Review

Coenzyme Q\textsubscript{10}: Clinical Applications in Cardiovascular Diseases

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Abstract: Coenzyme Q\textsubscript{10} (CoQ\textsubscript{10}) is a ubiquitous factor present in cell membranes and mitochondria, both in its reduced (ubiquinol) and oxidized (ubiquinone) forms. Its levels are high in organs with high metabolism such as the heart, kidneys, and liver because it acts as an energy transfer molecule but could be reduced by aging, genetic factors, drugs (e.g., statins), cardiovascular (CV) diseases, degenerative muscle disorders, and neurodegenerative diseases. As CoQ\textsubscript{10} is endowed with significant antioxidant and anti-inflammatory features, useful to prevent free radical-induced damage and inflammatory signaling pathway activation, its depletion results in exacerbation of inflammatory processes. Therefore, exogenous CoQ\textsubscript{10} supplementation might be useful as an adjuvant in the treatment of cardiovascular diseases such as heart failure, atrial fibrillation, and myocardial infarction and in associated risk factors such as hypertension, insulin resistance, dyslipidemias, and obesity. This review aims to summarize the current evidences on the use of CoQ\textsubscript{10} supplementation as a therapeutic approach in cardiovascular diseases through the analysis of its clinical impact on patients’ health and quality of life. A substantial reduction of inflammatory and oxidative stress markers has been observed in several randomized clinical trials (RCTs) focused on several of the abovementioned diseases, even if more RCTs, involving a larger number of patients, will be necessary to strengthen these interesting findings.

Keywords: coenzyme Q\textsubscript{10}; ubiquinone; cardiovascular disease; risk factors; prevention; supplementation

1. Introduction

Coenzyme Q\textsubscript{10} (CoQ\textsubscript{10}) is an organic molecule that was identified for the first time by Frederick Crane of Wisconsin (USA) in 1957 [1]. It is ubiquitously present in cell membranes and especially in the mitochondria in both reduced (ubiquinol) and oxidized (ubiquinone) forms (Figure 1). Chemically, it is constituted of a benzoquinone group and a poly-isoprenoid side chain that is species specific. In the human, it is composed of 10 units and called CoQ\textsubscript{10} or ubiquinone [2]. This molecule can sustain continuous oxidation–reduction cycles and is an excellent electron carrier. CoQ\textsubscript{10} concentration is particularly high in organs such as the kidneys, heart, and liver (Table 1) because they need it as an efficient energy transfer molecule supporting their high metabolic rate [3].
Physiologically, CoQ₁₀ is anchored in the cell membrane through the isoprenoid tail, whereas the benzoquinone ring moves in the membrane based on its redox state. The most prominent role of CoQ₁₀ is to facilitate the production of ATP through participation in the electron transport chain in the mitochondria. In fact, in the respiratory chain, CoQ₁₀ transfers electrons from complex I (nicotinamide-adenine dinucleotide (NADH)-coenzyme Q reductase) or complex II (succinate-coenzyme Q reductase) to complex III (cytochrome c reductase), and it is also a structural component of both CI and CIII, reducing the production of reactive oxygen species (ROS) [6,7].

Moreover, CoQ₁₀ is able to accept electrons from fatty acyl-coenzyme A (acyl-CoA) dehydrogenases and it is an obligatory factor in proton transport by uncoupling proteins (UCPs), thus regulating the opening of mitochondrial permeability transition pores [8]. Other functions of CoQ₁₀ in the cell membrane include stabilization of calcium-dependent channels, metabolic regulation, cell signaling, and cell growth through local regulation of cytosolic redox intermediates such as dihydronicotinamide-adenine dinucleotide phosphate (NADPH) [6].

CoQ₁₀, in its reduced form, has been shown to inhibit the peroxidation of cell membrane lipids and to reduce the oxidation of circulating lipids. Interestingly, in vitro, it inhibits the oxidation of low-density lipoprotein more than other antioxidant molecules, such as α-tocopherol or β-carotene [9,10].

CoQ₁₀ is mostly synthetized in the cell, although the pathway involved is not yet completely known. A biosynthetic complex for producing CoQ₁₀, containing proteins, lipids, and polar small molecules
(but with specific composition unknown), was recently revealed in yeast and mammals. In particular, multiple mitochondrial uncharacterized proteins (MXPs) have been linked to CoQ_{10} biosynthesis and recent progress was made also toward understanding the biochemistry of a dehydrogenase, a deaminase, a lipid-binding protein, and a protein kinase-like enzyme in the CoQ_{10} pathway [11]. In mammals, 4-hydroxybenzoate is the precursor of the quinone ring, derived from tyrosine, while the isoprenoid tail is derived from the mevalonate pathway, using the common way with cholesterol biosynthesis. The final step, rate limiting, occurs in the mitochondrial matrix [12,13].

On the other hand, CoQ_{10} can be derived from the diet; in particular, fatty fish (salmon, sardin, and tuna), soya, spinach, and nuts contain high levels of this cofactor. However, the intake from the diet is significant only in deficiency conditions [14]. Some factors may reduce plasma concentrations of CoQ_{10}, such as aging, genetic factors, drugs (e.g., statins), certain diseases (e.g., cardiovascular disease and degenerative muscle disorders), and increased demand [15].

Therefore, it is not surprising that its depletion is associated with a greater propensity to develop immune inflammatory responses through the activation of inflammatory processes such as the nuclear factor-kappa-light-chain-enhancer of activated B cell’s (NF-κB) gene expression [16]. Worthy to note, CoQ_{10} is endowed with potent antioxidant action able to prevent free radical damage by the regulation of transcriptional pathways in addition to deactivation of inflammatory pathways [17]. Therefore, supplementation with CoQ_{10} could be efficient in the prevention and/or treatment of a number of pathogenic disorders in relation to the significant reduction of inflammatory markers [18].

Due to its important place in organisms’ functioning, there are many diseases and degenerative states associated with CoQ_{10}’s deficiency, such as cardiovascular disease, muscular dystrophy, Alzheimer’s disease, Parkinson’s disease, and others [7]. However, if on the one hand clinical evidences in the cardiovascular field have demonstrated the potential role of CoQ_{10}, data concerning the supplementation of this nutraceutical in neurodegenerative diseases and other conditions such as cancer or muscular dystrophy are often old and still conflicting and need additional randomized controlled trials (RCTs) [19–21].

This review aims to sum up the current possibilities to use CoQ_{10} as an adjuvant in cardiovascular disease-affected patients, in cardiovascular disease risk factors, and in statin-intolerant ones, with an analysis of its impact on patients’ health and quality of life.

2. Methods

A systematic search strategy was conducted for this review in order to identify trials in both the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, UK) and MEDLINE (National Library of Medicine, Bethesda, Maryland, MD, USA; January 1970 to March 2020). The terms “coenzyme Q_{10}”, “dietary supplement”, “ubiquinol”, “ubiquinone”, “clinical trial”, and “human” were incorporated in an electronic search strategy. Overall, we screened 5278 abstracts. The selected references were then further screened for application on cardiovascular diseases or cardiovascular disease risk factors. After a general introduction with an overview on the pharmacodynamic profile of CoQ_{10}, for each potential therapeutic indication, a short description of the mechanism of action has been reported, followed by the clinically observed effects and the most relevant tolerability notes. The authors of the writing and reviewing panels completed Declaration of Interest forms where real or potential sources of conflicts of interest might be perceived.

3. Results

This review will focus our attention on the main potential evidence-based use of CoQ_{10} supplements in the management of some main cardiovascular disease risk factors and of cardiovascular disease-affected patients and in statin-intolerant ones (Figure 2).
A recent comparative assessment of the risk of health loss related to systolic blood pressure (SBP), prevalent cardiovascular and cerebrovascular disease risk factors, such as high blood pressure, diabetes, hypertension, dyslipidemia, migraine, and chronic kidney disease. Antioxidants 2020, 9, x FOR PEER REVIEW 4 of 27

![Figure 2. Involvement of CoQ10 deficiency and cardiovascular disease risk factors. ATP: adenosine triphosphate; CI: cardiac input; CO: cardiac output; CKD: chronic kidney disease; DBP: diastolic blood pressure; EDV: end-diastolic volume; EF: ejection fraction; GFAP: glial fibrillary acidic protein; hs-CRP: high sensitive C reactive protein; IL-6: interleukin-6; LVEF: left ventricular ejection fraction; MDA: malondialdehyde; mmSE: mini mental state examination; NIHSS: national institute of health stroke scale; NO: nitric oxide; NF-kB: nuclear factor kappa B; ROS: reactive oxygen species; SBP: systolic blood pressure; SOD: superoxide dismutase; SV: stroke volume; TNF-alpha: tumor necrosis factor-alpha.](image)

3.1. CoQ10 and Cardiovascular Risk Factors

As stated above, CoQ10 supplementation could find a role in the management of some highly prevalent cardiovascular and cerebrovascular disease risk factors, such as high blood pressure, insulin resistance, dyslipidemia, migraine, and chronic kidney disease.

3.1.1. High Blood Pressure

Hypertension is one of the major causes of morbidity and mortality worldwide, involving one in four men and one in five women, totalling 1.13 billion adults, who had raised blood pressure in 2015 [22]. A recent comparative assessment of the risk of health loss related to systolic blood pressure (SBP), based on 844 studies in 154 countries (published between 1980 and 2015) and 8.69 million participants, has estimated approximately 874 million of people in the world with SBP above 140 mmHg [23]. In 2025, it is estimated that there will be approximately 1.56 billion hypertensive adults [24].

CoQ10 seems to exert a direct effect on the endothelium, provoking vasodilation and lowering blood pressure [25,26]. This effect is linked to its ability to improve nitric oxides bioavailability and to induce vasodilatation especially in patients with hypertension. In addition, CoQ10 adjusts the angiotensin effect in sodium retention and decreases the level of aldosterone [27,28]. Despite exciting blood pressure results observed in preliminary trials (systolic and diastolic blood pressure reduced respectively by 6 and 5 mmHg vs. placebo) [29] and the positive results confirmed by old meta-analyses of RCTs [30,31], a recent meta-analysis of 17 randomized controlled trials including 684 subjects showed that CoQ10 supplementation significantly decreased systolic blood pressure (Standardized Mean Difference (SMD) −0.30; 95%CI −0.52, −0.08), but not diastolic blood pressure (SMD −0.08; 95%CI −0.46, 0.29) [32]. However, in patients with type 2 diabetes mellitus and ischemic left ventricular systolic dysfunction, when the blood pressure is on target, the supplementation of CoQ10 did not modify the
blood pressure [33–35]. In conclusion, despite some promising evidence, the antihypertensive effect of CoQ10 is still unclear in patients with primary hypertension [36,37].

3.1.2. Insulin-Resistance and Type 2 Diabetes

Mitochondria seem to play a key role in the development of insulin resistance. They are well known to convert nutrients from diet such as fats and sugars into ATP; however, ATP production can generate harmful intermediates such as ROS and the increase in the amount of oxidant agents produced in mitochondria has been linked to the increase of insulin resistance [38,39]. Several studies in vitro and in vivo as well [40] found that the concentrations of CoQ10 were lower in mitochondria from insulin-resistant fat and muscle tissue, probably for a change in expression of mevalonate/CoQ10 pathway proteins and thus altered CoQ10 metabolism, suggesting a direct correlation between the low levels of CoQ10 and the high levels of oxidants in the mitochondria. In addition, the administration of CoQ10 in deficient and insulin resistant mice has been shown to improve the insulin sensitivity by reducing ROS levels [40].

In patients with metabolic syndrome (MetS), a condition typically caused by insulin-resistance and strongly associated with the risk to developing cardiovascular disease, the intake of 100 mg/day of CoQ10 for 8 weeks significantly improved Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Homeostatic Model Assessment of β-cell Function (HOMA-B), serum insulin levels, and plasma total antioxidant capacity [41]. The effect of CoQ10 on insulin-resistance seems to not be related to its effect on body fat. In fact, a recent meta-analysis of RCTs showed that CoQ10 had no significant impact on body weight ($p = 0.64$) and body mass index (BMI) ($p = 0.86$), independent from the CoQ10 tested dosage and trial duration [42].

Another highly prevalent cardiovascular risk factor related to insulin-resistance is nonalcoholic fatty liver disease (NAFLD) [43]. Despite the numerous mechanisms investigated, the exact biological one related to increased hepatic inflammation and fat accumulation in NAFLD remains largely unknown [44,45]. However, recent studies have focused attention on the role of mitochondrial protein mitofusin 2 (Mfn2) that protects against liver disease. In fact, reduced Mfn2 expression was detected in liver biopsies from patients with nonalcoholic steatohepatitis [46]. The loss of Mfn2 seems to impair mitochondrial respiration and to reduce ATP production, and this defective oxidative phosphorylation process seems to unexpectedly originate from a depletion of the mitochondrial CoQ10 pool [47].

To date, the treatment of NAFLD is essentially based on lifestyle optimization because there are currently no specific drugs approved on the market for this condition. At the same time, few nutraceuticals have been adequately studied for their effects on NAFLD [48]. Among these, CoQ10 is a well-known anti-adipogenic molecule and thus could have a positive impact on NAFLD, even if its exact mechanism is still unclear. It is possible that CoQ10 downregulates the expression of fatty acid synthase (FAS), sterol regulatory element-binding protein-1c (SREBP-1c), and acetyl-CoA carboxylase (ACC), which are related to lipid synthesis, and increases in the expression of carnitine palmitoyltransferase-1 (CPT-1) and peroxisome proliferator-activated receptors α (PPARα) associated with fatty acid oxidation [49]. In addition, CoQ10 could change the response to inflammation through nuclear factor kappa B (NF-κB)-dependent gene expression [50]; thus, its deficiency might have a role in increasing levels of inflammatory molecules like NF-κB [51].

