

REVIEW



Metabolic reprogramming synergy: CoQ10 and SGLT2 inhibitors combination in heart failure - a narrative review

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ABSTRACT

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have fundamentally changed the treatment landscape of heart failure (HF), demonstrating cardiovascular benefit across the full ejection fraction spectrum. Among proposed mechanisms, the "ketone hypothesis" has drawn particular attention: SGLT2i raise circulating ketone bodies, shifting myocardial substrate utilization toward ketone oxidation, a more oxygen-efficient fuel for the energy-deprived failing heart. In parallel, coenzyme Q10 (CoQ10), an essential electron carrier in the mitochondrial electron transport chain (ETC), has shown efficacy in reducing mortality and hospitalization in HF. Despite the complementary nature of these two metabolic interventions, SGLT2i enhancing ketone oxidation and thereby increasing NADH flow into the ETC, and CoQ10 facilitating electron transfer from Complexes I and II to Complex III, no clinical study has investigated their combination. This narrative review examines the mechanistic basis for a potential synergistic interaction, proposing that CoQ10 may relieve the ETC bottleneck created by increased NADH delivery during SGLT2i-induced ketosis, optimizing mitochondrial energetics while reducing electron flow stress and reactive oxygen species production. We synthesize current evidence, identify critical knowledge gaps, and propose a framework for future investigation of this novel metabolic combination strategy. The CoQ10-SGLT2i combination represents a promising, mechanistically grounded approach that warrants preclinical and clinical evaluation.

KEYWORDS

SGLT2 inhibitors; Coenzyme Q10; Heart failure; Mitochondrial function; Ketone metabolism; Metabolic reprogramming

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Introduction

Heart failure remains a major global cause of morbidity and mortality, affecting approximately 1-2% of the adult population, with prevalence rising sharply with age. Despite advances in guideline-directed medical therapy, prognosis, particularly in heart failure with reduced ejection fraction (HFrEF), remains suboptimal. The failing heart is marked by deep metabolic disturbance: impaired mitochondrial oxidative phosphorylation, reduced ATP production, and a shift toward less efficient substrate use [1].

SGLT2 inhibitors have transformed heart failure management. Major cardiovascular outcome trials have consistently shown that SGLT2i significantly reduce cardiovascular mortality and heart failure hospitalization, in patients with and without type 2 diabetes, largely independent of glycemic control, and across the full spectrum of left ventricular ejection fraction [2,3,4,5,6]. Among proposed mechanisms, the ketone hypothesis is particularly compelling: SGLT2i raise circulating beta-hydroxybutyrate (beta-OH-B), an oxygen-efficient fuel that may relieve the energy deficit characteristic of the failing heart. Key outcome trials establishing this evidence base are summarized in Table 1.

In parallel, coenzyme Q10 has drawn growing interest as adjunctive heart failure therapy. A meta-analysis of 33 randomized controlled trials found that CoQ10 supplementation significantly reduces all-cause mortality (RR = 0.64, 95% CI 0.48-0.85) and heart failure hospitalization (RR = 0.50, 95% CI 0.37-0.67), while improving left ventricular ejection fraction and functional capacity. The landmark Q-SYMBIO trial found that long-term CoQ10 treatment reduced major

Table 1. Summary of key clinical trials of SGLT2 inhibitors in heart failure.

Trial	Agent	Population	Primary endpoint	Key result
EMPA-REG OUTCOME	Empagliflozin	T2DM + CVD	CV death, stroke	MI, 14% RRR [7]
CANVAS Program	Canagliflozin	T2DM + high CV risk	CV death, stroke	MI, 14% RRR [8]
DECLARE-TIMI 58	Dapagliflozin	T2DM + high CV risk	CV death, stroke	MI, 17% RRR [9]
DAPA-HF	Dapagliflozin	HFrEF T2DM	+/- CV death or worsening	HF 26% RRR [10]
EMPEROR-Reduced	Empagliflozin	HFrEF T2DM	+/- CV death or hospitalization	HF 25% RRR [11]
EMPEROR-Preserved	Empagliflozin	HFpEF T2DM	+/- CV death or hospitalization	HF 21% RRR [12]
DELIVER	Dapagliflozin	HFpEF T2DM	+/- CV death or worsening	HF 18% RRR [13]

adverse cardiovascular events (15% vs 26% with placebo; HR 0.50, $p = 0.003$) and cardiovascular mortality (9% vs 16%, $p = 0.026$).

