

ANALEPTIC PROPERTIES OF ROSUVASTATIN AND CQ10 COMBINATION

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Abstract

This article is an examination of the Analeptic properties of Rosuvastatin and cq10 (Ubiquinone) combination. The scientific development and subsequent analysis of the ability of two combinational drugs Rosuvastatin and cq10 to treat human disorders/ diseases by lowering cholesterol and displaying antioxidant activity respectively, continues to influence researchers all over the globe, today. This article examines the research done and published by researchers and scientists. Consideration of current trends and data in scientific queries demonstrates further aspects of Analeptic properties of Rosuvastatin and cq10 (Ubiquinone) combination. Additionally, this article explores options for Rosuvastatin and its effects on Dyslipidemia, glucose homeostasis and high-risk cardiovascular patients. This article also provides insights into Ubiquinone and its effects on cardiovascular diseases and hypertriglyceridemia. Lastly, from this article the combined effects of rosuvastatin and cq10 on cardiotoxicity, Ischemia and Induced Myopathy can also be gauged.

Keywords: Rosuvastatin Ubiquinone, Cardiovascular, Dyslipidemia, Ischemia

1. INTRODUCTION:

Combination therapy using two or more drugs has been a long-standing treatment option to treat several diseases. In this combination, usually one drug exerts its effects and the other drug serves as a buffer to counter/ negate the side effects of the first drug. This helps improve efficiency of treatment. Additionally, it has been seen that drugs when used in combinations can lower the possibility of development of resistance to those particular drugs

Statins are a class of drugs that lower the levels of cholesterol in the body, in doing so they reduce the risk of stroke, heart attacks and death due to heart disease by 25-35%. Cardiovascular diseases account for 17.8 million deaths, according to a study carried out by the World Health Organization (WHO) in 2017. One third of heart diseases are caused due to accumulation of cholesterol, which can be reduced using statins such as Rosuvastatin. Another condition called Dyslipidemia also occurs due to accumulation of bad cholesterol in the blood, this can also increase the risk of blockages. This condition can also be solved by administration of statins. About 26% of the global population uses statins, but statin suffers from a major drawback. While exerting its effects, statins reduce the levels of naturally occurring cq10 (Ubiquinone) in the body. Lowering of levels of this antioxidant causes muscle pain due to accumulation of reactive oxygen species. When

present, Ubiquinone lowers blood sugar levels and also reduces blood pressure. This is important as nearly 26% of the global population suffer from hypertension and its associated shortcomings.

Thus, a combination of Rosuvastatin and cq10 will help overcome this side effect. Additionally, the two drugs used together, has been shown to confer additional protection to tackle cardiac diseases. Our research paper has gathered information from a wide range of databases, over a wide time period, including the most recent advances. Our paper aims to elucidate the individual and combined effects of Rosuvastatin and Cq10, to devise better therapies and make the treatment robust. A through literature survey was carried out concentrating not only on the cardiac problems but also neurological problems, metabolomic problems and myopathic problems.

2. METHODS:

This study was conducted using four databases: Google Scholar, SAGE, DOAJ and PubMed. Selection of papers was done based on keywords and theme relevant to this review. Further, the published papers from these databases were arranged in systemic order with respect to year of publication.

3. RESULTS AND DISCUSSION:

3.1 Rosuvastatin¹⁻¹⁰

Sr. No.	Title of Paper	Year Published
1	A Comparative study with rosuvastatin in subjects with Metabolic Syndrome: results of the COMETS study	2005
2	Effectiveness of using rosuvastatin in difficult-to-control dyslipidaemia patients: an audit in secondary care	2005
3	Long-term use of rosuvastatin: a critical risk benefit appraisal and comparison with other antihyperlipidemics	2009
4	Comparison of Efficacy and Safety of Rosuvastatin, Atorvastatin and Pravastatin among Dyslipidemia Diabetic Patients	2013
5	Rosuvastatin: Role in Cardiovascular High-risk Patient	2013
6	Dual Effect of Rosuvastatin on Glucose Homeostasis Through Improved Insulin Sensitivity and Reduced Insulin Secretion	2016
7	Perioperative Rosuvastatin in Cardiac Surgery	2016
8	Rosuvastatin: the most efficient treatment option for patients with Dyslipidaemia	2017
9	Rosuvastatin alters the genetic composition of the human gut microbiome	2020
10	Comparing the Effect of Combining Exercise with Rosuvastatin versus Atorvastatin on Lipid Profile and Functional Capacity: A Retrospective Cohort Study	2020

Comparing the Efficacy of Rosuvastatin with Other Drugs in Subjects with Metabolic Syndromes

Patients with metabolic syndromes that increase the risk of coronary heart disease like dyslipidemia, hypertension and impaired glucose regulation were tested for the efficacy and safety of rosuvastatin in comparison to atorvastatin and placebo as part of a COMETS study. A randomized, three arm parallel-group study was conducted wherein patients were subjected to receive 10mg of rosuvastatin, atorvastatin or placebo for 6 weeks and then 20mg for another 6 weeks along with dietary control. Higher number of patients were observed to achieve low density lipoprotein cholesterol (LDL-C) goals with rosuvastatin in comparison to atorvastatin. It was found to improve overall lipid profile and was also well tolerated in patients with metabolic syndromes without significant side effects. Rosuvastatin was found to be more effective than atorvastatin in decreasing LDL-C in the first 6 weeks (41.7% vs 35.7% with p value <0.001). Furthermore, at the end of 12 weeks, same pattern of significant decrease in LDL-C was observed (48.9% vs 42.5% with p value <0.001). HDL-C levels were observed to increase by 10.4% in the rosuvastatin group as compared to 5.8% in the atorvastatin group. On the other hand, no significant difference was observed in levels of hsCRP, fasting plasma glucose and mean glycated hemoglobin. Both rosuvastatin and atorvastatin were well tolerated and produced similar treatment emergent adverse events, of which the most commonly reported were headache, back pain, myalgia and arthralgia. COMETS is the first study to compare statin efficacy in subjects with metabolic syndromes and its results were also found to be consistent with other studies of rosuvastatin that included patients with metabolic syndromes. Statin induced LDL-C reduction and HDL-C

increase have been shown to decrease the incidence of cardiovascular events by 24-37%. Further studies are required to evaluate the results of the present study to analyze whether the lipid profile improvements lead to increased survival and reduced morbidity. In conclusion, COMETS proved that rosuvastatin was more effective than atorvastatin in achieving desirable lipid profiles, while also improving certain aspects of atherogenic lipid profile in patients with metabolic syndromes.