CoQ10 could serve as an adenosine monophosphate-activated protein kinase (AMPK) activator and could regulate the hepatic lipid metabolism to inhibit the abnormal accumulation of hepatic lipids as well as to prevent NAFLD progression [49]. Finally, CoQ10 was also found to bind and activate both PPARs alpha and gamma, suggesting a key role in relaying the states of mitochondria and peroxisomes [52]. At the same time, the experiments performed with peroxisomal inducers indicate that nuclear receptors are involved in the regulation of CoQ10 biosynthesis [13].

In an RCT, 41 subjects with NAFLD were randomly divided into 2 groups to receive CoQ10 (100 mg/day) or placebo for 12 weeks. At the end of the study, the active group benefited from a significant decrease in aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT),
tumor necrosis factor \( \alpha \), high-sensitivity C-reactive protein (hs-CRP), and NAFLD grade compared to placebo \( (p < 0.05 \text{ for all}) \). In addition, patients who received the CoQ\textsubscript{10} supplement had higher serum levels of adiponectin \( (p = 0.016) \) even if serum leptin levels reduced marginally \( (p = 0.053) \) [53]. However, CoQ\textsubscript{10} administration (300 mg/day for 12 weeks) in patients with coronary artery disease did not find any significant effect on serum adiponectin levels [54], confirming previous data obtained by Gokbel et al. with the supplementation of CoQ\textsubscript{10} 100 mg/day in healthy volunteers [55]. In another RCT, the same dose of CoQ\textsubscript{10} in 44 NAFLD patients for 4 weeks was associated with significantly decreased waist circumference (WC), serum AST, and total antioxidant capacity (TAC) concentration \( (p < 0.05 \text{ for all}) \) [56].

CoQ\textsubscript{10} could also improve the atherogenic dyslipidemia typically associated with NAFLD (reducing triglycerides (TG) and increasing high-density lipoprotein cholesterol (HDL-C) as well as reduce oxidized low-density lipoprotein (LDL) levels and arterial pressure with a very high safety profile and without any risk of drug interactions [15]. In conclusion, the studies conducted to date emphasize a potential for CoQ\textsubscript{10} therapy in improving several anthropometric and biochemical variables in NAFLD.

A further disease typically characterized by insulin resistance is polycystic ovary syndrome (PCOS). In these women, as showed by the study of Samimi et al., the supplementation with CoQ\textsubscript{10} (100 mg/day) for 12 weeks could have beneficial effects on glucose metabolism and on serum total- and LDL-cholesterol levels [57]. Afterwards, the same research group carried out another RCT on 40 women with a diagnosis of PCOS, observing that a supplementation for 12 weeks with CoQ\textsubscript{10} (100 mg/day), beside the positive effects on lipid and glucose levels, was responsible for a downregulation of gene expression of oxidized low-density lipoprotein (LDL) receptor \( 1 \) \( (p < 0.001) \) and an upregulated gene expression of PPAR-\( \gamma \) \( (p = 0.01) \) in peripheral blood mononuclear cells. In addition, compared to the placebo group, CoQ\textsubscript{10} supplementation downregulated gene expression of interleukin-1 (IL-1) \( (p = 0.03) \), IL-8 \( (p = 0.001) \), and tumor necrosis factor-alpha (TNF-\( \alpha \)) \( (p < 0.001) \) in peripheral blood mononuclear cells of subjects with PCOS [58]. Similar results were obtained by Izadi et al. in a RCT of 85 PCO women treated with CoQ\textsubscript{10} and/or vitamin E or placebo. In particular, CoQ\textsubscript{10} alone improved the sex hormone profile, specially either reduced testosterone and luteinizing hormone (LH) levels, and improved insulin resistance. Moreover, it is noteworthy that CoQ\textsubscript{10} in coadministration with alfa-tocopherol presented a more pronounced effect and stimulated the release of sex hormone-binding globulin (SHBG), justifying the enhancement of insulin tolerance, since an insulin resistance condition is associated with a reduced synthesis of SHBG at the hepatic level. Then, CoQ\textsubscript{10} might promote steroid hormone biosynthesis and normal reproductive function (among which are oocyte maturation, fertilization, and embryonic development) through the improvement of mitochondrial functionality [59]. However, new, largerRCTs are needed to confirm the results obtained by Izadi et al.

The extreme consequence of insulin-resistance is Type 2 diabetes (T2DM). A deficiency of CoQ\textsubscript{10} plasma levels in patients with T2DM can be observed compared to healthy people [60,61]. In particular, the ubiquinone–ubiquinol ratio, a validated marker of oxidative stress [62], is much higher in a patient with T2DM after breakfast and throughout the day, which suggests heightened oxidative stress in the background of postprandial hyperglycemia [63]. In a recent pooled analysis of 14 trials including 693 overweight diabetic patients, CoQ\textsubscript{10} interventions significantly reduced fasting plasma glucose \( (\text{FPG}) \) \( (-0.59 \text{ mmol/L}; \text{95\%CI} -1.05 \text{ to } -0.12; p = 0.01) \), HbA1c \( (-0.28\%; \text{95\%CI} -0.53 \text{ to } -0.03; p = 0.03) \), and TG levels \( (0.17 \text{ mmol/L}; \text{95\%CI} -0.32 \text{ to } -0.03; p = 0.02) \). Even in the subgroup analysis, the low-dose consumption of CoQ\textsubscript{10} \( (<200 \text{ mg/d}) \) effectively reduced the values of FBS, HbA1c, fasting blood insulin, homeostatic model assessment for insulin resistance (HOMA-IR), and TG with high tolerability profile [64]. In a rat model, the administration of metformin combined with CoQ\textsubscript{10} showed a better renoprotective effect than CoQ\textsubscript{10} or metformin alone [65]. This is also confirmed for other oral antidiabetic drugs like sitagliptin [66]. This brings up an important point that CoQ\textsubscript{10} may potentiate the protective effects of some conventional treatments, but it is yet to be demonstrated in humans.
3.1.3. Dyslipidemias

Several mechanisms have been proposed by which CoQ\textsubscript{10} supplements could improve metabolic profiles which probably might be through the induction of gene expression of PPAR-\(\gamma\) [67], a nuclear receptor protein that regulates gene expression involved in insulin and lipid metabolism, differentiation, proliferation, survival, and inflammation [68]. In human endothelial cells, the exposure to CoQ\textsubscript{10} is associated with downregulation of the lectin-like oxidized LDL receptors, stimulation of the AMPK, and reduction of the ROS-induced endothelial damage [69]. In fact, the main effect of CoQ\textsubscript{10} on plasma lipids seems to be the increased LDL resistance to oxidative stress [70], as also demonstrated in healthy adults after acute strenuous physical exercise [71].

In an RCT, 101 dyslipidemic subjects without taking any lipid-lowering drugs were administrated 120 mg CoQ\textsubscript{10} or placebo daily for 24 weeks. At the end of the study, CoQ\textsubscript{10} supplementation mildly reduced TG (\(p = 0.020\)) and LDL-C (\(p = 0.016\)), increased apolipoprotein (Apo)A-I (\(p < 0.001\)) and serum total antioxidant capacity (TAC; \(p = 0.003\)), while decreased homeostasis model assessment of insulin resistance index (\(p = 0.009\)) compared to placebo [24]. In the meta-analysis conducted by Sharifi et al. [72], CoQ\textsubscript{10} administration to patients with metabolic diseases mildly but significantly reduced TG concentrations (SMD: \(-0.28\) mmol/L; 95% CI, \(-0.56\) to \(-0.005\), \(p = 0.001\)). A recent meta-analysis including six clinical trials suggests that CoQ\textsubscript{10} could mildly reduce the lipoprotein (a) plasma level [73]. Overall, the effect of CoQ\textsubscript{10} supplementation on plasma lipid levels is, however, quantitatively small and its clinical relevance has yet to be demonstrated.

3.1.4. Systemic Inflammation

Inflammation is considered a main process involved in atherosclerosis development [74]. A recent meta-analysis of nine RCTs and 509 patients showed that the CoQ\textsubscript{10} supplementation in chronic inflammatory diseases (60–500 mg/day for 8–12 weeks) is responsible for the significant reduction in the plasma levels of tumor necrosis factor alpha (TNF-\(\alpha\)) (SMD: \(-0.44\), 95% CI: \((-0.81\) to \(-0.07\) mg/dl; \(I^2 = 66.1\%\), \(p < 0.01\)) and in IL-6 levels (SMD: \(-0.37\), 95% CI: \((-0.65\) to \(-0.09\), \(p = 0.01\)) [75]. Similar results were obtained by the metaanalysis of Fan et al. that demonstrated a reduction of the C-reactive protein levels in addition to the abovementioned parameters in patients afflicted by inflammatory diseases [76]; in elderly people with low CoQ\textsubscript{10} levels; and in patients with metabolic diseases characterized by chronic, low grade inflammation [17]. However, the results are conflicting while not so evident in patients affected by metabolic syndrome [41] and dyslipidemia [29].

3.2. CoQ\textsubscript{10} and Cardiovascular Disease

CoQ\textsubscript{10} supplementation has been tested in a number of overt cardiovascular diseases, with the aim to evaluate its impact on self-perceived quality of life, instrumental parameters, and sometimes clinical outcomes as well.

3.2.1. CoQ\textsubscript{10} and Heart Failure (HF)

HF is defined by the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines as “a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood” [77,78]. It affects 23 million people worldwide [79], and the HF prevalence in the USA is 5 million people [80]. At the same time, this disease is also the main component for disability and hospitalization in the elderly and it is the cause of one in nine deaths in the USA [1]. In Europe, the prevalence and incidence of HF and the related costs are quite similar [81,82]. Despite that, in the last decades, the prevention and treatment of HF have improved significantly, quality of life is often impaired, and mortality rates are greater than 10% per year, reaching 20%–50% in more serious patients [83]. In the last years, a number of clinical studies have investigated the possibility that CoQ\textsubscript{10} can contribute to the prevention of incident HF and to the improvement of related symptoms and instrumental parameters. Being an essential
cofactor of the mitochondrial respiratory chain used for production of adenosine triphosphate (ATP), it is not surprising that the highest concentration compared to other tissues is focused on myocardium mitochondria [84].

A relative tissue CoQ10 deficiency could then play an etiopathogenic role in the development and progression of HF: some evidence suggests that the depletion of CoQ10 is proportional to the reduction of CoQ10 myocardial tissue concentrations and to the severity of the disease developed [85–87]. In fact, the lowest levels of myocardial CoQ10 have been observed in patients of New York Heart Association (NYHA) class IV compared to patients of NYHA class I [88,89]. Of course, one of the most important studies in the field of nutraceuticals, the Q-SYMBO multiclentre, randomized placebo-controlled trial, was used to assess the impact of the daily intake of CoQ10 on total mortality and not just on the surrogate endpoints. Patients with moderate or severe HF currently treated with the pharmacological gold standard treatments (420 patients) were randomized to a daily intake of 300 mg of CoQ10 (n = 202) or placebo (n = 218). After two years, a significant reduction in Major Adverse Cardiac Events (MACE) rate (15% in the CoQ10 group vs. 26% in the placebo group, HR: 0.50; 95%CI: 0.32 to 0.80; p = 0.003), CV mortality (9% vs. 16%, p = 0.026), all-cause mortality (10% vs. 18%, p = 0.018), and incidence of hospital stays for HF (p = 0.033) were registered in CoQ10-treated patients vs. the placebo treated ones [90]. This result was confirmed in a subsequent meta-analysis of 14 RCTs including 2149 patients. It has shown that administration of CoQ10 reduces mortality (RR = 0.69; 95%CI: 0.50–0.95; p = 0.02; F = 0%) and improves exercise capacity (SMD = 0.62; 95%CI: 0.02–0.30; p = 0.04; F = 54%) compared to the placebo. However, no significant difference was observed in the endpoints of left ventricular ejection fraction (LVEF) between “active group” and placebo (SMD = 0.62; 95% CI: 0.02–1.12; p = 0.04; F = 75%) [91]. The effect on LVEF could be more relevant in patients with preserved ejection fraction (EF) [92] (net change: 4.8% vs. subjects with EF < 30%) and patients untreated with statins and/or angiotensin converting enzyme inhibitors (ACEi) (+6.7%) compared to the subgroup of patients treated with these drugs (+1.2%) [93]. One of the possible explanations of the heterogeneity in results on EF may be the diversity of CoQ10 supplemented through different pharmaceutical forms and dosages. In fact, plasma concentrations of this molecule are extremely variable in relation to pharmaceutical form and administered dosages but were reported in few RCTs [94–96]. In addition, the diversity of HF grade of patients enrolled (NYHA I-II-III-IV), duration of treatments, and cotreatment with conventional therapies might be other factors that could explain the heterogeneity of results about EF [97].

3.2.2. CoQ10 and Myocardial Infarction

HF could be related to different causes: one of the most frequent is ischemic damage. As highlighted before, treatment with CoQ10 in HF could prevent myocardial cell damage and could restore tissue CoQ10 deficiency, especially in myocardial tissue, with the final result being significant improvement in HF [98–101]. The degree of deficiency of this molecule has also been found to correlate directly with the degree of impairment in left ventricular function [102]. For these reasons, another possible indication of CoQ10 supplementation is acute myocardial infarction (AMI). In fact, CoQ10 is an ATP-sparing agent and regenerable antioxidant capable of protecting cell structures from oxidative damage during ischemia and reperfusion injury [103,104].