Despite these independent successes, the potential synergistic

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interaction between SGLT2i and CoQ10 remains unexplored. This review examines the mechanistic rationale for combining these agents, focusing on their complementary effects on myocardial energetics and mitochondrial function, synthesizes the current evidence base, identifies critical knowledge gaps, and proposes a framework for future investigation.

Methodology

Search strategy and study selection

This narrative review was conducted through a comprehensive, non-systematic search of the published literature. Given its narrative nature, a formal PRISMA-guided systematic methodology was not applied; instead, a critical, interpretive approach was adopted to synthesize evidence from diverse sources. PubMed, Scopus, Web of Science, and Google Scholar were searched from inception to August 2026 using combinations of the terms "SGLT2 inhibitors," "sodium-glucose cotransporter 2 inhibitors," "empagliflozin," "dapagliflozin," "canagliflozin," "coenzyme Q10," "ubiquinone," "heart failure," "mitochondrial function," "electron transport chain," "ketone bodies," "metabolic reprogramming," and "oxidative stress." Reference lists of identified articles were manually screened for additional relevant publications.

Inclusion and exclusion criteria

Peer-reviewed original research articles, systematic reviews, meta-analyses, and narrative reviews in English addressing the mechanisms of SGLT2i action in heart failure (particularly metabolic and mitochondrial effects), the role of CoQ10 in cardiovascular disease and heart failure, mitochondrial bioenergetics and ETC function in the failing heart, and the potential for combination metabolic therapies in heart failure were included. Non-English publications, conference abstracts, editorials without original data, and animal studies without clear translational relevance were excluded unless they provided critical mechanistic insight.

Data synthesis

Given the narrative review format, data were synthesized thematically rather than through quantitative meta-analytic techniques. Key themes were: the ketone hypothesis and metabolic effects of SGLT2i; mitochondrial effects of SGLT2i, including ETC modulation and redox balance; the biochemical role and clinical evidence for CoQ10 in heart failure; the mechanistic rationale for synergy; and knowledge gaps and future directions. The synthesis is interpretive, aiming to construct a coherent mechanistic framework rather than a definitive quantitative summary.

SGLT2 Inhibitors and Cardiac Metabolic Reprogramming

The ketone hypothesis: A "thrifty substrate" for the failing heart

The ketone hypothesis proposes that SGLT2i-mediated elevation of circulating ketone bodies, particularly beta-hydroxybutyrate, provides the failing heart with an energetically advantageous fuel source. Ketone bodies yield more ATP per molecule of oxygen than glucose or fatty acids, making them a "thrifty substrate" for the energy-deficient myocardium.

SGLT2i promote ketogenesis through multiple mechanisms. By inhibiting renal glucose reabsorption, these agents induce glycosuria, creating a mild caloric deficit that stimulates hepatic ketone production, while also increasing the glucagon-to-insulin ratio, further promoting ketogenesis. The net effect is a sustained elevation of circulating beta-OH-B, typically 0.5-1.5 mmol/L, available for myocardial uptake and oxidation.

Clinical studies support the ketone hypothesis. Acute elevation of plasma beta-OH-B to approximately 1.6 mmol/L has been shown to

significantly increase cardiac output, ejection fraction, and stroke volume in patients with heart failure and type 2 diabetes. Consistent with this, the DEFINE-HF trial found that dapagliflozin improved patient-reported symptoms and functional status in HFrEF, independent of diabetes status [14]. Ketone oxidation appears to add an additional fuel source rather than simply replacing glucose utilization, increasing total ATP production for the energy-starved failing heart, a finding corroborated in murine models where myocardial ketone body oxidation directly contributed to empagliflozin-induced improvements in cardiac contractility [15].

