149] Interestingly, the blockage of NHE1, leading to reduced cardiomyocyte cell death, is recognized as one of the most prominent amongst the different actions proposed for SGLT2i.[150] Dedicated outcome trials in chronic HFrEF populations are now needed for GLP-1Ras.

Dyslipidaemia and heart failure with reduced ejection fraction

A Mendelian randomization study found positive causal associations of LDL-C [odds ratio (OR) 1.24] and total cholesterol (OR

1.21) with HFrEF risk.[151] Patients with HFrEF often present with a pro-atherogenic lipid profile early in the disease course. Mechanistically, dyslipidaemia not only promotes atherosclerosis in the coronary arteries but might also fuel myocardial lipotoxicity, mitochondrial dysfunction and impaired substrate oxidation, which worsen systolic dysfunction. Yet a large meta-analysis of statin trials so far showed a modest reduction of the risks of non-fatal HF hospitalization and a composite of non-fatal HF hospitalization and HF death.[152]

Metabolic risk and cardiac arrhythmias

Metabolic risk factors promote structural remodelling, autonomic imbalance, and ion channel dysfunction through oxidative stress, inflammation, and altered substrate metabolism, therefore influencing cardiac electrophysiology and predisposing to arrhythmias.[153] Understanding how metabolic derangements disrupt electrophysiological homeostasis provides a mechanistic foundation for developing targeted metabolic and antiarrhythmic therapies.

Diabetes, obesity, and arrythmias

Individuals with obesity and diabetes have an increased risk of atrial and ventricular arrhythmias as well as sudden cardiac death and typically display cardiac conduction and repolarization abnormalities.[154] T2D is associated with an overall 35% higher risk of atrial fibrillation (AF),[155] a higher prevalence of ventricular fibrillation,[156] and a 2–4 fold increase in the risk of sudden cardiac arrest.[157] Obesity has been estimated to account for one-fifth of AF cases and is considered the most common non-ischaemic cause of sudden cardiac death.[158–160] The increased risk of arrhythmia may be partly explained by the comorbidity of obesity and diabetes with IHD and associated risk factors, such as hypertension.[157] However, increased arrhythmia susceptibility is independent of baseline cardiovascular risk, with individuals with pre-diabetes already displaying an increased risk for arrhythmias and sudden cardiac death.[161,162] Also, while the excess risk for AF increased with poor glycaemic control or renal complications, patients with T2D that have good glycaemic control and normoalbuminuria still display a slight but significant increased risk for AF.[160] Moreover, the higher prevalence of ventricular fibrillation in patients with T2D is independent of coronary artery disease or HF.[161] Hence, a more direct causal and mechanistic link between metabolic disorders and cardiac arrhythmias exists. This has been underscored by observations from preclinical studies. For example, mice subjected to a high-fat diet-induced obesity develop an increased susceptibility to AF, accompanied by enhanced adipogenesis, inflammation, and altered atrial energy metabolism.[163] Such studies have also recapitulated the clinical observation of altered ventricular repolarization (i.e. QT prolongation) in both obesity and T2D, secondary to action potential prolongation.[162,164]

On a mechanistic level, ion channel remodelling, calcium dysregulation, structural alterations, autonomic dysfunction, impaired mitochondrial function, and oxidative stress collectively contribute to arrhythmogenesis in the context of obesity and diabetes.[165] The diabetic myocardium is characterized by alterations in energy metabolism and mitochondrial function, increased production of reactive oxygen species, enhanced oxidative stress, decreased autophagy and mitophagy and endoplasmic reticulum stress, ultimately resulting in dysregulation in intracellular calcium homeostasis. This is coupled to altered expression and function of the sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase (SERCA), leading to impaired calcium uptake into the sarcoplasmic reticulum and increased diastolic intracellular calcium levels. Dysregulation of RyR2, a critical calcium release channel in the sarcoplasmic reticulum, can lead to augmented diastolic calcium release, commonly observed as calcium sparks or waves in isolated cardiomyocytes, and can trigger pro-arrhythmic events such as delayed afterdepolarizations.[166,167] Increased activity of Ca^{2+}/calmodulin protein kinase II (CaMKII) is a key modulator of these calcium-dependent pro-arrhythmic effects. Increasing evidence suggests crosstalk between RyR2 and other intracellular targets and pathways, including mitochondria, with relevance to metabolic disorders. In a pre-diabetic cardiomyopathy model using fructose-fed mice, heightened calcium uptake by mitochondria resulted in increased production of reactive oxygen species, triggering RyR2 leak and promoting arrhythmogenesis.[168] In obesity, similar pro-arrhythmic mitochondrial dysfunction and intracellular calcium dysregulation is observed.[165,166]