Analyzing Effectiveness of Rosuvastatin in subjects with Difficult-to-Control Dyslipidemia

A large proportion of patients suffering from dyslipidemia are at a higher risk of developing severe cardiovascular diseases and fail to meet the desirable level of LDL-C, thus generating the need for improved lipid lowering treatment strategies. The efficacy and safety of rosuvastatin therapy and other lipid lowering treatments was checked in 216 patients. 24.2% patients achieved LDL-C level goal with lipid lowering treatment and 66.7% of patients achieved desirable LDL-C goals with rosuvastatin treatment. Mean reduction in serum cholesterol of patients with lipid lowering treatment was found to be 1.6 mmol/l with $p<0.05$ and that of patients with rosuvastatin therapy was found to be 0.7 mmol/l with $p<0.05$. Statin therapy was the most commonly used lipid lowering treatment with the most common prescriptions being 10mg atorvastatin, 40mg pravastatin and 20mg simvastatin. The patients who were exclusively subjected to statin treatment without rosuvastatin, experienced marked decrease in serum cholesterol and serum triglycerides but HDL-C remained unchanged. After switching to rosuvastatin therapy, mean serum cholesterol levels were found to be the lowest and most patients achieved target LDL-C. In comparison to other lipid lowering treatments, statin therapy was found to be the most effective with greater percentage of people (24.2%) achieving LDL-C levels (<3 mmol/l) and even higher percentage with rosuvastatin treatment (66.7%). Out of the 216 subjects, only 16 cases of mild adverse events were reported. The results of this study were found to corroborate with the clinical trials, concluding that rosuvastatin therapy was the most effective therapeutic treatment to achieve desirable LDL-C levels. It was found to be particularly effective for familial hypercholesterolemia. Along with its effectiveness, it also proved to be safer than any other statin belonging to the same class, as no adverse changes were reported in lipid profile and HDL-C remained unchanged. Following the cost efficiency analysis of statin therapy, cost benefit was estimated in using rosuvastatin over atorvastatin, pravastatin and simvastatin. More experiments need to be conducted to test for reduction in levels of triglycerides as the number of subjects on combination therapy was too less. It was concluded that rosuvastatin therapy provided not only an effective, but a safe option for achieving desirable LDL-C levels and reduction of mean serum cholesterol.

Comparison of Rosuvastatin with other Antihyperlipidemics for Long Term Use and Risk Benefit Analysis

Rosuvastatin is the most recent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) to be introduced as a blood cholesterol lowering agent as part of treatment of hyperlipidemia. Rosuvastatin proved to be the most efficient statin in lowering LDL-C and triglyceride levels in comparative trials with atorvastatin, pravastatin and simvastatin. It also helps in decreasing the probability of incidence of cardiovascular diseases in patients with elevated c-reactive protein levels. Due to its chemical and pharmacokinetic properties, it lowers the risk of muscle toxicity. This article explores the clinical and pharmacologic properties of rosuvastatin in detail to facilitate its correct use to treat hyperlipidemia. LDL-C lowering properties of rosuvastatin are derived from its inhibitory action on HMG-CoA due to its very high affinity for active site of HMG-CoA reductase in hepatocytes. The oral bioavailability of rosuvastatin is approximately 20% and the peak plasma concentration (C_{max}) of 6.1 ng/ml is reached after 5 hours. Inhibitory activity of rosuvastatin against P-glycoprotein might influence the pharmacokinetic and pharmacodynamic properties of the drug and other drug-drug interaction. Patients with hypercholesterolemia were subjected to a 6 week dietary program and were randomized to therapy with different statins that included rosuvastatin, atorvastatin, simvastatin and pravastatin. Rosuvastatin was found to be the most efficacious in reducing LDL-C levels and favorably modifying other apolipoprotein parameters. JUPITER trial conducted to check effectiveness of rosuvastatin vs placebo in reducing risk of cardiovascular diseases also resulted in unequivocal evidence of decrease in cardiovascular morbidity and mortality. Numerous studies conducted to check the safety of rosuvastatin have proved it to be a safer alternative to other statins and occurrence of only mild adverse events (headache, myalgia, flu syndrome and pain) was observed. Under experimental conditions, rosuvastatin has proved to decrease pro-inflammatory cytokines and reduction in production of reactive oxygen species production. Deeper laboratory and clinical examinations are required to study and exploit these anti-inflammatory properties of rosuvastatin. It was concluded that rosuvastatin could be considered as a second-generation HMG-CoA inhibitor as well as a well-tolerated and safe lipid lowering agent with significant anti-inflammatory properties due to its unique pharmacokinetic and pharmacodynamic properties.

Analyzing the Safety and Efficacy of Rosuvastatin in comparison to Atorvastatin and Pravastatin in Dyslipidemia Diabetic Patients

The objective of this study was to study and compare the safety and efficacy of Rosuvastatin, Atorvastatin and Pravastatin for managing diabetic patients with dyslipidemia in Qatar. The study was conducted on 350 diabetic subjects who were also diagnosed with dyslipidemia. It was found that rosuvastatin (10mg dose)

was the most efficient in lowering LDL-C levels. All three statins were also found to be safe with low incidence of adverse events in relation to muscular and hepatic functions. At a dose of 10mg Rosuvastatin was not only effective in reducing LDL-C levels but also triglyceride levels. All three statins were found to decrease HDL-C levels instead of increasing it. Onset of some adverse events was observed but it was limited to microalbuminuria, but none of these cases further progressed to the more serious macroalbuminuria. Results of the present study corroborated with the STELLAR trial which proved rosuvastatin to be the most efficient statin at all doses (10mg, 20mg, 40mg and 80mg). Rosuvastatin was also found to reduce triglyceride levels most efficiently followed by atorvastatin and pravastatin making these extremely important lipid lowering agents that also reduce risk of cardiovascular diseases among diabetic patients. On the contrary, results of the present study contradicted the STELLAR trial and other studies of literature due to the decrease in levels of HDL-C. Possible reasons for decrease in HDL-C might be the presence of two triggering factors for cardiovascular diseases (diabetes and hypertension) that most of the subjects had. Along with this, over two-thirds of the subjects were also obese. All three statins did not significantly affect the levels of serum creatinine and the glomerular filtration rate. Rosuvastatin was also found to be comparatively safe for patients with microalbuminuria. It was concluded that rosuvastatin was the most effective statin in Qatari diabetic patients to reduce the levels of LDL-C, triglycerides and total cholesterol.