However, whether ketone elevation alone accounts for the full pleiotropic cardiovascular benefit of SGLT2i remains debated; other mechanisms, including improved sodium handling, reduced cardiac fibrosis, and enhanced autophagy, may be equally or more important.

Myocardial substrate utilization shifts: Beyond simple ketosis

Preclinical studies using metabolic tracers show that SGLT2i effects on cardiac metabolism are more nuanced than the simple ketone hypothesis suggests. Goedeke and colleagues demonstrated that acute dapagliflozin administration shifts myocardial mitochondrial metabolism toward ketone oxidation, decreasing pyruvate oxidation while having minimal effect on fatty acid oxidation in awake rats [16]. In failing hearts, dapagliflozin increased relative rates of both ketone and fatty acid oxidation while decreasing pyruvate oxidation, changes associated with reduced myocardial oxidative stress and improved left ventricular ejection fraction after three weeks of treatment.

Notably, the metabolic effects of SGLT2i differ from simple ketone supplementation. Acute beta-OH-B infusion augments ketone oxidation but markedly reduces fatty acid oxidation without altering glucose uptake or pyruvate oxidation, a pattern not seen with SGLT2i [17]. This suggests SGLT2i exert pleiotropic metabolic effects beyond ketosis induction, including direct modulation of fatty acid metabolism and mitochondrial function.

The net effect is a fundamental reprogramming of myocardial metabolism toward greater metabolic flexibility, the capacity to adapt substrate utilization to changing conditions, which the failing heart typically loses.

Direct mitochondrial effects of SGLT2 inhibitors

Beyond substrate switching, SGLT2i directly modulate mitochondrial function through multiple pathways, enhancing cardiac energy dynamics by boosting mitochondrial ATP production [18,19,20]. Dapagliflozin significantly increases mitochondrial membrane potential and elevates Complex I expression in the ETC [21]. Empagliflozin similarly enhances myocardial energetics and increases cardiac ATP production in preclinical models of diabetic and non-diabetic heart failure [22,23].

Direct exposure of isolated cardiac mitochondria to dapagliflozin enhances respiration and induces membrane hyperpolarization [24]. Dapagliflozin significantly reduces mitochondrial ROS production at Complexes I and II, although electron leakage was increased at Complex I but unchanged at Complex II, suggesting differential modulation of ETC components. These findings indicate that SGLT2i may improve mitochondrial efficiency while paradoxically creating electron flow stress at specific ETC sites.

SGLT2i also restore mitochondrial biogenesis through AMPK/PGC-1 α pathway activation, with upregulation of peroxisome proliferator-activated receptor gamma coactivator 1 α and downstream mitochondrial biogenesis factors, alongside reduced oxidative stress and inflammation [25].

These effects are agent-specific: canagliflozin has been reported to inhibit ETC Complex I-dependent respiration, while dapagliflozin and empagliflozin do not exhibit this effect at pharmacologically relevant concentrations [26]. This differential profile has implications for combination strategies with CoQ10 (Table 2).

NADH/NAD⁺ dynamics and redox balance

Table 2. Comparison of SGLT2 inhibitor effects on mitochondrial function.

Agent	Complex effect	I Complex effect	II Complex effect	ROS production	Membrane potential	Mitochondrial biogenesis
Dapagliflozin	Increased electron leakage	Unchanged		Overall reduced	Increased (hyperpolarization)	Increased (AMPK/PGC-1α)
Empagliflozin	No direct inhibition	No direct inhibition		Reduced	Increased	Increased (PGC-1α)
Canagliflozin	Inhibits Complex dependent respiration	I-	Variable	Variable	Variable	Limited data

SGLT2i-mediated metabolic reprogramming alters the NADH/NAD⁺ redox balance. Ketone oxidation generates substantial NADH, which must be reoxidized to NAD⁺ through the ETC to sustain mitochondrial function; SGLT2i increase the NADH+H⁺/NAD⁺ ratio, potentially reflecting enhanced electron delivery to the ETC. Decreased mitochondrial calcium following SGLT2i treatment may also hamper TCA-derived NADH generation by suppressing calcium-induced upregulation of TCA-cycle dehydrogenases, attenuating both NADH and NADPH production. Multiple studies show benefits of raising NAD⁺ levels and normalizing the NAD⁺/NADH ratio in failing hearts, and this balance is increasingly recognized as a target for mitochondrial dysfunction, with parallels drawn to GLP-1 receptor agonists, another cardioprotective drug class whose benefits partly converge on mitochondrial function and oxidative stress [27].