Remodelling of ion currents also occurs in the setting of T2D, including a decrease of L-type calcium current and various potassium currents (the latter contributing to the observed prolongation of repolarization).[169] Metabolic alterations, oxidative stress and calcium dysregulation may furthermore induce alterations in connexins, gap junctional remodelling and conduction abnormalities, as well as an increase in late sodium current magnitude which in turn leads to increased calcium influx via the reverse mode of the sodium/calcium exchanger, further promoting calcium-dependent pro-arrhythmic events. In addition, concurrent myocardial hypertrophy, fibrosis, apoptosis, and inflammation further compromise conduction, setting the stage for re-entrant arrhythmias. Similar electrophysiological changes have been observed in the setting of obesity.[164] Increased epicardial adipose tissue (EAT) furthermore exerts pro-arrhythmic effects and increases the risk for arrhythmias, in particular AF, in obese individuals, through a direct impact following invasion of the myocardium and because of paracrine effects of e.g. pro-fibrotic and pro-inflammatory mediators secreted by the EAT.[166,170] Additionally, plasma levels of circulating branched chain amino acids (BCAA) are elevated in insulin-resistant individuals,[171] and may be elevated up to 12 years before the onset of T2D.[172] BCAA impact on (mitochondrial) metabolism and reactive oxygen species production, and regulate pathways such as mTOR pathway and AMPK.[173,174] Elevated BCAA levels induce pro-arrhythmic calcium dysregulation,[175] further underscoring a potential role for BCAA dysregulation in obesity/T2D-related arrhythmogenesis.

Finally, alterations in cardiac autonomic tone, or cardiac autonomic neuropathy, are often observed in patients with T2D, and preclinical studies in the db/db mouse model of T2D have implicated a cardiac sympathetic dysfunction in the increased susceptibility to ventricular arrhythmias.[176] Sleep-disordered breathing, including obstructive sleep apnoea, frequently occurs in patients with obesity and T2D and is associated with increased arrhythmia risk.[177] Moreover, imbalances in gut microbiota composition have also been proposed as contributors to AF.[178]

From a management perspective, weight reduction and dietary adjustments hold significant potential for preventing cardiac

arrhythmias, adverse structural and metabolic remodelling, and both systolic and diastolic dysfunction. Weight loss, either by diet or bariatric surgery, shortens QTc in patients with obesity, reduces BCAA plasma levels, restores cardiac electrical dysfunction and reduces the risk of AF.[179] In addition to caloric restriction, specific dietary interventions may be of benefit, including for instance reducing intake of BCAAs or following a Mediterranean diet.[165,180]