Studying Role of Rosuvastatin in High-Risk Cardiovascular Morbidity and Mortality

Statins are lipid lowering agents used for the treatment of hypercholesterolemia or mixed dyslipidemia and decrease in blood cholesterol levels. All commercially available statins have proven to be beneficial in terms of cardiovascular morbidity and mortality. Rosuvastatin, however possesses a pharmacokinetic as well as a cost benefit over other statins. HMG-CoA reductase is the enzyme involved in cholesterol endogen production, thus increasing level of serum cholesterol and LDL-C. The mechanism of action of statins is by inhibition of this enzyme, which in turn leads to decrease in LDL-C levels. The guidelines for clinical usage of these statins is however dependent on the cardiovascular risk specified in 4 levels i.e. very high risk, high risk, intermediate risk and latent risk. Rosuvastatin has higher affinity for active site of HMG-CoA reductase due to the presence of methyl sulfonamide group and its extended half-life (20hrs). Minimum dosage of rosuvastatin (10mg) was the most effective in lowering LDL-C levels (46%) as compared to all other statins. Occurrence of adverse events was limited to non-fatal side effects like constipation, stomach pain, myalgia, asthenia and nausea. The SPACE ROCKET study proved efficacy of rosuvastatin in reducing LDL-C levels in patients with myocardial infarction. The LUNAR study compared efficacy of rosuvastatin (20mg or 40mg/day) with

atorvastatin (80mg/day) in patients hospitalized with acute coronary syndrome and it was successful in proving effectiveness of rosuvastatin reducing LDL-C levels and increasing HDL-C. Randomized control trials like PULSAR, MERCURY II, DISCOVERY BELUX and POLARIS also proved superiority of rosuvastatin over other statins. It was found that branding rosuvastatin (10mg) was much more cost effective than atorvastatin and simvastatin. The DISCOVERY BELUX and POLARIS specifically studied cost effectiveness of rosuvastatin in patients with high-risk cardiovascular diseases and found it to be more economically benefits than other statins. It was concluded that along with being the most effective and safe statin for lowering of lipids, it was also the most cost effective and could be considered as a first choice of lipid lowering drug in cardiovascular high-risk patients.

Improving Insulin Sensitivity and Reducing Insulin Secretion to Study Dual Effect of Rosuvastatin on Glucose Homeostasis

Statins are effective in treatment of cardiovascular diseases but are found to increase incidence of new on set diabetes. This study was conducted on mice that were categorized into 2 groups, mice on normal diet (ND) and mice on high fat diet (HFD), both being subjected to rosuvastatin treatment. Mice on ND rosuvastatin were found to have decreases in blood glucose levels. Ca^{2+} signaling was impaired in the beta cells and density of granules in plasma membrane increased after treatment with rosuvastatin. HFD mice seemed to develop insulin resistance but after treatment with rosuvastatin, glucose uptake increased. Mice on the high fat diet had reduced insulin sensitivity and also a spike in insulin secretion. After being subjected to rosuvastatin therapy, HFD mice underwent an increase in glucose uptake and insulin secretion was also decreased. When ND mice were subjected to rosuvastatin treatment, insulin content was reduced and Ca^{2+} signaling was impaired, leading to more efficient glucose uptake. Rosuvastatin also improved the cell's sensitivity towards insulin and effectively increased glucose uptake leading to decrease in blood sugar levels. Several studies proposing an association between rosuvastatin and new onset diabetes have contrasting results and conclusions, some in favor of statin treatment and others reporting that statin treatment leads to increase in insulin resistance. The present study showed improvement in glucose uptake after rosuvastatin treatment. The mechanism of action of rosuvastatin in glucose uptake has not being identified yet but it is speculated to either basal GLUT4 translocation by membrane alteration or by affecting mechanisms downstream of the insulin receptor. Present study also shows rosuvastatin induced impairment of beta cell functions and decreased insulin secretion in vivo but not in vitro. The reduction in insulin levels along with the increase in number of dock granules show that rosuvastatin has several cellular effects that result in impaired insulin secretion. It was proved that rosuvastatin has a positive effect on glucose uptake and improved insulin sensitivity,

leading to the conclusion that rosuvastatin had an overall positive effect on glucose homeostasis. On the contrary, rosuvastatin was found to have delirious effects on beta cells that could be calamitous in the long run. Therefore, individuals with higher susceptibility to the occurrence of diabetes experienced the negative effects of rosuvastatin on glucose homeostasis and beta cells, that could induce new onset diabetes.

Perioperative Rosuvastatin Therapy for Cardiac Surgery Patients

Despite advances in perioperative care, complications after cardiac surgery lead to increase in morbidity and mortality. Randomized trials have put forward that perioperative statin therapy could prevent some of these complications. A randomized study with 1922 patients who were scheduled for elective cardiac surgery were subjected to receive rosuvastatin (20mg/day) or placebo. The levels of LDL-C and C reactive protein after surgery were lower in patient subjected to rosuvastatin treatment ($p < 0.001$). Perioperative statin treatment failed to prevent postoperative atrial fibrillation and perioperative myocardial infarction and also showed incidence acute kidney injury. Even though LDL-C levels decreased in both groups (rosuvastatin and placebo), significant decrease of C reactive protein level and LDL-C was observed in patients undergoing rosuvastatin treatment. Incidence of postoperative atrial fibrillation was not significantly affected after rosuvastatin treatment. Rosuvastatin had no significant side effects on troponin I release and secondary outcomes related to myocardial infarction. Monitoring of in-hospital adverse events was also done. Occurrence of atrial fibrillation was found in 16% of patients rosuvastatin group as compared to 12% in placebo. Plasma creatinine levels as well as acute kidney injury levels were higher in rosuvastatin group. After analysis of some previously conducted perioperative rosuvastatin therapy studies, it indicated almost halving of occurrence of atrial fibrillation, contrary to the present study. Similar discrepancies are observed in case of studies related to myocardial infarction as well. There is also no evidence that perioperative rosuvastatin therapy produced effective results in patients belonging to the high-risk category. A potential limitation in the present study may be the shorter duration of preoperative rosuvastatin therapy as it ranged from only 4 to 8 days. Comparison of rosuvastatin treatment in patients who had been taking rosuvastatin for a long time and those who were subjected to rosuvastatin for only the perioperative duration did not yield any significantly different results either. Lack of evidence of benefits of perioperative statin therapy in the present study may be due to the ethnic background of the subjects as well. Elaborate monitoring of plasma creatinine levels was conducted to analyze positive or negative effects of rosuvastatin therapy. It was concluded that contrary to other randomized small scale clinical trials, the present study proved that perioperative statin therapy did not prevent occurrence of postoperative atrial fibrillation and perioperative myocardial infarction. Cases of acute kidney

injury were also higher in the rosuvastatin group but no beneficial effects were observed in postoperative left ventricular function as well as incidence of serious cardiovascular adverse events.