Sirtuin 1 as a convergence point for NAD⁺-dependent signaling

The NAD⁺/NADH shifts discussed above have a further downstream consequence relevant to this review: Sirtuin 1 (SIRT1) is an NAD⁺-dependent protein deacetylase, and its enzymatic activity depends directly on the availability of NAD⁺ as an obligate cofactor, while NADH acts as a competitive inhibitor. SIRT1 is increasingly recognized as a central regulator of metabolic health, cardiovascular protection, and cellular stress resistance, with repression of this anti-aging gene implicated in diabetes and multi-organ dysfunction more broadly [28,29,30]. Ketone bodies, particularly beta-hydroxybutyrate, activate SIRT1 both directly and indirectly by raising cellular NAD⁺ levels, establishing a synergistic relationship between ketone metabolism and SIRT1-dependent epigenetic and metabolic regulation [31,32].

This connects mechanistically to the SGLT2i-CoQ10 relationship proposed in this review. Because CoQ10 deficiency impairs ETC efficiency and lowers the cytoplasmic and mitochondrial NAD⁺/NADH ratio, CoQ10 deficiency can be expected to compromise SIRT1 (and SIRT3) deacetylase activity by limiting the availability of their obligate substrate, NAD⁺ [33]. Consistent with this link, a sub-study of a long-term selenium and CoQ10 supplementation trial found that the intervention significantly increased serum SIRT1 concentration, an increase that was itself associated with reduced cardiovascular mortality over ten years of follow-up [34]. Separately, SGLT2i have been shown to upregulate SIRT1 and its downstream partner PGC-1α in preclinical models of heart failure with preserved ejection fraction, indicating that SGLT2i themselves may act, at least in part, as SIRT1 activators [35].

Taken together, this suggests that SIRT1 sits at a mechanistic crossroads relevant to the proposed CoQ10-SGLT2i combination: SGLT2i-induced ketosis and CoQ10-supported NAD⁺ availability may jointly sustain SIRT1 activity, with plausible downstream benefits for mitochondrial biogenesis and stress resistance in the failing heart.

Preclinical studies of this combination should consider plasma or myocardial SIRT1 concentration as a candidate diagnostic and mechanistic biomarker, consistent with its proposed role as a protein marker for chronic disease and therapeutic drug response more broadly, alongside the electron transport chain and redox measures already discussed [36].

Coenzyme Q10: The essential electron carrier

Biochemical role in the electron transport chain

Coenzyme Q10 (ubiquinone) is a lipid-soluble molecule integral to the mitochondrial electron transport chain. Incorporated into the inner mitochondrial membrane, CoQ10 facilitates electron passage from Complexes I and II to Complex III: fully oxidized CoQ10 accepts a pair of electrons from each of Complex I and Complex II and passes them to Complex III, where the Q cycle occurs (Figure 1) [37].

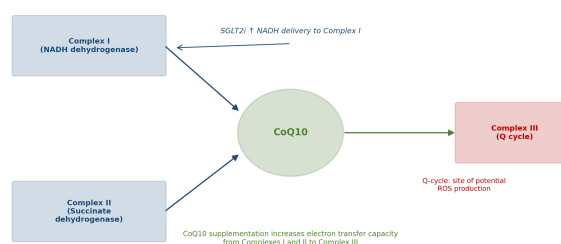


Figure 1. Mitochondrial electron transport chain with CoQ10 position.