The anti-diabetic drug metformin, at least in part via AMPK activation,[181] ameliorates mitochondrial dysfunction, calcium dysregulation, and repolarization abnormalities in preclinical studies.[182] SGLT2i have anti-arrhythmic effects in patients with T2D, and may attenuate intracellular calcium dysregulation, prevent autophagy hyperactivation, and reduce fibrosis, cardiomyopathy and inflammation.[183–186] Clinically, use of SGLT2i is associated with a reduced risk of AF in patients with HFrEF,[187] and with a lower AF recurrence following cryoballoon ablation.[188] In a small randomized controlled trial, the SGLT2i ertugliflozin reduced the incidence of sustained ventricular tachycardia or ventricular fibrillation in HFrEF patients with an implanted cardioverter-defibrillator.[189] Similarly, dapagliflozin treatment was associated with a reduction in ventricular arrhythmias in HFrEF patients, particularly in those with a worse functional class.[190] In diabetic db/db mice, GLP-1 and its agonist liraglutide prevented atrial remodelling and reduced AF.[191] Clinically, the use of GLP-1Ra has also been associated with a reduced risk of incident AF in T2D patients,[192] and with a lower risk of AF recurrence following ablation therapy.[193,194] However, GLP-1 also modulates heart rate due to the expression of its receptor in sinoatrial node cardiomyocytes,[195] and GLP-1Ra use was associated with an increase in heart rate and ventricular arrhythmic events in HFrEF patients,[196] underscoring the need for further evaluation.

Dyslipidaemia and arrhythmias

In addition to T2D and obesity, altered lipid metabolism is also associated with an increase of cardiac arrhythmias. While this increased arrhythmia risk is partly explained by an indirect consequence of hyperlipidaemia-induced atherosclerosis and IHD, it may also directly modulate cardiac electrophysiological properties through various mechanisms.[197] As discussed above, dyslipidaemia triggers a metabolic shift, favouring FA over glucose oxidation, ultimately resulting in increased reactive oxygen species production and consequently pro-arrhythmic dysregulation of intracellular calcium homeostasis, ion channels and connexins.[198] In addition, accumulation of lipids may lead to cardiac lipotoxicity and subsequent myocardial dysfunction and alteration of ion currents.[199] Dietary FAs and lipids furthermore impact on inflammatory pathways, cardiac fibroblasts and fibrosis formation, which are all established contributors to arrhythmogenicity.[200] Lipid composition of the cardiomyocyte membrane is a crucial determinant of ion channel function and hence for cardiac electrophysiological properties.[201] Preclinical studies have demonstrated that hypercholesterolaemia is associated with an increased L-type calcium current density leading to ventricular action potential prolongation (i.e. prolonged repolarization),[202] as well as a reduction of the fast inward sodium current which sets the stage for cardiac conduction slowing.[203] Conversely, altered dietary lipid composition and LDL-C lowering therapies shorten ventricular repolarization (QT interval), offering a potential anti-arrhythmic effect.[204,205] Regarding dyslipidaemia and AF, there is an apparent discrepancy between preclinical and clinical observations. While animal studies have revealed pro-arrhythmic atrial remodelling in dyslipidaemia models, a paradoxical inverse association is observed between serum lipid levels and AF risk, which may be explained by confounding factors such as age, statin use and inflammation.[206,207] Nevertheless, lipid-lowering therapies appear to be associated with a reduced risk for AF onset and recurrence,[208] and multiple meta-analyses of randomized controlled trials indicate that use of statins is associated with a reduced incidence or recurrence of AF, with OR approximately 0.49 (95% confidence interval 0.37–0.65).[209] Whether in humans this effect is dependent solely on LDL-C lowering or could also stem by electrophysiologic stabilizing actions of statins is still debated.

Conclusions: gaps in knowledge and future directions

Despite considerable progress in understanding the cardiovascular effects of drugs and their relation to multi-organ pathophysiology, critical knowledge gaps persist. A fundamental unresolved question is how organ-specific metabolic and inflammatory signals coordinate systemic disease progression. The molecular basis of inter-organ communication mediated for example by cardiomyokines, hepatokines, adipokines, gut-derived metabolites, inflammatory mediators, and extracellular vesicles remain poorly characterized. Deciphering these networks could reveal key regulatory nodes linking metabolic dysregulation to cardiovascular injury. Early molecular events that trigger multi-organ dysfunction also remain elusive. Existing clinical biomarkers largely reflect established organ damage rather than pre-symptomatic alterations. Identifying biomarkers capable of capturing integrated cardiovascular–hepatic–metabolic risk could enable earlier diagnosis and personalized intervention. It is unclear which organ initiates systemic metabolic dysfunction, and the impact of metabolic alterations in bone marrow response. Defining the hierarchy and directionality of inter-organ interactions is essential for prioritizing therapeutic targets.