AMI is typically characterized by complications such as left ventricular dysfunction related to necrosis and loss of functioning myocardium and consequently by pathological remodelling, which seem to be related to reperfusion-induced free radical damage, lipid peroxidation, and decreased energy production and thus the lack of CoQ10 [105–108]. Cardiac remodelling may be defined as “a group of molecular, cellular, and interstitial alterations that manifest clinically as changes in size, mass, geometry, and function of the heart after injury” [105]. These structural changes in ventricular remodelling in conjunction to tissue CoQ10 deficiency may result in poor prognosis for its negative association with HF, which is the major cause of morbidity and mortality in patients with AMI [109]. Oxidative stress may be important in the pathogenesis of remodelling which may begin via subcellular
remodelling leading to HF [110]. Therefore, any agent which can prevent remodelling in patients with AMI would be an important therapeutic aid for prevention of complications altering AMI [111,112]. In a recent RCT of 55 patients with LVEF < 50% after AMI, the effects of CoQ10 (120 mg/day) or placebo were studied for 24 weeks. The results revealed that wall thickness opposite the site of infarction decreased from 12.2 ± 2.0 mm to 10.0 ± 1.8 mm with CoQ10 compared with 12.8 ± 2.2 mm to 13.3 ± 2.3 mm with the placebo (p < 0.01). Left ventricular mass changed from 236 ± 72 g to 213 ± 61 g with CoQ10 compared with 230 ± 77 g to 255 ± 86 g with placebo (p < 0.01). In addition, treatment with CoQ10 also prevented alteration of the sphericity index (from 1.61 ± 0.28 to 1.63 ± 0.30 with CoQ10 compared with 1.61 ± 0.32 to 1.41 ± 0.31 with placebo (p < 0.05)) and alteration of the wall thickening abnormality at the infarct site (from 9.4 ± 3.0 cm² to 9.1 ± 2.8 cm² compared with 10.1 ± 3.1 to 13.7 ± 4.2 cm² with placebo (p < 0.05)). Finally, end diastolic and systolic volumes and serum ACE also showed significant reduction with CoQ10 compared to the control group [107]. The findings suggest that CoQ10 administered early after AMI may be protective against left ventricular remodelling in patients with persistent left ventricular dysfunction. However, long-term RCTs are needed to confirm preliminary data.

3.2.3. CoQ10 and Atrial Fibrillation

Atrial fibrillation (AF) is considered a frequent atrial arrhythmia in patients diagnosed with HF or ischemic heart disease, and its prevalence has been growing worldwide in the last years. It is associated with an increase in morbidity and mortality [113–115]. As underlined for HF, CoQ10 plays an important role in the production of ATP and its bioenergetic function associated with antioxidant and scavenge ROS function which is essential for proper heart functioning [116,117]. A meta-analysis of eight RCTs found that patients treated with CoQ10 were significantly less likely to develop ventricular arrhythmias (OR (95% CI) 0.05 (0.01–0.31)) and to require inotropic drugs after surgery (OR 95% CI 0.47 (0.27–0.81)). Twelve patients (22.2%) in the control group and three patients (6.3%) in the CoQ10 group had episodes of AF after 12 months of treatment (p = 0.02). [118] Similar results were obtained by other authors, concluding that CoQ10 as adjuvant treatment in patients with HF may attenuate the incidence of AF. The exact mechanisms of the effect are still unclear, even if one of the possible explanations could be attributed to the reduction of serum levels of malondialdehyde (MDA) [119].

3.2.4. CoQ10 and Nonischemic Cardiomyopathies

Cardiomyopathies are a number of debilitating conditions responsible for poor quality of life and high risk of mortality. Both in vitro and animal studies suggest a link between cardiomyopathies and oxidative stress [120]. CoQ10 deficiency appears to be frequent in people with dilated cardiomyopathy, and its supplementation may be able to restore plasmatic and myocardial levels [121]. However, new studies are needed to confirm this evidence.

In children with dilated cardiomyopathy, CoQ10 may improve the cardiothoracic ratio and shorten ventricular depolarization and NYHA class [122]. In a prospective RCT (duration 6 months) in children with dilated cardiomyopathy, the administration of CoQ10 resulted in a lower mean score for the index of cardiac failure (p < 0.024 compared to placebo) and in improvement of diastolic function (p < 0.011 compared to placebo) [123]. In subjects with hypertrophic cardiomyopathy treated with an average of 200 mg/day of CoQ10, a significant improvement in symptoms of fatigue and dyspnoea with no side effects was noted. In addition, the mean interventricular septal thickness (from 1.51 ± 0.17 cm to 1.14 ± 0.13 cm, a 24% reduction, p < 0.002) and mean posterior wall thickness improved significantly (from 1.37 ± 0.13 cm to 1.01 ± 0.15 cm, a 26% reduction, p < 0.005) [124]. There is also a significant improvement in quality of life (on a 6-min walk test) and NYHA class (≥1) [125].

In the last years, many studies have focused on the role of CoQ10 in iatrogenic cardiomiopathies induced by some drugs like anthracycline antibiotics used in the chemotherapy of hematological cancers as leukemias and lymphomas and in solid malignancies such as carcinomas and sarcomas [126]. Doxorubicin is used for the treatment of early-stage breast cancer, and it is known to improve
overall survival. However, side effects such as cardiomyopathy and HF can occur in some patients, probably also for a raised ROS generation. Today, there is data indicating that CoQ₁₀ did not have any influence on doxorubicin cell toxicity, thus making further studies urgent [127]. Nevertheless, the administration of CoQ₁₀ and L-carnitine in combination showed protection against oxidative stress by reducing levels of malondialdehyde and nitric oxide if started within 5 days before doxorubicin use. In addition, it also improved heart functions and decreased IL-1 and TNF-α Troponin-I and Troponin-T levels [128].

3.2.5. CoQ₁₀ and Ischemic Stroke

In the pathophysiology of ischemic stroke, some factors such as inflammation, excitotoxicity, and oxidative stress were demonstrated to play a pivotal role [129,130]. A recent study demonstrated the decrement of CoQ₁₀ in the acute phase of ischemic stroke and also the significant negative correlation between serum CoQ₁₀ levels and the scores of the NIHSS and MRS (respectively National Institutes of Health Stroke Scale and Modified Ranking Scale) [131]. Ischemia/Reperfusion (I/R) injury may induce oxidative stress and low levels of protective antioxidants such as CoQ₁₀ in the brain. In particular, it seems that a decrease of CoQ₁₀ induced by I/R overcomes the aging process [132]. In vivo studies (with symptomatic vasospasm model) have reported that pretreatment with CoQ₁₀ reduces the incidence of ischemic lesions and can alleviate the pathological outcomes following a stroke incidence [133].

In the last years, the relation between CoQ₁₀ and inflammation and oxidative stress has been reported in cell and animal models. Gial fibrillary acidic protein (GFAP), MDA, and superoxide dismutase (SOD) activity are important biomarkers in oxidative stress and neuroinflammatory processes after stroke, and they can predict functional outcomes [134–136]. In a short RCT, 60 patients with acute ischemic stroke were randomly assigned to a placebo or CoQ₁₀-supplemented group (300 mg/day) for 4 weeks. At the end of treatment, CoQ₁₀ supplementation improved NIHSS and mmSE scores significantly \( (p = 0.05, p = 0.03 \text{ respectively}) \) even if there were no significant differences in MRS score, SOD, MDA, and GFAP levels between the two groups. These results could be partially explained by the low dose and short duration of supplementation [137].

3.3. Special Conditions

CoQ₁₀ supplementation has been tested also in a number of “special conditions”, with the aim to evaluate its impact on self-perceived quality of life, instrumental parameters, and sometimes clinical outcomes as well.

3.3.1. Chronic Kidney Disease

Chronic kidney disease (CKD) is associated with an increased prevalence of all-cause mortality, cardiovascular events and hospitalization, and diabetic nephropathy, all regardless of existing risk factors and a history of cardiovascular disease (CVD) [138,139]. Increased biomarkers of oxidative stress in these patients have been identified as a major contributor to the pathogenesis of CKD and related CVD [140,141]. Circulating concentrations of CoQ₁₀ have been decreased in patients with CKD, suggesting that CoQ₁₀ supplementation may be a potentially useful antioxidant supplement for these patients [142]. Nevertheless, the relation between CoQ₁₀ and oxidative stress in patients with CKD is still controversial.

A meta-analysis of seven RCTs demonstrated that CoQ₁₀ supplementation to patients with CKD significantly reduced total cholesterol (TC) (SMD = −0.58; CI, −0.94, −0.21; \( p = 0.002 \)), LDL-C (SMD = −0.47; 95% CI, −0.78, −0.17; \( p = 0.003 \)), malondialdehyde (MDA) (SMD = −3.0; 95% CI, −5.10, −0.90; \( p = 0.005 \)), and creatinine levels (SMD = −1.65; 95% CI, −2.75, −0.54; \( p = 0.003 \)) yet did not affect fasting glucose, insulin, HOMA-IR, and C reactive protein (CRP) concentrations [143]. Moreover, in a study not included in the previously cited meta-analysis, CoQ₁₀ supplementation at a dosage of 100 mg/day for 12 weeks had positive effects on insulin metabolism and MDA levels among diabetic nephropathy
CoQ10 supplementation for diabetic hemodialysis patients for 12 weeks did not influence lipid profiles [70,146,147]. In hemodialysis patients, 100 mg/day of CoQ10 for 3 months could significantly reduce CRP levels (95% CI = −20.1 to −10.5, p < 0.001) [148], while daily supplementation with 1200 mg of CoQ10 significantly improved biomarkers of oxidative stress [149].

Finally, the supplementation of CoQ10 could have a positive impact in people with nephrotic syndrome caused also by a subgroup of mitochondrial diseases classified as primary CoQ10 deficiency (pathogenic variants in at least one of 10 genes termed COQ1 through COQ10). In contrast to other mitochondrial disorders, some patients with primary CoQ10 deficiency show significant improvements after CoQ10 supplementation, making early diagnosis and treatment essential in the management of these people [150].

### 3.3.2. Migraine

Migraine is an emerging risk factor for both coronary and cerebrovascular diseases [151], for which the pathophysiology has not yet been fully understood. Among other factors, a deficiency of CoQ10 is associated with the pathogenesis of migraine, specially in pediatric and adolescent populations [152].

A systematic review and dose-response meta-analysis has been performed evaluating four RCTs including 221 subjects. CoQ10 significantly reduced the frequency of migraine attack (p < 0.001); however, no significant effect on severity and duration has been observed (p = 0.105 and p = 0.086, respectively) [153]. A more recent, larger meta-analysis of three RCTs and two observational studies, including 346 patients (120 pediatric and 226 adult subjects), has been carried out. In particular, with a daily dosage of CoQ10 of 100 or 400 mg, the forest plot analysis confirmed a significant reduction of the duration of migraine attack/month (p < 0.00001) and of the migraine day/month (p = 0.009) if compared with placebo. Nevertheless, frequency and severity of attacks (p = 0.08) were not changed [154].

Based on this data, the American Academy of Neurology guidelines suggest a possible role of CoQ10 in migraine prevention, with a high safety profile in pediatric and adult populations [155].

In one double-blind placebo controlled clinical trial on 45 patients (22 treated with placebo and 23 treated with CoQ10 at a dose of 400 mg/day for 3 months), a significant prophylactic effect of the supplementation on migraine attacks was reported, resulting in less severe, shorter, and less frequent attacks. Interestingly, an increase in serum levels of CoQ10 and a reduction of TNFα and calcitonin gene-related peptide (GCPR) levels have also been observed, suggesting a role of CoQ10 as mitigation of inflammatory processes [156]. According to other studies [43,157], however, no significant differences in serum IL6 and IL10 have been observed compared with the control groups [83].

Interesting results emerge by co-supplementation of CoQ10 (100 mg/day) with other nutraceuticals, such as curcumin, magnesium, and Tanacetum parthenium L. and riboflavin. In particular, Gaul and collaborators observed on 173 adults affected by migraine that a fixed combination of magnesium (600 mg/day), riboflavin (400 mg/day), and CoQ10 (150 mg/day) after 3 months of treatment reduced migraine pain without any serious adverse events [158]. Moreover, preliminary but encouraging results in the prophylaxis of migraine have been observed in a recent RCT, where the assumption of soft gelatin capsules containing nano-micellar curcumin (80 mg/day) and CoQ10 (300 mg/day) determined a significant reduction of frequency, severity, and duration of migraine attacks (all p < 0.001) [159].
3.3.3. Pre-Eclampsia

Pre-eclampsia is a severe vascular complication of pregnancy. A growing collection of literature suggests that attention needs to be focused on the possible effect of CoQ₁₀ during pregnancy-related hypertensive disorders [160]. Pre-eclampsia consists of the gradual development of hypertension, with values of SBP >140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg. However, in some cases, there is worsening of preexisting hypertension, generalized edema, proteinuria (300 mg/L or more in 24 h), and sometimes blood clotting disorders that arise after 20 weeks of gestation [161]. Oxidative stress could be one of the causing factors of this dangerous condition [162]. From one side, pregnant women with established pre-eclampsia have significantly lower plasma levels of CoQ₁₀ compared to healthy pregnant women [163,164]. A single trial in which CoQ₁₀ has been assumed at the dose of 200 mg/day for 20 weeks until delivery concluded with a reduction of the risk of developing pre-eclampsia in women at risk for the condition ($p = 0.035$) [165]. However, a recent meta-analysis of twenty-nine RCTs highlighted that the antioxidant strategy, both by using of CoQ₁₀ and by using of other agents (vitamins, resveratrol, or/and arginine), did not exert significant beneficial effects on maternal and fetal outcomes [166]. Further research is needed in this field.