This three-phase redox cycle is fundamental to oxidative phosphorylation and ATP production. CoQ10 also functions as a mitochondrial antioxidant. The Q cycle is a major site of mitochondrial ROS production, since electrons can leak and react with oxygen to form superoxide; when CoQ10 levels are low, ETC efficiency is compromised, increasing superoxide production and reducing ATP synthesis. CoQ10 deficiency therefore creates a dual pathology: impaired energy production and enhanced oxidative stress.

CoQ10 deficiency in heart failure: A mechanistic link

Myocardial CoQ10 deficiency is well documented in heart failure and may be both a consequence and a driver of mitochondrial dysfunction. Myocardial tissue CoQ10 levels, measured by high-performance liquid chromatography, are significantly lower in patients with more advanced heart failure than in milder disease stages.

Preclinical work provides mechanistic insight: mouse models of cardiomyopathy exhibit myocardial CoQ10 deficiency, likely due to suppressed endogenous CoQ10 synthesis [38], suggesting the deficiency reflects a fundamental disturbance in biosynthesis rather than reduced intake alone. Primary CoQ10 deficiencies, though rare, can present with severe hypotonia, bradycardia, respiratory insufficiency, and heart failure, underscoring CoQ10's importance for cardiac function. Oral supplementation has been reported to reverse ETC dysfunction associated with CoQ10 deficiency.

Clinical evidence for CoQ10 in heart failure

The clinical evidence base for CoQ10 in heart failure has strengthened considerably over the past decade. The Q-SYMBIO trial, a randomized double-blind multicenter study of 420 patients with moderate to severe heart failure, found that CoQ10 100 mg three times daily as adjunctive therapy significantly reduced the primary composite endpoint of major adverse cardiovascular events (15% vs 26%, HR 0.50, $p = 0.003$), with significant reductions in cardiovascular mortality (9% vs 16%, $p = 0.026$), all-cause mortality (10% vs 18%, $p = 0.018$), and heart failure hospitalizations [39].

A comprehensive meta-analysis of 33 RCTs confirmed these findings: all-cause mortality (RR = 0.64, 95% CI 0.48-0.85, $P < 0.002$), heart failure hospitalization (RR = 0.50, 95% CI 0.37-0.67, $P < 0.00001$), NYHA classification (MD = -0.29, 95% CI -0.39 to -0.19, $P < 0.00001$), and BNP level (MD = -91.97, 95% CI -103.11 to -80.83, $P < 0.00001$) were all significantly lower with CoQ10, while LVEF (MD = 0.51%, 95% CI 0.31-0.71, $P < 0.00001$) and six-minute walk test distance (MD = 31.70 m, 95% CI 19.96-43.43, $P < 0.00001$) were significantly improved [40]. A separate randomized controlled trial similarly reported improvements in cardiac function and quality-of-life measures with CoQ10 supplementation in heart failure patients [41]. Ongoing trials, including DANUTRIO-HF, continue to evaluate CoQ10's role in heart failure management (Table 3).

Table 3. Summary of key clinical evidence for CoQ10 in heart failure.

Study /Trial	Design	Population	CoQ10 dose	Key findings
Q-SYMBI O (2014)	RCT, n=420	Chronic HF, NYHA III-IV	100 mg TID	MACE: 15% vs 26% (HR 0.50, $p=0.003$); CV mortality: 9% vs 16% ($p=0.026$)
Xu et al. (2024)	Meta-analysis, 33 RCTs	HF patients	Variable	All-cause mortality RR 0.64 (0.48-0.85); HF hospitalization RR 0.50 (0.37-0.67); LVEF MD +0.51% (0.31-0.71); 6MWT MD +31.70 m (19.96-43.43)

Mechanistic Rationale for Synergy

The ETC bottleneck hypothesis

The central premise of this review is that SGLT2i and CoQ10 may exert synergistic effects through complementary actions on mitochondrial energetics. SGLT2i increase ketone oxidation, generating additional NADH that must be processed through the ETC, placing increased demand on the CoQ10-dependent step where electrons from Complexes I and II converge before transfer to Complex III.