Analysis of Rosuvastatin Therapy as the Most Effective Treatment for Dyslipidemic Patients

Epidemiological studies have proven that reduction in serum cholesterol leads to decrease in risk of cardiovascular diseases. Due to noncompliance or ineffective use of cholesterol lowering therapy, a significant number of patients fail to reach desirable blood cholesterol even after lipid lowering treatment or some even being untreated or sub optimally treated and thus being exposed to a unacceptably high risk of incidence of cardiovascular diseases like myocardial infarction. There remains a need to find the most effective, safe and well tolerated agent or combination of agents that can help the patient reach desirable LDL-C goals. At daily doses of 5mg-40mg, rosuvastatin mono therapy has been proven to be the most efficacious and helped reach 48-89% of patients their desirable blood cholesterol levels. Rosuvastatin is also a broad-spectrum drug as it has shown significant regression in atherosclerosis as well at a dose of 40mg. Mechanism of action of rosuvastatin is by inhibition of HMG-CoA reductase enzyme which catalyses an important rate limiting step in the synthesis of cholesterol in the body. In comparison to other statins, rosuvastatin has more binding sites for the enzyme due to which it is more effective than other statins. The pharmacokinetic properties of rosuvastatin differ with dosage and maximum plasma concentration is reached within 3-5 hours. Other factors like age, gender, ethnic background and renal impairment did not have any significant effect on the pharmacokinetics of rosuvastatin. LDL-C reducing effects STELLAR, the largest study to be conducted to compare efficacy of all statins found that 10mg dose of rosuvastatin was the most effective in treating hypercholesterolemia than atorvastatin (10mg), simvastatin and pravastatin (10, 20 and 40mg). The results of the PULSAR and POLARIS study also corroborated with the results of the STELLAR study. HDL-C increasing effects STELLAR study shows that HDL-C levels increased by 8-10% in patients subjected to rosuvastatin as compared to 2-6% by atorvastatin, 5-7% by simvastatin and 3-6% by pravastatin. However, the CARDS and FIELD showed that the HDL-C levels did not significantly increase in patients suffering through diabetes type 2. Rosuvastatin was found to reduce triglyceride levels the most effectively at a dose range of 5-40mg in comparison to other statins i.e. atorvastatin, pravastatin and simvastatin. Elevated levels of triglycerides were observed in dyslipidemic patients with type 2 diabetes, in turn increasing the rate of morbidity and mortality. The studies CORALL, ANDROMEDA and URANUS showed that rosuvastatin worked most effectively in decreasing LDL-C levels in subjects suffering from diabetes type 2 and dyslipidemia. Presence of metabolic syndrome increases the risk of cardiovascular diseases by manifold. The

MERCURY I and the COMETS study exhibited that even with presence of metabolic syndrome, rosuvastatin remained the most effective statin for lowering of blood cholesterol level. The results of the POLARIS study also corroborated with the same. COMETS, the first large study that took in consideration the presence of metabolic syndromes proved that when compared to atorvastatin 10mg, rosuvastatin 10mg produced a better response and lowered LDL-C and triglyceride levels and increased HDL-C levels. Results of sub group analysis of the MERCURY I and STELLAR studies also verified the results of the COMETS. Rosuvastatin mono therapy has been extremely effective in lowering LDL-C levels, but sometimes subjects fail to meet the required levels of LDL-C and triglycerides, that stems for the need of combination therapy. Rosuvastatin in combination with fenofibrate significantly reduced triglyceride levels in patients suffering from type 2 diabetes and hypertriglyceridemia. A combination of rosuvastatin with niacin also significantly increased HDL-C levels. Rosuvastatin therapy led to emergence of very little, mild to moderate adverse events, the most common ones being headache, pharyngitis, diarrhea and nausea. It was well tolerated in terms of renal activity as well. Overall, it is a very safe and tolerable drug with very few side effects. Rosuvastatin does not metabolize in the presence of CYP3A4 isoenzyme unlike the other statins and thus leading to less likelihood of drug interactions. The approved dose range of rosuvastatin is 5-40mg and it is orally administered. It was concluded that rosuvastatin was the most effective statin in not only reducing LDL-C, triglycerides and increasing HDL-C but also reduced the risk of cardiovascular diseases and was just as effective in patients suffering from other ailments like metabolic syndromes and type 2 diabetes and did not undergo any major drug-drug interactions as well.

Role of Rosuvastatin in Altering the Composition of Human Gut Microbes

Statins are the most prescribed drugs for lipid lowering and their primary mode of action for reducing LDL-C is by inhibition of HMG-CoA reductase. Changes in composition of gut microbiota has been associated with the incidence of wide range of systemic disorders. After proton pump inhibitors, statins rank second in altering the metabolic capacity of the microbes. Since no randomized control trials have been conducted, available information about this alteration is scarce. Statins are known to reduce the risk of *Clostridioides difficile* infection. The present study aimed to investigate the effects of statins in gut microbiota in 66 subjects from a randomized placebo controlled, double blind trial. Participants subjected to rosuvastatin showed enhanced microbial richness, but not significantly comparable to the placebo. There were no observable changes in other diversity measurements like phylogenetic diversity. Rosuvastatin had very little effect on abundance of bacterial taxa at genus level. Despite the lack of significant compositional changes at genus level, pharmacological and pharmacokinetic changes may induce

more observable and significant changes. To study changes caused by rosuvastatin, samples based on 16S rRNA were studied. Out of the top 20 altered genes, then majority were unrelated orthologs and 4 out of those 20 were involved in metabolic activities and cellular transport. Despite of changes in microbial functions, no significant changes were seen in peripheral blood and renal activity. Although rosuvastatin did not induce any significant changes in the gut microbes, it induced changes in metabolic activities and transportational processes and patients with a lower HDL/LDL ratio had an increase in pro atherogenic gut microbiota. Enhancement of microbial population has been associated to rosuvastatin treatment, however since the sample size of the present study is very small, it is inadequate to study broader results. Due to changes in metabolic activities of the microbes, there is a chance of the microbes become opportunistic and causing infections. The human gut microbes vary for different people giving them different pharmacological properties that differently affect drug metabolism and interaction with the immune system. The main limitation of the present study is the very limited sample size, due to which none of the findings can be confirmed. There is a requirement to conduct more randomized control trials with larger sample sizes to reach definitive conclusions. It was concluded that rosuvastatin treatment had a very limited effect on the human gut microbiota. The findings suggest that the statin treatment could have a relevant impact on gut microbes and provides a greater base for further studies.