3.3.4. CoQ₁₀ and Statin-Intolerance

Statin-associated myopathy pathogenetic mechanisms are still not fully understood. The most probable hypotheses are related to the increased intracellular lipid production and lipid myopathy, decreased sarcolemmal cholesterol, and reduction in small guanosine triphosphate-binding proteins and in mitochondrial CoQ₁₀ [167]. Statins, the milestone in lipid-lowering treatment, inhibit hydroxyl-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate limiting enzyme not only in cholesterol synthesis but also in the synthesis of farnesyl pyrophosphate that is essential for CoQ₁₀ biosynthesis, thus explaining the link between statin use and CoQ₁₀ deficiency [168]. In fact, a recent meta-analysis of 12 RCTs involving 1776 participants concluded that, compared to the placebo, statin treatment resulted in a reduction of circulating CoQ₁₀ (SMD $-2.12; 95\% \text{ CI } -3.40$ to $-0.84; p = 0.001$) independently from statin solution, intensity, and treatment time [169]. No study has yet been designed to demonstrate that CoQ₁₀ supplementation could prevent statin-related myalgia. However, a meta-analysis of 12 RCTs involving 575 patients concluded that, compared to the placebo, CoQ₁₀ supplementation ameliorated statin-associated muscle symptoms, such as muscle pain (weighted mean difference (WMD) $-1.60; 95\% \text{ CI } -1.75$ to $-1.44; p < 0.001$), muscle weakness (WMD $-2.28; 95\% \text{ CI } -2.79$ to $-1.77; p = 0.006$), muscle cramping (WMD $-1.78; 95\% \text{ CI } -2.31$ to $-1.24; p < 0.001$), and muscle tiredness (WMD $-1.75; 95\% \text{ CI } -2.31$ to $-1.19; p < 0.001$), whereas no reduction in plasma creatine kinase levels was observed after CoQ₁₀ supplementation (WMD 0.09; 95% CI $-0.06$ to 0.24; $p = 0.23$) [170]. These positive effects are usually achieved only with high dosages of CoQ₁₀ ($≥200 \text{ mg/day}$).

However, CoQ₁₀ could have a positive impact on the management of patients more likely to develop statin-related side effects. In fact, it has been clinically proven that CoQ₁₀ supplementation could be able to improve self-perceived fatigue in healthy subjects, [171] in obese patients [172], and in patients affected by fibromyalgia [173,174] even if larger RCTs are needed to confirm this preliminary data.

4. Discussion

Theoretically, CoQ₁₀ is an ideal dietary supplement. It is contained in some foods, its dosage in blood is feasible, and its deficiency is associated with some diseases, while its supplementation tends to restore a physiological condition (Table 2). Moreover, the supplementation with CoQ₁₀ is safe, even with chronic exposure to 900 mg/day [175] and in frail patients, like elderly and CKD patients, without any known pharmacological interactions [3].
Table 2. Coenzyme Q₁₀: clinical applications in cardiovascular diseases.

| Condition                     | Level of Evidence | Active Daily Doses | Effects on Symptoms and/or Grade of Disease                                                                 | Effects on Lab or Instrumental Parameters                                                                 | Effects on Hard Outcomes                                                                 |
|-------------------------------|-------------------|--------------------|-----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Heart Failure (HF)            | Meta-analysis of RCTs | 100–300 mg        | ↑ self-perceived quality of life and improvement in NYHA class                                            | ↑ EF (if >30%), ↑ LVEF, ↑ CO and CI, ↑ SV, ↑ EDP, ↓ exercise capacity, ↓ ventricular arrhythmias after surgery and need of inotropic drugs (after cardiac surgery), and ↓ low-grade inflammation (TNF-alpha, IL-6, and hsCRP) | ↓ MACE, total mortality, and incidence of hospital stays for HF                                |
| Acute Myocardial Infarction (AMI) | RCTs              | 120 mg            | Not investigated                                                                                         | Prevention of alteration of the wall thickening abnormality at the infarct site and sphericity index and ↓ wall thickness opposite the site of infarction | Not investigated                                                                       |
| Ischemic Stroke (IS)          | RCTs              | 300 mg            | ↑ NIHSS and mmSE Prevention of alteration of the wall thickening abnormality at the infarct site and sphericity index and ↓ wall thickness opposite the site of infarction | Reduction of oxidative stress (?)                                                                       | Not investigated                                                                       |
| Atrial Fibrillation (AF)      | Meta-analysis of RCTs | 100–300 mg        | Improvement in NYHA class, reduction of risk to develop ventricular arrhythmias, and use of inotropic drugs after surgery | Reduction of malondialdehyde and oxidative stress                                                       | Not investigated                                                                       |
| Cardiomyopathy                | RCTs              | 200–300 mg        | Improvement of fatigue and dyspnea                                                                       | Improvement of mean interventricular septal thickness, mean posterior wall thickness, diastolic function, and mean score for the index of cardiac failure | Not investigated                                                                       |
| Cardiotoxicity                | RCTs              | 200–300 mg        | Improvement of heart’s functions (in association with L-carnitine)                                       | Reduction of oxidative stress (nitric oxide and malondialdehyde) and ↓ LVEF, ↓ TNF-α and Troponin-I levels (in association with L-carnitine) | Not investigated                                                                       |
| Hypertension                  | Meta-analysis of RCTs | 100–300 mg        | Not reported                                                                                             | ↓ Exercise capacity and arterial stiffness, ↓ NO bioavailability, and ↓ SBP and DBP (only in prehypertensive or hypertensive patients) | Not investigated                                                                       |
| Diabetes type II, Metabolic syndrome (MetS) | RCTs              | 100–300 mg        | Not reported                                                                                             | ↓ Lipid peroxidation, FPG, triglycerides, and low-grade inflammation (TNF-alpha, IL-6, and hsCRP) and ↑ insulin sensitivity | Not investigated                                                                       |
| Dyslipidemia                  | RCTs              | 100–300 mg        | ↑ self-perceived quality of life (reduction side effects of lipid-lowering drugs)                       | ↑ Lipid peroxidation, TC*, LDL-C*, TG*, BP*, FPG*, and low-grade inflammation (TNF-alpha, IL-6, and hsCRP), and ↑ insulin sensitivity | Not investigated                                                                       |
| Non-Alcoholic Fatty Liver Disease (NAFLD) | Meta-analysis of RCTs | 100–300 mg        | Improvement in NAFLD grade                                                                               | ↑ Adiponectin (?) and leptin levels; ↑ AST, GGT, hsCRP, and TNF-alpha levels, and ↓ WC and lipid peroxidation | Not investigated                                                                       |
| Chronic Kidney Disease (CKD)  | Meta-analysis of RCTs | 100–300 mg        | Not investigated                                                                                         | ↓ Lipid peroxidation, TC (?), LDL-C (?), Lp(a) (?), triglycerides (?), fasting plasma glucose (?), HbA1c (?), inflammation, and oxidative stress biomarkers (hsCRP (? and malondialdehyde)) and ↑ insulin sensitivity | Not investigated                                                                       |

AST = Aspartate Aminotransferase, BP = Blood Pressure, CI = Cardiac Input, CO = Cardiac Output, DBP = Diastolic Blood Pressure, EDV = End-Diastolic Volume, EF = Ejection Fraction, FPG = Fasting Plasma Glucose, GGT = Gamma-Glutamyl Transpeptidase, HF = Heart Failure, hsCRP = high sensible C-Reactive Protein, IL-6 = Interleukin 6, LDL-C = LDL-Cholesterol, Lp(a) = Lipoprotein a, LVEF = Left Ventricular Ejection Fraction, MACE = Major Adverse Cardiac Events, mmSE = Mini Mental State Examination, NIHSS = National Institute of Health Stroke Scale, NYHA = New York Heart Association, NO = Nitric Oxide, RCTs = Randomized Clinical Trials, SBP = Systolic Blood Pressure, SV = Stroke Volume, TC = Total Cholesterol, TG = triglycerides, TNF-alpha = Tumor Necrosis Factor-alpha, WC = Waist Circumference. ↑: Improvement; ↓: Worsening; ?: Unclear.
To date, various formulations and dosages of CoQ10 are present on the market, such as tablets, chewable tablets, capsules, and gels containing oily suspensions. However, the oral bioavailability of this supplement is extremely variable in relation to many aspects. For example, the type of formulation and the release method, the dosage of CoQ10, and the mode of administration (e.g., with or without water
and before or after meals) are biopharmaceutical factors that may affect bioavailability, as highlighted before [181]. Regarding the molecule, the ubiquinol form is the most available compared to ubiquinone, in particular if supplemented in fed state and conveyed through specific strategies like the use of liposomes, nano-emulsions, nanostructured lipid carriers, and micelles [182,183]. The reduction of particle size (including the use of nanoparticles), the use of oily suspensions, and the solubilization and increase of solubility in water are also viable strategies [184]. In particular, the CoQ10 and β-cyclodextrin complex has been developed in addition to the intention of improving solubility in water to implement the technological properties and stability of CoQ10 [185], permitting the preparation of aqueous formulations, such as syrups. The improvement of bioavailability with CoQ10 + β-cyclodextrins and with ubiquinol have already been demonstrated in humans [186–188], with satisfactory results. Table 3 summarizes the main biopharmaceutical strategies used to increase the bioavailability of CoQ10.

Table 3. Comparative study of ΔC_{max} after a single dose of different formulations of CoQ10 (adapted from López-Lluch et al. [188]).

| Type of Formulation | Subjects | Tested Dosage | ΔC_{max} | Reference |
|---------------------|----------|---------------|----------|-----------|
| Myoqinon (softgel)  | Both gender (10 M, 4 F), age 18–30 | 100 mg | 1.069 | [189] |
| KOF, CoQ10 (softgel)| Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.238 |
| ICT, CoQ10 (softgel)| Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.351 |
| ERG, CoQ10 (softgel)| Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.258 |
| Ubiquinol QH (softgel)| Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.473 |
| NVD CoQ10 (hard gel)| Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.384 |
| SMF CoQ10 | Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.184 |
| Capsule CoQ10 | 9 M, age 18–30 | 30 mg | 0.31 | [190] |
| Gelatin capsule CoQ10 + vitamin E | Both gender (12 M, 12 F) | 100 mg | 0.025 | [191] |
| NanoSolve (particulate phospholipid) capsule CoQ10 + vitamin E | Both gender (12 M, 12 F) | 100 mg | 0.160 |
| Capsule CoQ10 (powder-filled hard-shell gelatin capsule) | Both gender (3 M, 3 F), age 18–40 | 250 mg | 0.490 | [192] |
| Liquid (O/W liquid emulsion (20 mg/mL)) | Both gender (3 M, 3 F), age 18–40 | 250 mg | 0.980 |
| Chewable wafer | Both gender (15 M, 10 F), elderly people | 600 mg | 0.770 |
| Chewable wafer + 300 IU vitamin E | Both gender (15 M, 10 F), elderly people | 600 mg | 0.660 | [193] |
| Softgel capsules (Mega Q Gel + 100 IU CoQ10 solubilized in an oil-based vehicle + 900 IU α-tocopherol) | Both gender (15 M, 10 F), elderly people | 600 mg | 0.690 |
| Hard gelatin capsule | Both gender (15 M, 10 F), elderly people | 600 mg | 0.660 |
| Powder | 333 mg | 0.980 |
| Kaneka QH, ubiquinol (softgel capsules) | Both gender (5 M, 5 F) | 150 mg | 1.064 | [194] |
| Chewable tablets | 10 M, age 21–28 | 150 mg | 0.120 |
| Capsule liquid | 10 M, age 21–28 | 150 mg | 0.149 |
| Capsule liquid | 10 M, age 21–28 | 150 mg | 0.152 |
| Capsule powder | 10 M, age 21–28 | 150 mg | 0.175 |
| Capsule liquid | 10 M, age 21–28 | 150 mg | 0.197 |
| Softgel | 10 M, age 21–28 | 150 mg | 0.277 |
| Q-gel (CoQ10 solubilized in an oil-based vehicle + vitamin E) softgel | 10 M, age 21–28 | 150 mg | 0.506 |
| Q-gel (CoQ10 solubilized in an oil-based vehicle + vitamin E) softgel | 8 M, age 20–26 | 60 mg | 0.267 | [195] |
| Softgel CoQ10 | 36 M, age 18–40 | 100 mg | 0.259 | [196] |
| Softgel CoQ10 + sterols | 36 M, age 18–40 | 100 mg | 0.189 |
| Hardgel (CoQ10 + 400 mg Emcompress) | Both gender (5 M, 5 F), age 24–30 | 100 mg | 0.775 |
| Softgel Bioqinon (CoQ10 + 400 mg of soybean oil) | Both gender (5 M, 5 F), age 24–30 | 100 mg | 1.454 | [197] |
| Softgel (CoQ10 + 20 mg of polysorbate 80, 100 mg of lecithin + 280 mg of soybean oil) | Both gender (5 M, 5 F), age 24–30 | 100 mg | 0.837 |
| Softgel (CoQ10 + 20 mg of polysorbate 80 + 380 mg of soybean oil) | Both gender (5 M, 5 F), age 24–30 | 100 mg | 0.863 | [188] |

Myoqinon (soy-oil matrix, drug specification heat/cold recrystallization procedure); KOF, CoQ10 (same as Myoqinon but without heat/cooling procedure); ICT, CoQ10 (olive oil, cocoa-butter produced accordingly normal softgel filling technology); ERG, CoQ10 (olive oil, cocoa-butter, 25 mg vitamin C produced accordingly normal softgel filling technology); Ubiquinol QH (MCT-oil, 12 mg vitamin C); NVD, CoQ10 (fine grinded (micronized) CoQ10 powder); SMF, CoQ10 (olive-oil/soy-oil matrix produced accordingly normal softgel filling technology); NanoSolve (Lipoid GmbH, Ludwigshafen, Germany); Kaneka QH (ubiquinol emulsified with diglycerol monooleate, rapeseed oil, soy lecithin, and beeswax).
Even though these formulations allow an important increase of bioavailability, it is important to underline that most of the orally supplemented CoQ$_{10}$ is eliminated via faeces [175]. Furthermore, CoQ$_{10}$ exerts many mild positive effects on different tissues and metabolism. They could individually not be so relevant from a quantitative point of view, but it is really difficult to quantify their impact as a whole on human health. In fact, the long-term contemporary reduction of systemic inflammation and oxidative stress, a mild reduction of blood pressure, and insulin-resistance could have positive impacts on cardiovascular disease risk.

5. Conclusions

Clinical evidence supports supplementation with high doses of bioavailable-CoQ$_{10}$ (≥200 mg/day) to support heart health in patients affected by coronary heart disease and heart failure, partly modulating a number of risk factors for these conditions, and partly directly acting on myocardial cell metabolism. Long-term RCTs are still needed to confirm and better understand the efficacy and safety profile of this molecule in a large number of patients and CV diseases.