CoQ10, as the electron carrier facilitating this transfer, could relieve this bottleneck, enabling the heart to fully realize the energetic benefits of SGLT2i-induced ketosis without encountering ETC limitations (Figure 2). This is supported by evidence that CoQ10 deficiency causes defects in respiratory chain activities (reduced Complex I+III and II+III activity), while CoQ10 supplementation increases Q-dependent activities. Under enhanced NADH delivery from SGLT2i-induced ketosis, adequate CoQ10 levels become even more critical to prevent ETC congestion.

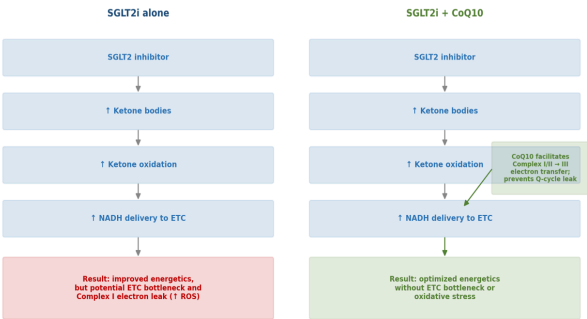


Figure 2. Proposed mechanistic model of CoQ10-SGLT2i synergy.

Offsetting electron flow stress and ROS production

SGLT2i may paradoxically create electron flow stress at specific ETC sites: dapagliflozin, while reducing overall mitochondrial ROS, increases electron leakage at Complex I, suggesting that enhanced electron delivery may raise the risk of electron leak and ROS production at vulnerable sites. CoQ10, by facilitating efficient electron transfer and acting as an antioxidant, could offset this stress, functionally widening the ETC's capacity and reducing the risk of electron "collisions" that generate free radicals.

Complementary mitochondrial effects

SGLT2i and CoQ10 also appear complementary in mitochondrial function more broadly: SGLT2i enhance mitochondrial biogenesis and ATP production, while CoQ10 helps ensure existing and newly formed ETC components function optimally. Both agents modulate oxidative stress through distinct but complementary mechanisms: SGLT2i reduce mitochondrial ROS production, while CoQ10 directly scavenges ROS and prevents electron leak at the Q cycle. SGLT2i activate the AMPK/PGC-1α pathway to increase mitochondrial biogenesis; CoQ10, by ensuring newly formed mitochondria have adequate electron carrier capacity, may enhance the functional consequences of this biogenesis (Table 4).

Table 4. Mechanistic comparison of SGLT2 inhibitors and CoQ10.

Mechanism	SGLT2 inhibitors	Coenzyme Q10	Synergistic potential
Substrate utilization	Increased oxidation, increased fatty acid oxidation	No direct effect	SGLT2i increases substrate supply; CoQ10 enables utilization
ETC electron flux	Increased delivery	Facilitates Complex I/II to III transfer	CoQ10 relieves bottleneck created by increased NADH
ATP production	Increased mitochondrial ATP	Enables efficient OXPHOS	Complementary: supply + capacity
ROS production	Overall decreased (but increased Complex I leak)	Direct scavenging; prevents Q cycle leak	CoQ10 offsets SGLT2i-induced Complex I leak
Mitochondrial biogenesis	Increased (AMPK/PGC-1α pathway)	No direct effect	CoQ10 ensures new mitochondria function optimally
Metabolic flexibility	Increased (substrate switching)	Supports ETC function	CoQ10 enables SGLT2i-induced flexibility

Potential for enhanced metabolic flexibility

The failing heart suffers from metabolic inflexibility, an inability to adapt substrate utilization to changing conditions. SGLT2i enhance metabolic flexibility by promoting ketone oxidation, while CoQ10 supports the mitochondrial machinery required to execute this flexibility. Together, they may represent a form of "metabolic infrastructure investment": SGLT2i increase demand for mitochondrial electron transport, and CoQ10 increases the capacity to meet that demand, a demand-capacity matching principle that may explain why the combination could be more than additive.

Current Evidence and Knowledge Gaps

Absence of dedicated combination studies

Despite the compelling mechanistic rationale, no clinical study has specifically investigated the combination of SGLT2i and CoQ10 in heart failure. A recent trial examining CoQ10 supplementation in heart failure reported SGLT2i use at 28% of the study population, but this represents concomitant use rather than a dedicated combination study. No trial has been designed to evaluate whether CoQ10 enhances or modifies the effects of SGLT2i. This absence represents a critical knowledge gap: while both agents have demonstrated independent efficacy, whether their combination provides additive, synergistic, or merely redundant benefit remains unknown.