A Retrospective Cohort Study Comparing the Effect on Lipid Profile Combining Exercise with Rosuvastatin vs Atorvastatin

The efficacy of rosuvastatin in lowering blood cholesterol was compared with the efficacy of atorvastatin by combining exercise. A retrospective cohort study of 282 patients was conducted wherein statin dosage was determined through prescriptions and exercise minutes/week (109.4 for atorvastatin and 106.7 for rosuvastatin) were decided with the help of exercise logs. Observable changes were seen LDL-C levels, triglycerides, HDL-C levels and functional capacity (6-minute walk test - 6MWT). Rosuvastatin was found to blunt the beneficial effect of exercise on LDL-C and total serum cholesterol level but no significant differences were found in triglycerides, HDL-C and functional capacity. Along the course of the 12-week rehabilitation program, no clinically meaningful changes were observed in rosuvastatin users in term of LDL-C and HDL-C levels. Amongst the atorvastatin users, there was significant increase in HDL-levels and decrease in triglycerides but other blood cholesterol parameters did not change much. For a desirable outcome of LDL-C and total cholesterol, exercise was more beneficial in the atorvastatin group and for enhancement in 6MWT results, exercise was more efficacious in the rosuvastatin group. The relation between type of statin prescribed and number of minutes of exercise was more useful in sensitivity analysis for LDL-C levels. A distinct

difference was observed in the effect of exercise between patients using rosuvastatin and atorvastatin. Rosuvastatin appeared to be more effective in lowering LDL-C levels and it may be attenuated by engaging in more exercise. This observation helps in relation to direct clinical significance as patients with different cardiovascular diseases are prescribed rosuvastatin and are advised to exercise more, both of which are individually known to decrease risk of cardiovascular diseases. The results of the present studies corroborate with the results of Toyama *et. al.*, who also did not observe any significant differences in triglyceride levels and functional capacity. The results of the present study also necessitate the requirement of more experimentation and exploration in this arena to study the mechanism of action of both drugs involved. Rosuvastatin has more hydrophilicity than atorvastatin due to which it is more efficacious in restricting the access of lipids in different cell types through passive diffusion. More studies also need to be conducted to study the mechanism of rosuvastatin in blunting the beneficial effects of exercise. Strengths of the present study include the examination of the beneficial effects of a statin-exercise combination in a sample pool of patients who don't essentially represent the general population but their health condition reflects several patients subjected to statin treatment. On the contrary, due to being a nonrandomized study, scientists were unable to reduce bias and there was no data available on the acute effects of rosuvastatin therapy. It was concluded that rosuvastatin usage could blunt the benefits of exercise on LDL-C and total cholesterol in comparison to atorvastatin.

Clinical evidences: extracted from clinicaltrials.gov

JUPITER - Crestor 20mg Versus Placebo in Prevention of Cardiovascular (CV) Events

NCT00239681

Results- After oral administration of rosuvastatin (Crestor) vs placebo it was found that there was unequivocal evidence that CRESTOR (rosuvastatin) led to reduction in cardiovascular morbidity and mortality amongst patients who were subjected to rosuvastatin as compared to placebo.

Platelet reactivity in patients with venous thrombosis who use rosuvastatin: a randomized controlled clinical trial

NCT01613794

Results- 94% of patients enrolled in the study had two valid PRU (platelet reaction units) measurements. The mean PRU value of rosuvastatin users was 609. Rosuvastatin was not found to affect platelet reactivity when arachidonic acid is used as an agonist in patients with a history of venous thrombosis.

AURORA: Crestor 10mg Versus Placebo in Subjects With End-stage Renal Disease (ESRD)

NCT00240331

Results- Patients suffering from end stage renal disease were not affected due to rosuvastatin administration and the probability of incidence of adverse events was also significantly small.

A randomized, double-blind clinical trial to evaluate the efficacy and safety of a fixed-dose combination of amlodipine/rosuvastatin in patients with dyslipidemia and hypertension
NCT03103256.

Results- The most decrease in systolic blood pressure was observed in the patients subjected to rosuvastatin + amlodipine group. The most decrease in the LDL-C levels was also observed in patients subjected to rosuvastatin + amlodipine group as compared to amlodipine and rosuvastatin being administered individually. Occurrence of serious adverse events was also not observed in any of the groups.

Crestor Versus Placebo in Subjects With Heart Failure
NCT00206310

Results- Rosuvastatin reduced the combined endpoint of cardiovascular death.
(Other results not posted)

A Study to Evaluate the Efficacy and Safety of Rosuvastatin in Children and Adolescents With Homozygous Familial Hypercholesterolemia (HYDRA)
NCT02226198

Results- Change in LDL-C values was significant in rosuvastatin users and occurrence of fatal adverse events was also negligible making it a safe drug with efficacy significantly more than that of placebo.

3.2 coQ10 (Ubiquinone)¹¹⁻²⁰

Sr. No.	Title of Paper	Year Published
1	Perspectives on therapy of cardiovascular diseases with Coenzyme Q10 (Ubiquinone).	1993
2	The effects of lifelong Ubiquinone Q10 supplementation on the Q9 and Q10 tissue concentrations and life span of male rats and mice	1998
3	Overview of the use of CoQ(10) in cardiovascular disease.	1999
4	Ubiquinone: Cholesterol's Reclusive Cousin	2003
5	Possible role of ubiquinone in the treatment of massive hypertriglyceridemia resistant to PUFA and fibrates.	2005
6	Enhancement of antibody production by addition of Ubiquinone-Q10.	2006
7	Discovery of ubiquinone (coenzyme Q) and an overview of function.	2007
8	Therapeutic use of coenzyme Q10 and Coenzyme Q10-related compounds.	2010
9	Plasma coenzyme Q10 concentration, antioxidant status and serum N-terminal pro-brain natriuretic peptide concentration in dogs with various cardiovascular diseases and the effect of cardiac treatment on measured variables.	2016
10	Coenzyme Q10: Clinical Applications in cardiovascular diseases.	2020

Overview of the Treatment of Cardiovascular Afflictions Using Ubiquinone (CoQ₁₀)