Differences in obesity phenotypes (for example visceral vs subcutaneous), lipid profile (TG, saturated vs unsaturated FAs), presence or absence of comorbidities, age, sex, might all affect cardiac metabolism but remain under-studied. Furthermore, since isolated dyslipidaemia with normal glycaemic status is less well studied in the heart, clarifying how excess circulating lipids (e.g. due to dietary overload or dyslipidaemia) without insulin resistance might affect cardiac substrate competition would be valuable. The reversibility of shared pathogenic mechanisms, such as insulin resistance, mitochondrial dysfunction, and impaired autophagy, also remains uncertain, with implications for interventions aimed at halting or reversing disease progression. Similarly, the systemic effects of emerging lipid-lowering and metabolic therapies are incompletely understood, including whether profound reductions in circulating lipids induce compensatory metabolite redistribution in the liver or other tissues. Finally, the effects of medications in driving substrate supply and utilization needs deeper mechanistic research, potentially considering their potential pleiotropic effects that may extend beyond their primary metabolic targets.

Most mechanistic and intervention studies have been performed in rodents, and human data are more limited,[210] especially *in vivo* measurement of substrate flux in obese or diabetic hearts across disease stages. Although animal models have been helpful in reproducing aspects of human disease, they rarely capture the full spectrum of multi-organ interactions or fully reflect established metabolic syndrome. Established models (such as mice, rats, rabbits, and pigs) often involve a combination of a high-cholesterol diet and monogenic modifications, with additional diets or pharmacological/surgical interventions frequently required to induce further risk factors such as diabetes. Despite these efforts, animal models do not reflect the complex situation in humans, who have a heterogeneous, polygenic risk profiles for developing metabolic syndrome. Experimental models that develop a full metabolic syndrome on a polygenic background are rare and have not yet been well characterized.[211,212] Validation of preclinical findings requires large, longitudinal human cohorts integrating clinical, imaging, and molecular data, with structured collection of biospecimens across liver, cardiovascular, and metabolic tissues.[210] Next-generation experimental models, including organoids, assembloids, and organ-on-chip platforms,[213–215] complement *in vivo* models by recreating physiologically relevant tissue–tissue interactions using human cells. Further development of these human-based experimental systems is essential to enhance understanding of the impact of metabolic disorders on CVD and test novel interventions.

A limitation in this field includes the scarcity of sex- and age-specific studies and a focus on single-organ mechanisms rather than systemic evolution over time.[216–218] Longitudinal, multi-organ studies integrating multi-omics datasets remain rare, underscoring the need for cross-tissue, integrative approaches that combine genomic, epigenomic, transcriptomic, proteomic, metabolomic, and metagenomic data across liver, heart, adipose tissue, kidneys, and gut. The implementation of artificial intelligence-driven approaches, such as machine learning and deep learning, may efficiently help to analyse and interpret multi-omics datasets across multiple organs providing a systems-level understanding and helping to reveal shared regulatory networks, causal drivers, and organ-specific adaptations in cardiovascular dysfunction.

Finally, addressing the complex basis for metabolic disorders and CVD requires a systems-based, multidisciplinary framework spanning cardiology, hepatology, nephrology, endocrinology, metabolism, primary care, and patient-centred perspectives. Both research and clinical care must evolve towards integrated risk assessment, co-management strategies, and early targeting of shared pathophysiological mechanisms, with the goal of preventing multi-organ dysfunction and improving long-term outcomes.