Safety and drug interactions

Preliminary evidence suggests no significant drug interactions between CoQ10 and SGLT2i; drug interaction databases report no interactions with empagliflozin, dapagliflozin, canagliflozin, or ertugliflozin. As with all combination strategies, careful monitoring for additive effects on blood pressure is warranted, given that SGLT2i can cause intravascular volume contraction and symptomatic hypotension after initiation. Both agents individually have well-established safety profiles; CoQ10 is safe in long-term use with no major adverse effects, and SGLT2i carry well-characterized risks of genital infections, rare diabetic ketoacidosis, and volume depletion. The combination is unlikely to introduce new safety concerns beyond those of the individual agents, though formal safety data are lacking.

Critical unanswered questions

Several key questions should guide future research. Optimal dosing: whether the Q-SYMBIO dose of 100 mg three times daily remains optimal in the context of enhanced ETC demand, or whether higher doses or mitochondria-targeted formulations (such as MitoQ) are required. Patient selection: which heart failure patients, perhaps those with the most severe mitochondrial dysfunction, highest baseline CoQ10 deficiency, or greatest ketone response to SGLT2i, would benefit most. Timing of initiation: whether CoQ10 should be started concurrently with SGLT2i or after establishing SGLT2i therapy. Agent specificity: whether canagliflozin's inhibition of Complex I-dependent respiration produces different CoQ10 interactions than dapagliflozin or empagliflozin. Clinical endpoints: whether combination therapy would reduce major adverse cardiovascular events beyond SGLT2i alone, or whether benefit would be confined to secondary endpoints such as quality of life and functional capacity.

Future Directions

Preclinical studies

Well-designed preclinical studies are needed to test the synergy hypothesis. Isolated mitochondrial studies could examine whether CoQ10 supplementation normalizes ETC function in the presence of SGLT2i-induced ketosis. Animal heart failure models could evaluate whether combination therapy provides additive benefit on LVEF,

mitochondrial function, and survival compared with either agent alone. The BDH1cko mouse model, incapable of oxidizing beta-OH-B, could help dissect ketone-dependent versus ketone-independent components of synergy. Dose-response studies for CoQ10 in the context of SGLT2i treatment would help determine whether optimal CoQ10 dosing shifts when ETC demand is elevated (Figure 3).

Clinical trial design

A randomized controlled trial comparing SGLT2i plus CoQ10 versus SGLT2i plus placebo in heart failure patients would provide definitive evidence. Key considerations include: population, HFrEF patients with NYHA class II-III given the established evidence base, with possible inclusion of HFpEF patients in a secondary cohort; CoQ10 dosing at 100 mg three times daily (as in Q-SYMBIO) or higher, with a dose-finding phase if warranted; a primary composite endpoint of cardiovascular death and heart failure hospitalization; secondary endpoints including LVEF, NT-proBNP, six-minute walk test, quality of life (KCCQ), and mitochondrial biomarkers; mechanistic substudies using cardiac PET/MRI and biomarkers such as FGF21 and GDF15; and a sample size powered to detect a clinically meaningful reduction in the primary composite endpoint, likely requiring several thousand patients given contemporary heart failure trial event rates.

Biomarker development

Identifying biomarkers of CoQ10 deficiency and ETC stress could enable personalized combination therapy. Myocardial CoQ10 levels, plasma CoQ10, and markers of mitochondrial dysfunction could help identify patients most likely to benefit, as could the magnitude of ketone response to SGLT2i. Genetic factors influencing CoQ10 biosynthesis, such as polymorphisms in PDSS1, PDSS2, COQ2, and COQ6, may also be relevant to a precision-medicine approach.