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References

1. Cicero, A.F.; Colletti, A. Nutraceuticals and Dietary Supplements to Improve Quality of Life and Outcomes in Heart Failure Patients. *Curr. Pharm. Des.* 2017, 23, 1265–1272. [CrossRef] [PubMed]
2. Bentinger, M.; Brismar, K.; Dallner, G. The antioxidant role of coenzyme Q. *Mitochondrion* 2007, 7, S41–S50. [CrossRef] [PubMed]
3. Saini, R. Coenzyme Q$_{10}$: The essential nutrient. *J. Pharm. Biomed. Anal.* 2011, 3, 466–467. [CrossRef] [PubMed]
4. Aberg, F.; Appelkvist, E.L.; Dallner, G.; Ernster, L. Distribution and redox state of ubiquinones in rat and human tissues. *Arch. Biochem. Biophys.* 1992, 295, 230–234. [CrossRef]
5. Miles, M.V.; Horn, P.S.; Morrison, J.A.; Tang, P.H.; DeGrauw, T.; Pesce, A.J. Plasma coenzyme Q$_{10}$ reference intervals, but not redox status, are affected by gender and race in self-reported healthy adults. *Clin. Chim. Acta* 2003, 332, 123–132. [CrossRef]
6. Hernández-Camacho, J.D.; Bernier, M.; López-Lluch, G.; Navas, P. Coenzyme Q$_{10}$ Supplementation in Aging and Disease. *Front. Physiol.* 2018, 9, 44. [CrossRef]
7. Garrido-Maraver, J.; Oropesa-Avila, M.; Cordero, M.D.; Vega, A.F.; de la Mata, M.; Delgado, A.; de Miguel, M.; Calero, C.P.; Villanueva Paz, M.; Cotán, D.; et al. Coenzyme Q$_{10}$ Therapy. *Mol. Syndromol.* 2014, 5, 187–197. [CrossRef]
8. De Barcelos, I.P.; Haas, R.H. CoQ$_{10}$ and Aging. *Biology* 2019, 8, 28. [CrossRef]
9. Littarru, G.P.; Tiano, L. Bioenergetic and antioxidant properties of coenzyme Q$_{10}$: Recent developments. *Mol. Biotechnol.* 2007, 37, 31–37. [CrossRef]
10. Malekmohammad, K.; Sewell, R.D.E.; Rañiean-Kopaei, M. Antioxidants and Atherosclerosis: Mechanistic Aspects. *Biomolecules* 2019, 9, 301. [CrossRef]
11. Stefely, J.A.; Pagliarini, D.J. Biochemistry of Mitochondrial Coenzyme Q Biosynthesis. *Trends Biochem. Sci.* 2017, 42, 824–843. [CrossRef] [PubMed]
12. Szkopińska, A. Ubiquinone. Biosynthesis of quinone ring and its isoprenoid side chain. Intracellular localization. *Acta Biochim. Pol.* 2000, 47, 469–480. [CrossRef] [PubMed]
13. Turunen, M.; Olsson, J.; Dallner, G. Metabolism and function of coenzyme Q. *Biochim. Biophys. Acta* 2004, 1660, 171–199. [CrossRef] [PubMed]
14. Zhang, Y.; Aberg, F.; Appelkvist, E.L.; Dallner, G.; Ernster, L. Uptake of dietary coenzyme Q supplement is limited in rats. *J. Nutr.* 1995, 125, 446–453. [CrossRef] [PubMed]
15. Gutierrez-Mariscal, F.M.; Yubero-Serrano, E.M.; Villalba, J.M.; Lopez-Miranda, J. Coenzyme Q10: From bench to clinic in aging diseases, a translational review. *Crit. Rev. Food Sci. Nutr.* 2018, 16, 1–18. [CrossRef]

16. Boroujeni, M.B.; Khayat, Z.K.; Anbari, K.; Niapour, A.; Gholami, M.; Gharravi, A.M. Coenzyme Q10 Protects Skeletal Muscle From Ischemia-Reperfusion Through the NF-kappa B Pathway. *Perfusion* 2017, 32, 372–377. [CrossRef]

17. Zhai, J.; Bo, Y.; Lu, Y.; Liu, C.; Zhang, L. Effects of Coenzyme Q10 on Markers of Inflammation: A Systematic Review and Meta-Analysis. *PloS ONE* 2017, 12, e0170172. [CrossRef]

18. Mantle, D.; Hargreaves, I. Coenzyme Q10 and Degenerative Disorders Affecting Longevity: An Overview. *Antioxidants* 2019, 8, 44. [CrossRef]

19. Galasko, D.R.; Peskind, E.; Clark, C.M.; Quinn, J.F.; Ringman, J.M.; Jicha, G.A.; Cotman, C.; Cottrell, B.; Montine, T.J.; Thomas, R.G.; et al. Alzheimer’s Disease Cooperative Study Antioxidants for Alzheimer disease: A randomized clinical trial with cerebrospinal fluid biomarker measures. *Arch. Neurol.* 2012, 69, 836–841. [CrossRef]

20. Müller, T.; Büttner, T.; Gholipour, A.F.; Kuhn, W. Coenzyme Q10 supplementation provides mild symptomatic benefit in patients with Parkinson’s disease. *Neurosci. Lett.* 2003, 341, 201–204. [CrossRef]

21. Parkinson Study Group QE3 Investigators. A randomized clinical trial of high-dosage coenzyme Q10 in early Parkinson disease: No evidence of benefit. *JAMA Neurol.* 2014, 71, 543–552. [CrossRef] [PubMed]

22. NCD Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 to 2015: A pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017, 389, 37–55. [CrossRef]

23. Forouzanfar, M.H.; Liu, P.; Roth, G.A.; Ng, M.; Biryukov, S.; Marczak, L.; Estep, K.; Abate, K.A.; Akinyemiju, T.F.; et al. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990–2015. *JAMA* 2017, 317, 165–182. [CrossRef] [PubMed]

24. Hednerm, T.; Kjeldsen, S.E.; Narkiewicz, K. State of global health-hypertension burden and control. *Blood Press* 2012, 21, 12. [CrossRef]

25. Digiesi, V.; Cantini, F.; Oradei, A.; Bisi, G.; Guarino, G.C.; Brocchi, A.; Bellandi, F.; Mancini, M.; Littarru, G.P. Coenzyme Q10 in essential hypertension. *Mol. Aspects Med.* 1994, 15, s257–s263. [CrossRef]

26. Ignarro, L.J. Biological actions and properties of endothelium-derived nitric oxide formed and released from artery and vein. *Circ. Res.* 1989, 65, 1–21. [CrossRef]

27. Fabre, L.F.; Banks, R.C., Jr.; McIsaac, W.M.; Farrell, G. Effects of ubiquinone and related substances on secretion of aldosterone and cortisol. *Am. J. Physiol.* 1965, 208, 1275–1280. [CrossRef]

28. Langsjoen, P.; Willis, R.; Folkers, K. Treatment of essential hypertension with coenzyme Q10. *Mol. Aspects Med.* 1994, 15, S265–S272. [CrossRef]

29. Zhang, P.; Yang, C.; Guo, H.; Wang, J.; Lin, S.; Li, H.; Yang, Y.; Ling, W. Treatment of coenzyme Q10 for 24 weeks improves lipid and glycemic profile in dyslipidemic individuals. *J. Clin. Lipidol.* 2018, 12, 417–427. [CrossRef]

30. Ho, M.J.; Belluscì, A.; Wright, J.M. Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension. *Cochrane Database Syst. Rev.* 2009, CD007435. [CrossRef]

31. Rosenfeldt, F.L.; Haas, S.J.; Krum, H.; Hadj, A.; Leong, J.Y.; Watts, G.F. Coenzyme Q10 in the treatment of hypertension: A meta-analysis of the clinical trials. *J. Hum. Hypertens.* 2007, 21, 297–306. [CrossRef] [PubMed]

32. Tabrizi, R.; Akbari, M.; Sharifi, N.; Lankarani, K.B.; Kolahdooz, F.; Taghizadeh, M.; Asemi, Z. The Effects of Coenzyme Q10 Supplementation on Blood Pressures Among Patients with Metabolic Diseases: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *High Blood Press. Cardiovasc. Prev.* 2018, 25, 41–50. [CrossRef] [PubMed]

33. Dai, Y.L.; Luk, T.H.; Yi, K.H.; Wang, M.; Yip, P.M.C.; Lee, S.W.L.; Li, S.W.; Tam, S.; Fong, B.; Lau, C.P.; et al. Reversal of mitochondrial dysfunction by coenzyme Q10 supplement improves endothelial function in patients with ischaemic left ventricular systolic dysfunction: A randomized controlled trial. *Atherosclerosis* 2011, 216, 395–401. [CrossRef]

34. Lim, S.C.; Lekshminarayanan, R.; Goh, S.K.; Ong, Y.Y.; Subramaniam, T.; Sum, C.F.; Ong, C.N.; Lee, B.L. The effect of coenzyme Q10 on microcirculatory endothelial function of subjects with type 2 diabetes mellitus. *Atherosclerosis* 2008, 196, 966–969. [CrossRef]
38. Cicero, A.F.G.; Fogacci, F.; Colletti, A. Commentary to: “The Effects of Coenzyme Q10 Supplementation on Blood Pressures Among Patients with Metabolic Diseases: A Systematic Review and Meta-analysis of Randomized Controlled Trials”. *Hypertension*. 2018, 75, 51–52. [CrossRef] [PubMed]

39. Anderson, E.J.; Lustig, M.E.; Boyle, K.E.; Woodlief, T.L.; Kane, D.A.; Lin, C.T.; Price, J.W.; Kang, L.; Cummins, C.L.; Krause, H.M. Idebenone and coenzyme Q10 supplementation on body weight and body mass index: A systematic review and meta-analysis of randomized controlled clinical trials. *Diabetes Metab. Syndr.* 2019, 13, 1179–1185. [CrossRef] [PubMed]

40. Araújo, A.R.; Rosso, N.; Bedogni, G.; Tribelli, C.; Bellentani, S. Global epidemiology of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: What we need in the future. *Liver Int.* 2018, 38, 47–51. [CrossRef] [PubMed]

41. Raygan, F.; Rezavandi, Z.; Dadkhah Tehrani, S.; Farrokhian, A.; Asemi, Z. The effect of coenzyme Q10 administration on glucose homeostasis parameters, lipid profiles, biomarkers of inflammation and oxidative stress in patients with metabolic syndrome. *Eur. J. Nutr.* 2016, 55, 2357–2364. [CrossRef] [PubMed]

42. Saboori, S.; Rad, E.Y.; Mardani, M.; Khosroshahi, M.Z.; Nouri, Y.; Falahi, E. E. Mitochondrial H2O2 emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. *J. Clin. Investig.* 2009, 119, 573–581. [CrossRef] [PubMed]

43. Fazakerley, D.J.; Chaudhuri, R.; Yang, P.; Maghzal, G.J.; Thomas, K.C.; Krycer, J.R.; Humphrey, S.J.; Parker, B.L.; Fisher-Wellman, K.H.; Meoli, C.C.; et al. Mitochondrial CoQ deficiency is a common driver of mitochondrial oxidants and insulin resistance. *Elife* 2018, 7, e32111. [CrossRef] [PubMed]

44. Buzzetti, E.; Pinzani, M.; Tsochatzis, E.A. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD): The Available Clinical Evidence. *Antioxidants* 2020, 9, 341. [CrossRef] [PubMed]

45. Chen, K.; Chen, X.; Xue, H.; Zhang, P.; Fang, W.; Chen, X.; Ling, W. Coenzyme Q10 supplementation on blood pressure, inflammation, and lipid profile in type 2 diabetics. *Iran. J. Nutr. Sci. Food Technol.* 2018, 12, 145–153. [CrossRef] [PubMed]

46. Hernández-Alvarez, M.I.; Sebastian, D.; Vives, S.; Ivanova, S.; Bartocciioni, P.; Kakimoto, P.; Plana, N.; Veiga, S.R.; Hernández, V.; Vasconcelos, N.; et al. Deficient Endoplasmic Reticulum-Mitochondrial Phosphatidylserine Transfer Causes Liver Disease. *Cell* 2019, 177, 881–895. [CrossRef] [PubMed]

47. Tiefenbach, J.; Magomedova, L.; Liu, J.; Reunov, A.A.; Tsai, R.; Eappen, N.S.; Jockusch, R.A.; Nislow, C.; Cummins, C.L.; Krause, H.M. Idebenone and coenzyme Q10 are novel PPARα/γ ligands, with potential for treatment of fatty liver diseases. *Dis. Model. Mech.* 2018, 11. [CrossRef] [PubMed]

48. Farsi, F.; Mohammadshahi, M.; Alavinejad, P.; Rezagadeh, A.; Zarei, M.; Engali, K.A. Functions of Coenzyme Q10 Supplementation on Liver Enzymes, Markers of Systemic Inflammation, and Adipokines in Patients Affected by Nonalcoholic Fatty Liver Disease: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial. *J. Am. Coll. Nutr.* 2016, 35, 346–353. [CrossRef] [PubMed]
54. Lee, B.J.; Tseng, Y.F.; Yen, C.H.; Lin, P.T. Effects of coenzyme Q10 supplementation (300 mg/day) on antioxidant and anti-inflammation in coronary artery disease patients during statins therapy: A randomized, placebo-controlled trial. *Nutr. J.* 2013, 12, 1–9. [CrossRef] [PubMed]

55. Gokbel, H.; Gergerlioglu, H.S.; Okudan, N.; Belviranli, M. Effects of coenzyme Q10 supplementation on plasma adiponectin, interleukin-6, and tumor necrosis factor-alpha levels in men. *J. Med. Food* 2010, 13, 216–218. [CrossRef]