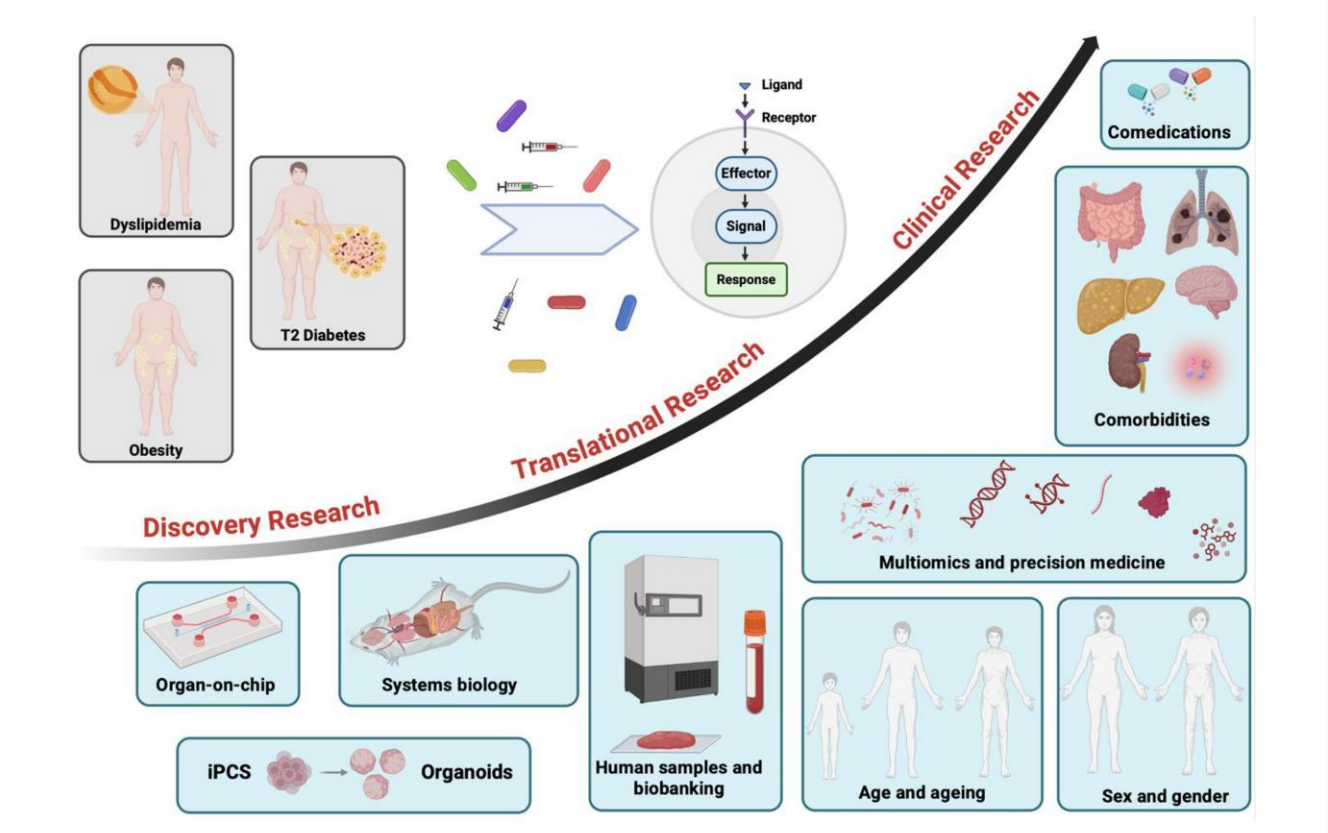


Figure 3 Future perspectives of discovery, translational and clinical research to gain mechanistic insights in metabolic disorders. Schematic representation of mechanistic studies that future research should prioritize to identify precision and preventive strategies that mitigate multi-organ dysfunction in metabolic disorders and cardiovascular diseases. iPCS, ...; T2, type 2 (created with BioRender.com)

Future research should prioritize mechanistic studies, longitudinal cohort integration, and translational platforms that reflect the true interdependence of metabolic and cardiovascular systems, in relation to sex, gender and ageing (*Figure 3*). Through these coordinated, multidisciplinary efforts, the field can move closer to precision and preventive strategies that mitigate multiorgan dysfunction, reduce morbidity, and ultimately improve long-term patient outcomes.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

Nothing to declare.

Data Availability

No data were generated or analysed for or in support of this paper.

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