A deficient myocardial energy supply due to lack of substrates and/or critical cofactors and a low consumption efficiency of oxygen can be a typical final pathway in the development of myocardial diseases of different etiologies. A biological basis for using coenzyme Q10 as a treatment in heart disease was developed years ago by

Folkers and associates; however, this has been further reinforced by investigations of viable myocardial tissue from the author's series of 45 patients with different cardiomyopathies. High efficiency determination of myocardial tissue levels of coenzyme Q10 in patients with more advanced heart disease, lipid chromatography was considered slightly lower than in the milder phases of heart failure. In addition, in selected circumstances, the loss of myocardial tissue coenzyme Q10 may be substantially restored by oral supplementation. In almost two-thirds of patients demonstrated clinical development, which was more pronounced in those with dilated cardiomyopathy, in the author's Open Clinical Protocol Review of Coenzyme Q10 Therapy (100 mg daily). Double-blind placebo-controlled trials have certainly established that coenzyme Q10 has a role as adjunctive therapy in heart failure with positive effects on the clinical outcome, the patients' physical activity, and their quality of life. Positive effects went beyond and above the clinical status gained from therapy with conventional principles - like angiotensin-converting enzyme inhibitors. Potential clinical applications of CoQ10 have been evaluated for different cardiovascular and non-cardiovascular diseases. The cardiovascular diseases include: Congestive heart failure, Angina pectoris, Arterial hypertension, Prophylactic in anthracycline therapy and the non-cardiovascular diseases cover Mitochondrial myopathies, Muscular dystrophies, Periodontal disease etc. Regulated trials tend to be important on a multicentre basis in the environment of arterial hypertension, a subject not included in this survey. Over a 2-year period, two of the transplant patients were excluded from the waiting list due to clinical progress and a substantial growth in LV-EF percent. This improvement may have been accidental, but in end-stage patients approved in transplant programmes, this is quite rare. Additional regulated, double-blind trials of ischemic heart disease which continued to be needed as experimental and tentative clinical results indicate that CoQ10 is an appealing metabolic modifier. In bioenergetics, it is believed to have a crucial function.

The Impacts of Constant Ubiquinone Q10 Fortification on the Q9 and Q10 Tissue Fixations and Life Expectancy of Male Rodents and Mice.

Ubiquinone, in its reduced form Ubiquinol, has antioxidant properties by inhibiting lipid peroxidation both in model system and in biological membranes in vitro and in vivo. These observations have led to the insinuation that antioxidants such as Ubiquinol may play a role in the prevention of the aging process. It was also found that the tissue content of Ubiquinone also decreases during aging which may be partially responsible for the decline of energy metabolism. The experiments consisted of two studies, i.e., a survival study with rats and mice, and a concentration study with rats. At the age of two months, a total of 86 mice were randomly divided into two groups: receiving food with Q10 or receiving control food. The rats were of the Sprague-Dawley strain while the mice used were of the c57/B17 strain. Determination of plasma and tissue total Q9 and Q10

concentrations from the samples obtained from the concentration study was carried out using biochemical measurements. The tissue samples were stirred with an ultrasonicator. The Ubiquinol was extracted into 500 μ l of hexane for tissue samples; 700 μ l of 19:1 hexane-isopropanol solution was used for plasma samples. For rats, the average survival in the control group was 26.5 months and in the experimental group 24.3 months. For mice, the average survival times in the control and experimental groups were 28.1 and 29.0 months, respectively. There was no statistical difference in survival between the control and experimental group in the case of mice ($p=0.24$). However, there was a slight inclination towards longer survival in the control rats ($p=0.0727$). In macroscopic examination it was noted that 39 % of the experimental rats had renal stones compared to only 21% in the control rats. The difference was not statistically significant (Incidence Proportion Ratio, IPR 1.8, Confidence Interval(CI) from 0.78 to 4.17) Microscopic analysis revealed no difference between the two groups in renal cystic changes (IPR 1.16, CI from 0.50 to 2.70). Alveolar histiocytosis was seen in lungs in 31% of the control group rodents yet in just 9.7 % of the experimental group rats. However, this distinction was not measurably critical (IPR 3.21, 95 % CI 0.96 to 10.7). The Q10 concentrations were 2.6 to 8.4 times higher in the plasma and 3.2 to 6.6 times higher in the liver at all ages in the Q10 fortified group than in the control group. It was peculiar to note that the plasma and liver Q9 concentrations were also higher in the Q10 fortified group at ages 18 and 24 months than in the control group. In both the experiment and the control group, the plasma Q10 concentration increased with age up to 18 months and then decreased. The decrease after 18 months was significant in both the experimental and the control group: the p -values were 0.0269 and 0.0417, respectively. Both Q9 and Q10 concentrations in the liver increased with age up to 18 months and then decreased. Moreover, there was no remarkable change in the concentrations of Q9 and Q10 with age in the tissues observed through the study. No substantial distinction was found between the two groups (control and experimental) via the rat tissue histopathology. The fortification caused an increase in tissue concentrations of Q10 only in plasma and liver, but not in heart, kidney or brain tissue. It was also noted that the enhancement of Q10 caused an increase in liver Q9 concentration. The constant supply of Q10 had no consequential impact on the lifespan of either rats or mice.

Evaluation of the utilization of CoQ-10 in Cardiovascular Disease.

CoQ₁₀ supplementation corrects measurable deficiencies of CoQ₁₀ in blood and tissue. Exogenous CoQ₁₀ is taken up by CoQ₁₀ deficient cells and can be incorporated into the mitochondria. Considering the Japanese groundbreaking experiments in the late 1960's, there have been at least 15 randomized controlled trials involving a total of 1,366 patients with both primary and secondary forms of myocardial failure. In 1991, Rossi *et al.* showed significant