56. Farhangi, M.A.; Alipour, B.; Jafarvand, E.; Khoshbaten, M. Oral coenzyme Q10 supplementation in patients with nonalcoholic fatty liver disease: Effects on serum vaspin, chemerin, pentraxin 3, insulin resistance and oxidative stress. *Arch. Med. Res.* 2014, 45, 589–595. [CrossRef]

57. Samimi, M.; Zarezade Mehrizi, M.; Foroozanfard, F.; Akbari, H.; Jamilian, M.; Asemi, Z. The effects of coenzyme Q10 supplementation on glucose metabolism and lipid profiles in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. *Clin. Endocrinol.* 2017, 86, 560–566. [CrossRef]

58. Rahmani, E.; Jamilian, M.; Samimi, M.; Zarezade Mehrizi, M.; Aghadavod, E.; Akbari, E.; Tamtaji, O.R.; Asemi, Z. The effects of coenzyme Q10 supplementation on gene expression related to insulin, lipid and inflammation in patients with polycystic ovary syndrome. *Gynecol. Endocrinol.* 2018, 34, 217–222. [CrossRef]

59. Izadi, A.; Shirazi, S.; Taghizadeh, S.; Gargari, B.P. Independent and Additive Effects of Coenzyme Q10 and Vitamin E on Cardiovascular Outcomes and Visceral Adiposity in Women with Polycystic Ovary Syndrome. *Arch. Med. Res.* 2019, 50, 1–10. [CrossRef]

60. Ates, O.; Bilen, H.; Keles, S.; Hakan Alp, H.; Keles, M.S.; Yildirim, K.; Ondas, O.; Pinar, L.C.; Civelekler, C.; Baykal, O. Plasma coenzyme Q10 levels in type 2 diabetic patients with retinopathy. *Int. J. Ophthalmol.* 2013, 6, 675–679. [CrossRef]

61. El-ghoroury, E.A.; Raslan, H.M.; Badawy, E.A.; El-Saaid, G.S.; Agybi, M.H.; Siam, I.; Salem, S.I. Malondialdehyde and coenzyme Q10 in platelets and serum in type 2 diabetes mellitus: Correlation with glycemic control. *Blood Coagul. Fibrinolysis* 2009, 20, 248–251. [CrossRef] [PubMed]

62. Yamashita, S.; Yamamoto, Y. Simultaneous detection of ubiquinol and ubiquinone in human plasma as a marker of oxidative stress. *Anal. Biochem.* 1997, 256, 66–73. [CrossRef]

63. Hasegawa, G.; Yamamoto, Y.; Zhi, J.G.; Yamasaki, M.; Yano, M.; Nakajima, T.; Fukui, M.; Yoshikawa, T.; Nakamura, N. Daily profile of plasma %CoQ10 level, a biomarker of oxidative stress, in patients with diabetes manifesting postprandial hyperglycaemia. *Acta Diabetol.* 2005, 42, 179–181. [CrossRef] [PubMed]

64. Huang, H.; Chi, H.; Liao, D.; Zou, Y. Effects of coenzyme Q10 on cardiovascular and metabolic biomarkers in overweight and obese patients with type 2 diabetes mellitus: A pooled analysis. *Diabetes Metab. Syndr. Obes.* 2018, 11, 875–886. [CrossRef] [PubMed]

65. Maheshwari, R.A.; Balaraman, R.; Sen, A.K.; Seth, A.K. Effect of coenzyme Q10 alone and its combination with metformin on streptozotocin-nicotinamide-induced diabetic nephropathy in rats. *Indian J. Pharmacol.* 2014, 46, 627–632. [CrossRef] [PubMed]

66. Maheshwari, R.; Balaraman, R.; Sen, A.K.; Shukla, D.; Seth, A. Effect of concomitant administration of coenzyme Q10 with sitagliptin on experimentally induced diabetic nephropathy in rats. *Ren. Fail.* 2017, 39, 130–139. [CrossRef] [PubMed]

67. Lee, S.K.; Lee, J.O.; Kim, J.H.; Kim, N.; You, G.; Moon, J.W.; Sha, J.; Kim, S.J.; Lee, Y.W.; Kang, H.J.; et al. Coenzyme Q10 increases the fatty acid oxidation through AMPK-mediated PPARalpha induction in 3T3-L1 preadipocytes. *Cell Signal.* 2012, 24, 2329–2336. [CrossRef] [PubMed]

68. Feige, J.N.; Gelman, L.; Michalik, L.; Desvergne, B.; Wahli, W. From molecular action to physiological outputs: Peroxisome proliferator activated receptors are nuclear receptors at the crossroads of key cellular functions. *Prog. Lipid Res.* 2006, 45, 120–159. [CrossRef]

69. Tsai, K.L.; Chen, L.H.; Chiou, S.H.; Chiou, G.Y.; Chen, Y.C.; Chou, H.Y.; Chen, L.K.; Chen, H.Y.; Chiou, T.H.; Tsai, C.S.; et al. Coenzyme Q10 suppresses oxLDL-induced endothelial oxidative injuries by the modulation of LOX-1-mediated ROS generation via the AMPK/PKC/NADPH oxidase signaling pathway. *Mol. Nutr. Food Res.* 2011, 55, S227–S240. [CrossRef]

70. Kaikkonen, J.; Nyyssönen, K.; Porkkala-Sarataho, E.; Poulsen, H.E.; Metsä-Ketelä, T.; Hayn, M.; Salonen, R.; Salonen, J.T. Effect of oral coenzyme Q10 supplementation on the oxidation resistance of human VLDL+LDL fraction: Absorption and antioxidative properties of oil and granule-based preparations. *Free Radic. Biol. Med.* 1997, 22, 1195–1202. [CrossRef]
71. Sarmiento, A.; Diaz-Castro, J.; Pulido-Moran, M.; Moreno-Fernandez, J.; Kajarabille, N.; Chirosa, I.; Guisado, I.M.; Javier Chirosa, L.; Guisado, R.; Ochoa, J.J. Short-term ubiquinol supplementation reduces oxidative stress associated with strenuous exercise in healthy adults: A randomized trial. *Biofactors* 2016, 42, 612–622. [CrossRef] [PubMed]
72. Sharifi, N.; Tabrizi, R.; Moosazadeh, M.; Mirhosseini, N.; Lankarani, K.B.; Akbari, M.; Chamani, M.; Kolahdooz, F.; Asemi, Z. The effects of coenzyme Q10 supplementation on lipid profiles among patients with metabolic diseases: A systematic review and meta-analysis of randomized controlled trials. *Curr. Pharm. Des.* 2018, 24, 2729–2742. [CrossRef]
73. Sahebkar, A.; Simental-Mendia, L.E.; Stefanutti, C.; Pirro, M. Supplementation with coenzyme Q10 reduces plasma lipoprotein(a) concentrations but not other lipid indices: A systematic review and meta-analysis. *Pharmacol. Res.* 2016, 105, 198–209. [CrossRef] [PubMed]
74. Geovanini, G.R.; Libby, P. Atherosclerosis and inflammation: Overview and updates. *Clin. Sci.* 2018, 132, 1243–1252. [CrossRef] [PubMed]
75. Farsi, F.; Heshmati, J.; Keshtkar, A.; Irandoost, P.; Meri, A.; Akbari, A.; Jannani, L.; Morshedzadeh, N.; Vafa, M. Can Coenzyme Q10 Supplementation Effectively Reduce Human Tumor Necrosis Factor-α and interleukin-6 Levels in Chronic Inflammatory Diseases? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pharmacol. Res.* 2019, 148, 104290. [CrossRef] [PubMed]
76. Fan, L.; Feng, Y.; Chen, G.C.; Qin, L.Q.; Fu, C.L.; Chen, L.H. Effects of coenzyme Q10 supplementation on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol. Res.* 2017, 119, 128–136. [CrossRef] [PubMed]
77. Bozkurt, B. What Is New in Heart Failure Management in 2017? Update on ACC/AHA Heart Failure Guidelines. *Curr. Cardiol. Rep.* 2018, 20, 39. [CrossRef]
78. Jessup, M.; Marwick, T.H.; Ponikowski, P.; Voors, A.A.; Yancy, C.W. 2016 ESC and ACC/AHA/HFSA heart failure guideline update—What is new and why is it important? *Nat. Rev. Cardiol.* 2016, 13, 623–628. [CrossRef] [PubMed]
79. Liu, L.; Eisen, H.J. Epidemiology of heart failure and scope of the problem. *Cardiol. Clin.* 2014, 32, 1–8. [CrossRef] [PubMed]
80. Mozaffarian, D.; Benjamin, E.J.; Go, A.S.; Arnett, D.K.; Blaha, M.J.; Cushman, M.; Das, S.R.; de Ferranti, S.; Després, J.P.; Fullerton, H.J.; et al. American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2016 Update: A Report from the American Heart Association. *Circulation* 2016, 133, e38–e360.
81. Maggioni, A.P. Epidemiology of Heart Failure in Europe. *Heart Fail. Clin.* 2015, 11, 625–635. [CrossRef] [PubMed]
82. Meyer, S.; Brouwers, F.P.; Voors, A.A.; Hillege, H.L.; de Boer, R.A.; Gansevoort, R.T.; van der Harst, P.; Rienstra, M.; van Gelder, I.C.; van Veldhuisen, D.J.; et al. Sex differences in new-onset heart failure. *Clin. Res. Cardiol.* 2015, 104, 342–350. [CrossRef] [PubMed]
83. Kannell, W.B. Incidence and epidemiology of heart failure. *Heart Fail. Rev.* 2000, 5, 167–173. [CrossRef] [PubMed]
84. Florkowski, C.M.; Molyneux, S.L.; Young, J.M. Coenzyme Q10 and congestive heart failure: An evolving evidence base. *Kardiol. Polska.* 2015, 73, 73–79. [CrossRef] [PubMed]
85. Folkers, K.; Vadhanavikit, S.; Mortensen, S.A. Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. *Proc. Natl. Acad. Sci. USA* 1985, 82, 901–904. [CrossRef] [PubMed]
86. Kitamura, N.; Yamaguchi, A.; Otaki, M.; Sawatani, O.; Minoji, T.; Tamura, H.; Atobe, M. Myocardial tissue level of coenzyme Q10 in patients with cardiac failure. *Biomed. Clin. Asp. Coenzyme Q.* 1984, 4, 221–229.
87. Judy, W.V.; Stogsdill, W.W.; Folkers, K. Myocardial preservation by therapy with coenzyme Q10 during heart surgery. *Clin. Investig.* 1993, 71, 155–161. [CrossRef]
88. Weber, C.; Bysted, A.; Hillmer, G. The coenzyme Q10 content of the average Danish diet. *Int. J. Vitam. Nutr. Res.* 1997, 67, 123–129.
89. Onur, S.; Niklowitz, P.; Jacobs, G.; Lieb, W.; Menke, T.; Döring, F. Association between serum level of ubiquinol and NT-proBNP, a marker for chronic heart failure, in healthy elderly subjects. *Biofactors* 2015, 41, 35–43. [CrossRef]
90. Mortensen, S.A.; Rosenfeldt, F.; Kumar, A.; Dolliner, P.; Filipiak, K.J.; Pella, D.; Alehagen, U.; Steurer, G.; Littarru, G.P. Q-SYMBO Study Investigators. The effect of coenzyme Q\textsubscript{10} on morbidity and mortality in chronic heart failure: Results from Q-SYMBO: A randomized double-blind trial. *JACC Heart Fail.* 2014, 2, 641–649. [CrossRef]  
91. Lei, L.; Liu, Y. Efficacy of coenzyme Q\textsubscript{10} in patients with cardiac failure: A meta-analysis of clinical trials. *BMC Cardiovasc. Disord.* 2017, 17, 196. [CrossRef] [PubMed]  
92. Fotino, A.D.; Thompson-Paul, A.M.; Bazzano, L.A. Effect of coenzyme Q\textsubscript{10} supplementation on heart failure: A meta-analysis. *Am. J. Clin. Nutr.* 2013, 97, 268–275. [CrossRef]  
93. Sander, S.; Coleman, C.I.; Patel, A.A.; Kluger, J.; White, C.M. The impact of coenzyme Q\textsubscript{10} on systolic function in patients with chronic heart failure. *J. Card Fail.* 2006, 12, 464–472. [CrossRef] [PubMed]  
94. Belardinelli, R.; Mucaj, A.; Lacalaprice, F.; Solenghi, M.; Principi, F.; Tiano, L.; Littarru, G.P. Coenzyme Q\textsubscript{10} improves contractility of dysfunctional myocardium in chronic heart failure. *BioFactors* 2005, 25, 137–145. [CrossRef]  
95. Munkholm, H.; Hansen, H.H.; Rasmussen, K. Coenzyme Q\textsubscript{10} treatment in serious heart failure. *Biofactors* 1999, 9, 285–289. [CrossRef] [PubMed]  
96. Keogh, A.; Fenton, S.; Leslie, C.; Aboyoun, C.; Macdonald, P.; Zhao, Y.C.; Bailey, M.; Rosenfeldt, F. Randomised double-blind, placebo-controlled trial of coenzyme Q\textsubscript{10} therapy in class II and III systolic heart failure. *Heart Lung Circ.* 2003, 12, 135–141. [CrossRef]  
97. Langsjoen, P.H. Lack of effect of coenzyme Q on left ventricular function in patients with congestive heart failure. *J. Am. Coll. Cardiol.* 2000, 35, 816–817. [CrossRef]  
98. Soja, A.M.; Mortensen, S.A. Treatment of congestive heart failure with coenzyme Q\textsubscript{10} illuminated by metanalysis of clinical trials. *Mol. Asp. Med.* 1997, 18, 159–168. [CrossRef]  
99. Swedberg, K.; Hoffman-Bang, C.; Rehnqvist, N.; Astrom, H. Coenzyme Q\textsubscript{10} as adjunctive in treatment of congestive heart failure. *J. Card Fail.* 1995, 1, 101–107. [CrossRef]  
100. Shi, H.; Noguchi, N.; Niki, E. Dynamics of antioxidant action of ubiquinol: A reappraisal. *Biofactors* 1999, 9, 141–148. [CrossRef]  
101. Morisco, C.; Trimuco, B.; Condorelli, M. Effect of coenzyme therapy in patients with congestive heart failure: A long term multicentre randomized study. *Clin. Investig.* 1993, 71, S134–S136. [CrossRef] [PubMed]  
102. Mortensen, S.A.; Leth, A.; Agner, E.; Rohde, M. Coenzyme Q\textsubscript{10}: Clinical benefits with biochemical correlates suggesting a scientific breakthrough in the management of chronic heart failure. *Int. J. Tissue React.* 1990, 12, 155–162. [PubMed]  
103. Beyer, R. An analysis of coenzyme Q in free radical generation and as an antioxidant. *Biochem. Cell Biol.* 1992, 70, 390–403. [CrossRef] [PubMed]  
104. Niibori, K.; Wrobleswki, K.P.; Yokoyama, H.; Juan, A.; Crestanello, J.A.; Whitman, G.J.R. Bioenergetic effect of liposomal coenzyme Q\textsubscript{10} on myocardial ischaemia reperfusion injury. *Biofactors* 1999, 9, 307–313. [CrossRef] [PubMed]  
105. Cohn, J.N.; Ferrari, R.; Sharpe, N. Cardiac remodelling. Concepts and clinical implications: A consensus paper from an international forum on cardiac remodeling. *Behalf of an International Forum on Cardiac Remodeling. J. Am. Coll. Cardiol.* 2000, 35, 569–582. [CrossRef]  
106. Ulla, A.; Mohamed, M.K.; Sikder, B.; Rahman, A.T.; Sumi, F.A.; Hossain, M.; Mahmud, H.; Rahman, G.M.S.; Alam, M.A. Coenzyme Q\textsubscript{10} prevents oxidative stress and fibrosis in isoprenaline induced cardiac remodeling in aged rats. *BMC Pharmacol. Toxicol.* 2017, 18. [CrossRef]  
107. Singh, R.B.; Niaz, M.A.; Rastogi, S.S.; Sharma, J.P.; Kumar, R.; Bishnoi, I.; Beegom, R. Plasma levels of antioxidant vitamins and oxidative stress in patients with suspected acute myocardial infarction. *Acta Cardiol.* 1994, 49, 411–452.  
108. Grench, E.D.; Jackson, M.; Ramsdale, D.R. Reperfusion injury after acute myocardial infarction. *Br. Med. J.* 1995, 310, 477–478. [CrossRef]  
109. Singh, R.B.; Fedacko, J.; Mojto, V.; Pella, D. Coenzyme Q\textsubscript{10} Modulates Remodeling Possibly by Decreasing Angiotensin-Converting Enzyme in Patients with Acute Coronary Syndrome. *Antioxidants* 2018, 7, 99. [CrossRef]  
110. Dhalla, A.K.; Hill, M.; Singal, P.K. Role of oxidative stress in the transition of hypertrophy to heart failure. *J. Am. Coll. Cardiol.* 1996, 28, 506–514. [CrossRef]
111. Senior, R.; Basu, S.; Kinsey, C.; Schaeffer, S.; Lahiri, A. Carvidiol prevents remodeling in patients with left ventricular dysfunction after acute myocardial infarction. *Am. Heart J.* 1999, 137, 646–652. [CrossRef]