Novel formulations

Emerging formulations such as MitoQ, a mitochondria-targeted CoQ10 analogue that penetrates mitochondrial membranes more efficiently and directly scavenges ROS at Complex III, may offer advantages over standard CoQ10 and warrant investigation for synergy with SGLT2i. Other delivery systems, including nanoparticle and liposomal formulations, may enhance CoQ10 bioavailability and mitochondrial targeting, potentially reducing required dose and improving adherence.

Discussion

Synthesis of evidence

The evidence reviewed here supports a coherent mechanistic framework for CoQ10-SGLT2i synergy in heart failure. SGLT2i enhance myocardial ketone oxidation, increasing NADH delivery to the ETC and improving myocardial energetics. CoQ10, as the essential electron carrier at the convergence of Complexes I and II, may relieve the ETC bottleneck created by this enhanced electron flow while providing antioxidant protection against electron leak and ROS production. The independent clinical efficacy of both agents is well established, and their complementary mechanisms, matching increased demand for ETC function (from SGLT2i) with increased capacity for ETC function (from CoQ10), provide a strong theoretical basis for expecting additive or synergistic benefit, consistent with broader state-of-the-art reviews of SGLT2i cardiovascular mechanisms [42,43].

Comparison with other combination strategies

The proposed CoQ10-SGLT2i combination is conceptually distinct from combinations of neurohormonal antagonists (such as ACE inhibitors plus beta-blockers), which target different aspects of the same pathophysiological pathway. Instead, it targets different levels of the same metabolic pathway, substrate utilization (SGLT2i) and electron transport capacity (CoQ10), a form of "vertical" integration addressing both the supply side and demand side of myocardial energy metabolism. It also differs from other metabolic therapies such

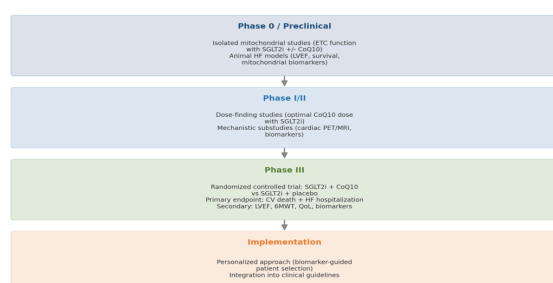


Figure 3. Conceptual framework for clinical development of the CoQ10-SGLT2i combination.

as trimetazidine or ranolazine, which modulate substrate utilization without directly enhancing ETC capacity.

Limitations

This narrative review has several limitations. The absence of dedicated combination studies means much of the mechanistic rationale remains theoretical; while the individual effects of SGLT2i and CoQ10 are well characterized, their interaction has not been directly tested. The heterogeneity of SGLT2i agents, with differential effects on mitochondrial function, means synergy may be agent-specific. The optimal dosing and timing of CoQ10 alongside SGLT2i remain unknown, and the clinical significance of any additional benefit from combination therapy cannot be estimated without trial data.

Clinical Implications

Despite these limitations, if validated, the combination could provide incremental benefit beyond SGLT2i alone, potentially further reducing cardiovascular mortality and heart failure hospitalization, and could be particularly beneficial for patients with evidence of CoQ10 deficiency or mitochondrial dysfunction. Given the established, favorable safety profiles of both agents individually, and the absence of known drug interactions, the combination is an attractive candidate for clinical evaluation.

Conclusion

The combination of SGLT2 inhibitors and coenzyme Q10 represents a novel, mechanistically grounded strategy for metabolic reprogramming in heart failure. SGLT2i enhance ketone oxidation, increasing NADH delivery to the electron transport chain and improving myocardial energetics. CoQ10, as the essential electron carrier at the convergence of Complexes I and II, may relieve the resulting ETC bottleneck while providing antioxidant protection against electron leak and ROS production. Although neither agent alone is a panacea, their complementary mechanisms suggest genuine potential for synergy. The absence of combination studies is a critical knowledge gap that warrants urgent investigation through rigorous preclinical mechanistic studies followed by well-designed clinical trials with appropriate patient selection, dosing strategies, and endpoint ascertainment.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

All authors contributed equally to the conceptualization, research, drafting, and revision of this manuscript.

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