improvement in ischemic cardiomyopathy in 20 patients using 200 mg of CoQ₁₀ per day. The only controlled study to show no benefit in heart failure was published by Permanetter *et al.* in 1992. It is conceivable that many of the cardiomyopathy patients may have had poor absorption of the CoQ₁₀ and, therefore, had only marginal increases in their plasma Q levels. In 1993, Rengo *et al.* documented clinical and echocardiographic improvement in 60 patients treated with 100 mg of CoQ₁₀ for seven months. The largest controlled trial to date was published in 1993 by Morisco *et al.*, in which 641 patients were randomly assigned to receive either placebo or CoQ₁₀ at 2 mg/kg per day in a one year double blind trial. Before 1984, Dr Yuichi Yamamura released an outstanding analysis of all early Japanese trials. Several long-term studies have been carried out to assess the sustainability of this impact and the long-term wellbeing of the patient. The sustained gain and protection for idiopathic cardiomyopathy was found by Mortensen *et al.* in 1985 with 100 mg a day of CoQ₁₀. In 1990, 126 patients with dilated cardiomyopathy were published in the author's findings for six years, again with substantial long-term protection and lack of adverse effects. The largest clinical trial of cardiac defects of 2,664 patients treated with up to 150 mg of CoQ₁₀ a day was published by Baggio *et al.* in 1994. Diastolic dysfunction often precedes more advanced stages of congestive heart failure and is commonly seen in a wide spectrum of clinical syndromes. Administration of CoQ₁₀ resulted in improvement in diastolic function, reduced myocardial thickness, and an improvement in functional classification. Diastolic Dysfunction is easily identified by non-invasive techniques and appears to be readily reversible with supplemental Co Q10, authors say. The improvement occurs earlier and is more consistent than improvements in systolic function and occurs in the elderly as well.

Controlled trials in angina did not begin until the mid 1980's with the first publication by Hiasa in 1984. The treated patients showed an increase in exercise tolerance of one stage or greater in a modified Bruce protocol. No significant alteration in heart rate or blood pressure was observed with CoQ₁₀ treatment. The mechanism of action was related to a direct effect on myocardial metabolism, authors say. The prevention of QT-interval prolongation can be explained by an enhancement in myocardial bioenergetics with an improvement in sodium potassium ATPase function, they say. CoQ₁₀ may have no clinically relevant antioxidant function in terms of decreasing the oxidation of cholesterol. Supplementation with vitamin E alone resulted in an LDL which was more prone to oxidation as compared to the combination of CoQ₁₀ and vitamin E which increased the resistance to oxidation. The oxidation of LDL cholesterol is widely assumed to be of primary importance in the development of atherosclerosis. In the biosynthesis of CoQ₁₀, Harry Rudney was among the first to identify the significance of HMG-CoA reductase. 1990's Willis *et al.* revealed substantial depletion in Co Q10 tissue in the heart and liver of lovastatin treated rats. With a substantial loss of plasma and

platelets in humans, the CoQ 10 lowering effect of statins is now well established. The CoQ 10-lowering effect will be more pronounced as the "target" or "ideal" cholesterol level is gradually decreased and the risk for long-term adverse health effects will be increased. The concern about the long-term effects of statin-induced CoQ10 deficiency is heightened by the steadily rising number of patients hospitalized and the increasing number of patients hospitalized. In patients with proven hypertension, a propensity to lower blood pressure was observed by Nagano as far back as 1976. We postulate that CoQ10's blood pressure lowering effect may partially be an indirect effect, leading to a decrease in the adaptive high catecholamine state of hypertensive disease by enhancing diastolic function. In 1982 Tanaka *et al.* published the first controlled analysis, which measured the efficacy of CoQ10, which was carried out pre-operatively. Fifty patients underwent either placebo or CoQ 10 randomly at a dosage of 30–60 mg per day, six days before the surgery for removal of the cardiac valve. During the post-operative rehabilitation phase, the treatment group reported substantially decreased incidences of poor heart output. In 1996, Chello randomized 30 patients to receive 150 mg of oral CoQ10 for 7 days before aortic abdominal surgery, and a substantial reduction in peroxidative markers in the treated patients was reported. Oral supplementation CoQ10 typically seldom causes measurable effectiveness before a week. The mitochondrial ATP development core is an adroitly basic enzyme. Congestive insecurity was a paradigm for CoQ10's detectable blood and tissue deficiency, which increases myocardial efficiency when reversed. The beginning of therapeutic progress nearly typically takes one to four weeks and there is a further period of several months in the full clinical gain. CoQ 10 does not endorse the conventional organs-specific or disease-specific approach and needs to be reassessed and medical policy and procedure reconsidered.

Ubiquinone: Cholesterol's Remote Counterpart

The major source of ubiquinone is coenzyme Q10 (CoQ10). A set of diseases have reported lower blood and tissue levels of CoQ10. A benzoquinone nucleus and an isoprenoid side-chain are present in Coenzyme Q10 (CoQ10). CoQ10's biosynthesis is a multi-stage process that can be divided into three main stages. In the mitochondrial respiratory chain (MRC), the key function of CoQ10 is to serve as an electron carrier. This is also used to relay electrons freed from fatty acids complex III β -oxidation of the MRC. Protons from the mitochondrial matrix to the intermembranous region may also be moved, which may help to conserve energy at the binding site 2 of the respiratory chain. It was reported that CoQ₁₀H₂ is strongly related to vitamin E and serves to regenerate the vitamin's reduced (active) α -tocopherol type. In most tissues of the body, CoQ10 is present, mainly as ubiquinol (CoQ₁₀H₂), but in the brain and lungs, where CoQ10 predominates (67% and 65% of the sum, respectively) this may lead to a higher oxidative stress in these tissues. CoQ10 has been

reported in a wide range of disorders and conditions. It is uncertain to what extent a failure in energy metabolism and/or oxidative damage contributes to disease pathogenesis. CoQ10 biosynthesis is caused by a deficiency in mevalonate kinase (MK). Patients with this deficiency have mevalonic aciduria (MVA). MVA has a broad range of clinical symptoms, including psychomotor retardation, ataxia, cerebral atrophy and myopathy. As a heterogeneous category of diseases marked by morphological, biochemical and genetic defects of mitochondria, mitochondrial encephalomyopathies occur. Reports of somewhat reduced CoQ10 muscle levels in patients with mitochondrial encephalopathy may be associated with CoQ10 oxidative loss as a result of respiratory chain degeneration. Multiple organ failure in conjunction with hypothermia and lactic acidosis in the neonatal period suggests CoQ10 deficiency and prompt appropriate biochemical investigation. The high energy requirements of the heart make it particularly vulnerable to deficits in mitochondrial energy metabolism. This explains the high incidence of cardiomyopathy in patients with deficiencies of enzymes in the β -oxidation of fatty acids and/or the respiratory chain. Phenylketonuria (PKU) patients who avoid food rich in CoQ10 such as poultry, meat, soybean food products and nuts, may lead to a lower concentration of serum CoQ10 in these patients. Matsubara *et al.* reported lower serum CoQ10 in Parkinson's disease patients than in age-matched controls. Insufficient details were given of the treatment regimen of patients in the study. Anti-parkinsonian drugs such as deprenyl may have been used in those patients. Statins are HMG(Hydroxymethylglutaryl)-CoA reductase inhibitors of fungal or synthetic origin that are used to lower serum LDL- cholesterol in patients with hypercholesterolaemia. Some clinical studies have reported a diminution of serum CoQ10 after administration of the drug. In rats, statin treatment for 4 weeks and 6 months did not reduce the skeletal muscle CoQ10, but patient numbers were low in these studies. These myotoxic impacts were dose-related and can result from a deficiency in muscle CoQ10. HPLC connected to an ultraviolet (UV) or electrochemical (EC) detector is normally quantitated by CoQ10. The system is hindered by CoQ₁₀H₂'s volatility during the handling, storage and preparation of samples. Concentration of Plasma CoQ10 is strongly dependent on concentrations of serum lipids. It was proposed that serum lipid concentration should be standardized for plasma CoQ10. It is also stated that the serum level of γ -glutamyltransferase, a marker of liver injury, is associated with plasma CoQ10. Substantial evidences show that plasma CoQ9 comes directly from dietary consumption. No measurable human plasma amounts of CoQ9 have been identified. CoQ11 has been used as well, but it is not commercially available. As an internal standard, Diethoxy-CoQ10, readily synthesized from CoQ10, was proposed. Platelets, lymphocytes and fibroblasts are recommended as replacements for the intracellular CoQ10 status assessment. The use of CoQ10 in disease management has been of great concern. There is no commercial opportunity to finance research or perform