112. Kaper, N.; Singal, P.K. Effects of after load reducing drugs on the pathogenesis of antioxidant changes and congestive heart failure in rats. *J. Am. Coll. Cardiol.* 1997, 219, 856-861. [CrossRef]

113. Wang, T.J.; Larson, M.G.; Levy, D.; Vasan, R.S.; Leip, E.P.; D’Agostino, R.B.; Kannel, W.B.; Benjamin, E.J. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham Heart Study. *Circulation* 2003, 107, 2920–2925. [CrossRef] [PubMed]

114. Zozina, V.I.; Covantev, S.; Goroshko, O.A.; Krasnykh, L.M.; Kukes, V.G. Coenzyme Q10 in patients undergoing cardiac surgery: Could an antioxidant reduce complications? A systematic review and meta-analysis. *Interact. Cardiovasc. Thorac. Surg.* 2015, 20, 254–259. [CrossRef] [PubMed]

115. de Frutos, F.; Gea, A.; Hernandez-Estefania, R.; Rabago, G. Prophylactic treatment with coenzyme Q10 in patients with heart failure. *Curr. Opin. Cardiol.* 2003, 91, 2D–8D. [CrossRef]

116. Maisel, W.H.; Stevenson, L.W. Atrial fibrillation in heart failure: Epidemiology, pathophysiology, and rationale for therapy. *Am. J. Cardiol.* 2003, 91, 32–38. [CrossRef]

117. Kumar, A.; Kaur, H.; Devi, P.; Mohan, V. Role of coenzyme Q10 (CoQ10) in cardiac disease, hypertension and Meniere-like syndrome. *Pharmacol. Ther.* 2009, 124, 259–268. [CrossRef]

118. Hynes, B.J.; Luck, J.C.; Wolbrette, D.L.; Bhatta, L.; Khan, L.; Samii, S.; Naccarelli, G.V. Atrial fibrillation in patients with heart failure. *Curr. Opin. Cardiol.* 2003, 10, 382–386. [CrossRef] [PubMed]

119. Zhao, Q.; Kebbati, A.H.; Zhang, Y.; Tang, Y.; Okello, E.; Huang, C. Effect of coenzyme Q10 on the incidence of atrial fibrillation in patients with heart failure. *J. Investig. Med.* 2015, 63, 735–739. [CrossRef] [PubMed]

120. Senes, M.; Erbay, A.R.; Yilmaz, F.M.; Topkaya, C.; Zengi, O.; Dogan, M.; Yucel, D. Coenzyme Q10 and high-sensitivity C-reactive protein in ischemic and idiopathic dilated cardiomyopathy. *Clin. Chem. Lab. Med.* 2008, 10, 462–466. [CrossRef] [PubMed]

121. Manzoli, U.; Rossi, E.; Littarru, G.P.; Frustaci, A.; Lippa, S.; Oradei, A.; Aureli, V. Coenzyme Q10 in dilated cardiomyopathy. *Int. J. Tissue React.* 1990, 12, 173–178.

122. Soongswang, J.; Sangtawesin, C.; Durongpisitkul, K. The effect of coenzyme Q10 on idiopathic chronic dilated cardiomyopathy in children. *Pediatr. Cardiol.* 2005, 26, 361–366. [CrossRef]

123. Kocharian, A.; Shabanian, R.; Rafiei-Khorgami, M.; Kiani, A.; Heidari-Bateni, G. Coenzyme Q10 improves diastolic function in children with idiopathic dilated cardiomyopathy. *Cardiol. Young* 2009, 19, 501–506. [CrossRef]

124. Langsjoen, P.H.; Langsjoen, A.; Willis, R.; Folkers, K. Treatment of hypertrophic cardiomyopathy with coenzyme Q10. *Mol. Asp. Med.* 1997, 18, S145–S151. [CrossRef]

125. Adarsh, K.; Kaur, H.; Mohan, V. Coenzyme Q10 (CoQ10) in isolated diastolic heart failure in hypertrophic cardiomyopathy (HCM). *Biofactors* 2008, 32, 145–149. [CrossRef]

126. Conklin, K.A. Coenzyme Q10 for prevention of anthracycline-induced cardiotoxicity. *Integr. Cancer Ther.* 2005, 4, 110–130. [CrossRef] [PubMed]

127. Greenlee, H.; Shaw, J.; Lau, Y.L.; Naini, A.; Maurer, M. Lack of effect of coenzyme Q10 on doxorubicin cytotoxicity in breast cancer cell cultures. *Integr. Cancer Ther.* 2012, 11, 243–250. [CrossRef] [PubMed]

128. Mustafa, H.N.; Hegazy, G.A.; Awdan, S.A.E.; AbdellBaset, M. Protective role of COQ10 or L-carnitine on the integrity of the myocardium in doxorubicin induced toxicity. *Tissue Cell* 2017, 49, 410–426. [CrossRef] [PubMed]

129. Moskowitz, M.A.; Lo, E.H.; Iadecola, C. The science of stroke: Mechanisms in search of treatments. *Neuron* 2010, 67, 181–198. [CrossRef]

130. Kleinig, T.J.; Vink, R. Suppression of inflammation in ischemic and hemorrhagic stroke: Therapeutic options. *Curr. Opin. Neurol.* 2009, 22, 294–301. [CrossRef]

131. Simani, L.; Ryan, F.; Hashemifard, S.; Hooshmandi, E.; Madahi, M.; Sahraei, Z.; Razaei, O.; Heydari, K.; Ramezami, M. Serum Coenzyme Q10 is associated with clinical neurological outcomes in acute stroke patients. *J. Mol. Neurosci.* 2018, 51, 1–6. [CrossRef] [PubMed]

132. Allen, C.; Baylaktutan, U. Oxidative stress and its role in the pathogenesis of ischaemic stroke. *Int. J. Stroke* 2009, 4, 461–470. [CrossRef] [PubMed]

133. Nasoohi, S.; Simani, L.; Khodagholi, F.; Nikseresht, S.; Faizi, M.; Naderi, N. Coenzyme Q10 supplementation improves acute outcomes of stroke in rats pretreated with atorvastatin. *Nutr. Neurosci.* 2017, 22, 264–272. [CrossRef] [PubMed]
134. Liu, G.; Geng, J. Glial fibrillary acidic protein as a prognostic marker of acute ischemic stroke. *Hum. Exp. Toxicol.* **2018**, *37*, 1048–1053. [CrossRef]

135. Sharpe, P.C.; Mulholland, C.; Trinick, T. Ascorbate and malondialdehyde in stroke patients. *Ir. J. Med. Sci.* **1994**, *163*, 488–491. [CrossRef]

136. Milanlioglu, A.; Aslan, M.; Ozkol, H.; Çilingir, V.; Nuri Aydan, M.; Karadas, S. Serum antioxidant enzymes activities and oxidative stress levels in patients with acute ischemic stroke: Influence on neurological status and outcome. *Wien. Klin Wochenschr.* **2016**, *128*, 169–174. [CrossRef]

137. Ramezani, M.; Sahraei, Z.; Simani, L.; Heydari, K.; Shahidi, F. Coenzyme Q10 supplementation in acute ischemic stroke: Is it beneficial in short-term administration? *Nutr. Neurosci.* **2018**, 1–6. [CrossRef]

138. Girndt, M.; Seibert, E. Premature cardiovascular disease in chronic renal failure (CRF): A model for an advanced ageing process. *Exp. Gerontol.* **2010**, *45*, 797–800. [CrossRef]

139. Go, A.S.; Chertow, G.M.; Fan, D.; McCulloch, C.E.; Hsu, C.Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N. Engl. J. Med.* **2004**, *351*, 1296–1305. [CrossRef]

140. Stenvinkel, P.; Diczfalusy, U.; Lindholm, B.; Heimburger, O. Phospholipid plasmalogen, a surrogate marker of oxidative stress, is associated with increased cardiovascular mortality in patients on renal replacement therapy. *Nephrol. Dial. Transplant.* **2004**, *19*, 972–976. [CrossRef] [PubMed]

141. Himmelfarb, J.; McMenamin, M.E.; Loetto, G.; Heinecke, J.W. Myeloperoxidase-catalyzed 3-chlorotyrosine formation in dialysis patients. *Free Radic. Biol. Med.* **2001**, *31*, 1163–1169. [CrossRef]

142. Mehmetoglu, I.; Yerlikaya, F.H.; Kurban, S.; Erdem, S.S.; Tonbul, Z. Oxidative stress markers in hemodialysis patients, including coenzyme Q10 and ischemia-modified albumin. *Int. J. Artif. Organs* **2012**, *35*, 226–232. [CrossRef] [PubMed]

143. Bakhshayeshkaram, M.; Lankarani, K.B.; Mirhosseini, N.; Tabrizi, R.; Akbari, M.; Dabbaghmanesh, M.H.; Asemi, Z. The Effects of Coenzyme Q10 Supplementation on Metabolic Profiles of Patients with Chronic Kidney Disease: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Curr. Pharm. Des.* **2018**, *24*, 3710–3723. [CrossRef] [PubMed]

144. Gholnari, T.; Aghadavod, E.; Soleimani, A.; Hamidi, G.A.; Sharifi, N.; Asemi, Z. The Effects of coenzyme Q10 supplementation on glucose metabolism, lipid profiles, inflammation, and oxidative stress in patients with diabetic nephropathy: A randomized, double-blind, placebo-controlled trial. *J. Am. Coll. Nutr.* **2018**, *37*, 188–193. [CrossRef]

145. Zhang, X.; Shi, Z.; Liu, Q.; Quan, H.; Cheng, X. Effects of coenzyme Q10 intervention on diabetic kidney disease: A systematic review and meta-analysis. *Medicine* **2019**, *98*, e15850. [CrossRef]

146. Shojaei, M.; Djalali, M.; Khatami, M.; Siassi, F.; Esraghian, M. Effects of carnitine and coenzyme Q10 on lipid profile and serum levels of lipoprotein(a) in maintenance hemodialysis patients on statin therapy. *Iran. J. Kidney Dis.* **2011**, *5*, 114–118. [CrossRef]

147. Fallah, M.; Askari, G.; Soleimani, A.; Feizi, A.; Asemi, Z. Clinical trial of the effects of coenzyme Q10 supplementation on glycemic control and markers of lipid profiles in diabetic hemodialysis patients. *Int. J. Urol. Nephrol.* **2018**, *50*, 2073–2079. [CrossRef]

148. Zahed, N.S.; Ghassami, M.; Nikbakht, H. Effects of coenzyme Q10 supplementation on C-reactive protein and homocysteine as the inflammatory markers in hemodialysis patients; a randomized clinical trial. *J. Nephropathol.* **2016**, *5*, 38–43. [CrossRef]

149. Rivara, M.B.; Yeung, C.K.; Robinson-Cohen, C.; Phillips, B.R.; Ruzinski, J.; Rock, D.; Linke, L.; Shen, D.D.; Ikizler, T.A.; Himmelfarb, J. Effect of Coenzyme Q10 on Biomarkers of Oxidative Stress and Cardiac Function in Hemodialysis Patients: The CoQ10 Biomarker Trial. *Am. J. Kidney Dis.* **2017**, *69*, 389–399. [CrossRef]

150. Starr, M.C.; Chang, I.J.; Finn, L.S.; Sun, A.; Larson, A.A.; Goebel, J.; Hanevold, C.; Thies, J.; Van Hove, J.L.K.; Hingorani, S.R.; et al. COQ2 nephropathy: A treatable cause of nephrotic syndrome in children. *Pediatr. Nephrol.* **2018**, *33*, 1257–1261. [CrossRef]

151. Mahmoud, A.N.; Mentias, A.; Elgendy, A.Y.; Qazi, A.; Barakat, A.F.; Saad, M.; Mohsen, A.; Abuzaid, A.; Mansoor, H.; Mojadidi, M.K.; et al. Migraine and the risk of cardiovascular and cerebrovascular events: A meta-analysis of 16 cohort studies including 1152407 subjects. *BMJ Open* **2018**, *8*, e020498. [CrossRef] [PubMed]

152. Hershey, A.D.; Powers, S.W.; Vockell, A.L.; Lecates, S.L.; Ellinor, P.L.; Segers, A.; Burdine, D.; Manning, P.; Kabbouche, M.A. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. *Headache* **2007**, *47*, 73–80. [CrossRef] [PubMed]
153. Parohan, M.; Sarraf, P.; Javanbakht, M.H.; Ranji-Burachaloo, S.; Djalali, M. Effect of coenzyme Q10 supplementation on clinical features of migraine: A systematic review and dose-response meta-analysis of randomized controlled trials. *Nutr. Neurosci.* 2019, 6, 1–8. [CrossRef] [PubMed]

154. Zeng, Z.; Li, Y.; Lu, S.; Huang, W.; Di, W. Efficacy of CoQ10 as supplementation for migraine: A meta-analysis. *Acta Neurol. Scand.* 2019, 139, 284–293. [CrossRef] [PubMed]

155. Rajapakse, T.; Pringsheim, T. Nutraceuticals in Migraine: A Summary of Existing Guidelines for Use. *Headache* 2016, 56, 808–816. [CrossRef] [PubMed]

156. Dahri, M.; Tarighat-Esfanjani, A.; Asghari-Jafarabadi, M.; Hashemilar, M. Oral coenzyme Q10 supplementation in patients with migraine: Effects on clinical features and inflammatory markers. *Nutr. Neurosci.* 2018, 3, 1–9. [CrossRef]

157. Abdollahzad, H.; Aghdashi, M.A.; Asghari Jafarabadi, M.; Alipour, B. Coenzyme Q10 supplementation on inflammatory cytokines (TNF-α, IL-6) and Oxidative Stress in Rheumatoid Arthritis Patients: A Randomized Controlled Trial. *Arch. Med. Res.* 2015, 46, 527–533. [CrossRef]

158. Gaul, C.; Diener, H.C.; Danesch, U.; MigraVent Study Group. Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: A randomized, placebo-controlled, double-blind, multicenter trial. *J. Headache Pain* 2015, 16, 516. [CrossRef]

159. Parohan, M.; Sarraf, P.; Javanbakht, M.H.; Foroushani, A.R.; Ranji-Burachaloo, S.; Djalali, M. The synergistic effects of nano-curcumin and coenzyme Q10 supplementation in migraine prophylaxis: A randomized, placebo-controlled, double-blind trial. *Nutr. Neurosci.* 2019, 26, 1–10. [CrossRef]

160. Fogacci, S.; Fogacci, F.; Cicero, A.F.G. Nutraceuticals and Hypertensive Disorders in Pregnancy: The Available Clinical Evidence. *Nutrients* 2020, 12, 378. [CrossRef]

161. WHO. Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia; WHO: Geneva, Switzerland, 2011.

162. Rana, S.; Lemoine, E.; Granger, J.; Karumanchi, S.A. Preeclampsia: Pathophysiology, Challenges, and Perspectives. *Circ. Res.* 2019, 124, 1094–1112. [CrossRef] [PubMed]

163. Teran, E.; Racines-Orbe, M.; Vivero, S.; Escudero, C.; Molina, G.; Calle, A. Preeclampsia is associated with a decrease in plasma coenzyme Q10 levels. *Free Radic. Biol. Med.* 2003, 35, 1453–1456. [CrossRef] [PubMed]

164. Palan, P.R.; Shaban, D.W.; Martino, T.; Mikhail, M.S. Lipid-soluble antioxidants and pregnancy: Maternal serum levels of coenzyme Q10, alpha-tocopherol and gamma-tocopherol in preeclampsia and normal pregnancy. *Gynecol. Obstet. Invest.* 2004, 58, 8–13. [CrossRef] [PubMed]

165. Teran, E.; Hernandez, I.; Nieto, B.; Tavara, R.; Ocampo, J.E.; Calle, A. Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. *Int. J. Gynaecol. Obstet.* 2009, 105, 43–45. [CrossRef]

166. Tenório, M.B.; Ferreira, R.C.; Moura, F.A.; Bueno, N.B.; Goulart, M.O.F.; Oliveira, A.C.M. Oral antioxidant therapy for prevention and treatment of preeclampsia: Meta-analysis of randomized controlled trials. *Nutr. Metab. Cardiovasc. Dis.* 2018, 28, 865–876. [CrossRef] [PubMed]

167. Corsini, A. Statin-Related Muscle Complaints: An Underestimated Risk. *Cardiovasc. Drugs Ther.* 2005, 19, 379–381. [CrossRef]

168. Deichmann, R.; Lavie, C.; Andrews, S. Coenzyme Q10 and statin-induced mitochondrial dysfunction. *Ochsner J.* 2010, 10, 16–21.

169. Qu, H.; Meng, Y.Y.; Chai, H.; Liang, F.; Zhang, J.Y.; Gao, Z.Y.; Shi, D.Z. The effect of statin treatment on circulating coenzyme Q10 concentrations: An updated meta-analysis of randomized controlled trials. *Eur. J. Med. Res.* 2018, 23, 57. [CrossRef]

170. Qu, H.; Guo, M.; Chai, H.; Wang, W.T.; Gao, Z.Y.; Shi, D.Z. Effects of Coenzyme Q10 on Statin-Induced Myopathy: An Updated Meta-Analysis of Randomized Controlled Trials. *J. Am. Heart Assoc.* 2018, 7, e009835. [CrossRef]

171. Mizuno, K.; Tanaka, M.; Nozaki, S.; Mizuma, M.; Ataka, S.; Tahara, T.; Sugino, T.; Shirai, T.; Kajimoto, Y.; Kuratsune, H.; et al. Antifatigue effects of coenzyme Q10 during physical fatigue. *Nutrition* 2008, 24, 293–299. [CrossRef]

172. Lee, YJ.; Cho, WJ.; Kim, JK.; Lee, DC. Effects of coenzyme Q10 on arterial stiffness, metabolic parameters, and fatigue in obese subjects: A double-blind randomized controlled study. *J. Med. Food* 2011, 14, 386–390. [CrossRef] [PubMed]
173. Cordero, M.D.; Cano-Garcia, F.J.; Alcocer-Gómez, E.; de Miguel, M.; Sánchez-Alcázar, J.A. Oxidative stress correlates with headache symptoms in fibromyalgia: Coenzyme Q_{10} effect on clinical improvement. *PLoS ONE* 2012, 7, e35677. [CrossRef] [PubMed]

174. Di Pierro, F.; Rossi, A.; Consensi, A.; Giacomelli, C.; Bazzichi, L. Role for a water-soluble form of CoQ_{10} in female subjects affected by fibromyalgia. A preliminary study. *Clin. Exp. Rheumatol.* 2017, 35, 20–27.

175. Kikkawa, K.; Takehara, I.; Miyakoshi, T.; Miyawaki, H. Safety of High Dose Supplementation of Coenzyme Q_{10} in Healthy Human Adults. *Ipn. J. Food Chem.* 2007, 14, 76–81.

176. Bentinger, M.; Dallner, G.; Choknacki, T.; Swiezewska, E. Distribution and breakdown of labeled coenzyme Q in rats. *Free Radic. Biol. Med.* 2003, 34, 563–575. [CrossRef]

177. Nukui, K.; Yamagishi, T.; Miyawaki, H.; Kettawan, A.; Okamoto, T.; Sato, K. Comparison of uptake between PureSorb-Q40 and regular hydrophobic coenzyme Q_{10} in rats and humans after single oral intake. *J. Nutr. Sci. Vitaminol.* 2007, 53, 187–190. [CrossRef]

178. Bhagavan, H.N.; Chopra, R.K. Coenzyme Q_{10}: Absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radic. Res.* 2006, 40, 445–453. [CrossRef]

179. Bhagavan, H.N.; Chopra, R.K. Plasma coenzyme Q_{10} response to oral ingestion of coenzyme Q_{10} formulations. *Mitochondrion* 2007, 7, S78–S88. [CrossRef]

180. Tomono, Y.; Hasegawa, J.; Seki, T.; Moteki, G.; Morishita, N. Pharmacokinetic study of deuterium-labeled Coenzyme-Q_{10} in man. *Int. J. Clin. Pharmacol. Ther.* 1986, 24, 536–541.

181. Weis, M.; Mortensen, S.A.; Rassing, M.R.; Møller-Sonnergaard, J.; Poulsen, G.; Rasmussen, S.N. Bioavailability of four oral coenzyme Q_{10} formulations in healthy volunteers. *Mol. Asp. Med.* 1994, 15, 273–280. [CrossRef]

182. Miles, M.V.; Horn, P.; Miles, L.; Tang, P.; Steele, P.; De Grauw, T. Bioequivalence of coenzyme Q_{10} from over-the-counter supplements. *Nutr. Res.* 2002, 22, 919–929. [CrossRef]

183. Pravst, I.; Prosek, M.; Wondra, A.G.; Zmitek, K.; Zmitek, J. The Stability of Coenzyme Q_{10} in Fortified Foods. *Acta Chim. Slov.* 2009, 56, 953–958.

184. Evans, M.; Baisley, J.; Barss, S.; Guthrie, N. A randomized, double-blind trial on the bioavailability of two CoQ_{10} formulations. *J. Funct. Foods* 2009, 1, 65–73. [CrossRef]

185. Zhang, Y.; Liu, J.; Chen, X.Q.; Chen, C.Y.O. Ubiquinol is superior to ubiquinone to enhance Coenzyme Q_{10} status in older men. *Food Funct.* 2016, 9, 5635–5659. [CrossRef] [PubMed]

186. Zmitek, J.; Smidovnik, A.; Fir, M.; Prosek, M.; Zmitek, K.; Walczak, J.; Pravst, I. Relative bioavailability of two forms of a novel water soluble Coenzyme Q_{10}. *Ann. Nutr. Metab.* 2008, 52, 281–287. [CrossRef]

187. López-Lluch, G.; Del Pozo-Cruz, J.; Sánchez-Cuesta, A.; Cortés-Rodríguez, A.B.; Navas, P. Bioavailability of coenzyme Q_{10} supplements depends on carrier lipids and solubilization. *Nutrition* 2019, 57, 133–140. [CrossRef]

188. Weber, C.; Bysted, A.; Helmer, G. Coenzyme Q_{10} in the diet-daily intake and relative bioavailability. *Mol. Asp. Med.* 1997, 18, S251–S254. [CrossRef]

189. Wąda, R.; Zirkel, J.; Schaffer, T. Increase of bioavailability of coenzyme Q_{10} and vitamin E. *J. Med. Food* 2007, 10, 731–734. [CrossRef]

190. Martinefski, M.; Samassa, P.; Buontempo, F.; Höcht, C.; Lucangioli, S.; Tripodi, V. Relative bioavailability of coenzyme Q_{10} formulation for paediatric individualized therapy. *J. Pharm. Pharmacol.* 2017, 69, 567–573. [CrossRef] [PubMed]

191. Constantinescu, R.; McDermott, M.P.; Dicenzo, R. A randomized study of the bioavailability of different formulations of coenzyme Q_{10} (ubiquinone). *J. Clin. Pharmacol.* 2007, 47, 1580–1586. [CrossRef] [PubMed]

192. Lucker, P.W.; Wetzelsberger, N.; Hennings, G.; Rehn, D. Pharmacokinetics of coenzyme ubiquedecarone in healthy volunteers. In *Biomedical and Clinical Aspects of Coenzyme Q*; Elsevier: Amsterdam, The Netherlands, 1984; pp. 141–151.

193. Hosoe, K.; Kitano, M.; Kishida, H.; Kubo, H.; Fujii, K.; Kitahara, M. Study on safety and bioavailability of ubiquinol (Kaneka QH) after single and 4-week multiple oral administration to healthy volunteers. *Regul. Toxicol. Pharmacol.* 2007, 47, 19–28. [CrossRef]
196. Molyneux, S.; Florkowski, C.; Lever, M.; George, P. The bioavailability of coenzyme Q10 supplements available in New Zealand differs markedly. *N. Z. Med. J.* **2004**, *117*, U1108.

197. Young, J.M.; Molyneux, S.L.; Florkowski, C.M.; Frampton, C.M.; George, P.M.; Scott, R.S. Pharmacokinetic comparison of a generic coenzyme Q10 solubilizate and a formulation with soybean phytosterols. *Phytother. Res.* **2012**, *26*, 1092–1096. [CrossRef]