major clinical trials for pharmaceutical firms. Standardization of age-related, gender-specific and tissue comparison cycles will allow a more coherent approach to patient monitoring in the absence of a central reference laboratory within the UK.

Viable Aspects of Ubiquinone in the Medication of Extensive Hypertriglyceridemia Impervious to PUFA and Fibrates

The main objective of this analysis was to determine the effect of coenzyme Q10 (CoQ10) administration in patients treated with or in conjunction with fibrates or PUFAs. The inclusion criteria for the patients were TG constantly > 1000 mg/dl; familial history of hypertriglyceridemia; no personal history of cardiovascular disease; body Mass Index < 30 kg/m²; correct and stable dietary habits; absence of secondary causes of hypertriglyceridemia: mainly diabetes mellitus, alcoholism and chronic intake of glucocorticoids. Among the total of 86 selected patients, only 18 subjects were hyporesponsive to fibrates, PUFA and fibrates-PUFA association (arbitrarily defined as TG reduction less than 20%), and 15 of them accepted to participate in the study. Systolic and diastolic blood pressure was recorded using a standard mercury sphygmomanometer and a cuff of appropriate size, on the right arm with the patient in the seated position. Measurements were always taken by the same investigator in the morning before daily drug intake and after the subject was at rest for 10 min in a quiet room. Heart rate was monitored at each clinical visit and was measured after with the patient seated for at least 10 min. Medication compliance was assessed by counting the number of drug doses returned at the clinic visits. Plasma was obtained by centrifugation at 1000 g for 25 min at 4 °C and was assayed for TC and TG concentrations using enzymatic methods on a semi-automatic analyser. The interassay coefficient of variation for glucose was 3.0%. A Shapiro Wilk test was carried out to evaluate the distribution of the studied continuous variables. Because of the large range the TG value distribution, statistical analysis for TG levels was repeated after TG log-transformation. During the study, in any group of participants, no substantial improvement in eating habit or body weight was detected. Any treatment regimen did not detect any adverse drug events or major elevations of CPK and GOT/GPT. The reduction of uric acid and γ -GT levels ($P < 0.05$) was more successful than the PUFA in both classes. Coenzyme Q10 (Ubiquinone) is also a co-factor of the mitochondrial respiratory chain. Recently, it has been successfully associated to fenofibrate in the treatment of type 2 diabetic patients. The most relevant result in this study was the effect of CoQ10 on drug efficacy in previously drug resistant MHTG patients. In fact, the supplementation of CoQ10 induced a significant decrease in plasma TG during fenofibrate treatment, but not during the PUFA treatment. This effect was not observed in the control group, where patients adequately answered to PUFA, fenofibrate and the combined fenofibrate-PUFA treatment, nor when CoQ10 was administered alone to non-

responders. The explanation of this effect was not clear; however, it could be relevant to improve the vascular reactivity of this kind of patients. The Fibrinogen lowering effect of fenofibrate was already known, but generally associated with a decrease in PAI-1 plasma level, not observed in our study (maybe because of the large standard deviation of this parameter and the small patient number). The small patient sample was due to a very selected type of patients and to the rarity of patients not responding to fibrates and PUFA treatments. Another methodological bias was that the treatments were in consecutive order, so that some observed results might be underestimated due to the residual effect of the previous treatment regimen. In conclusion, even if the mechanism of action is not yet clear, a CoQ10 supplementation to fenofibrate treatment could improve the drug efficacy in previously resistant MHTG patients. This association seem to be even more efficacious in improving the global cardiovascular risk of hypertriglyceridaemic patients than that of high dosage of omega 3 PUFA with CoQ10.

Elevation of Immune Response Creation by Expansion of Ubiquinone- Q10.

About 17 medicinal Mabs in the United States are launched, lowering the cost of goods is one of the concerns of Mabs industrialization. Since efficiency explicitly has an impact on the cost effect. SANOMITTM Q10 was added to a culture medium (Q-Media) and it was found that it easily absorbed and incorporated into cells. The anchorage-dependent NS0 cell line was cultivated in 225 cm² T-flask. Viable cells and dead cells were counted by CedexTM using the trypan blue dye exclusion method. The released assay with ⁵¹Cr as previously reported has been observed with an antibody-dependent cell cytotoxicity (ADCC). Mab concentration was determined by Protein A HPLC. 8-OHdG concentrations were quantified using an ELISA (8-OHdG check) and glucose and Lactate concentrations were determined by biosensor YSI 2700. The cultures were inoculated with a density at least of 2×10⁵ cells/mL and cultivated until the decline phase at 37°C, pH7.1. It was found that SPR was enhanced in Q10/Tween-80 additive media supplemented with 50 micro mol/L. Whereas, Tween-80 additive media was not affected to SPR. It was also known that addition of Q10 to cell culture media promotes the growth of several cell lines, such as HeLa cell and murine fibroblast cell or bovine embryo cell. Q10 is a well known strong anti-oxidant. 8-OHdG is a well-known oxidative DNA damage as a marker. Q-Media supplemented with 500 micro-mol/L was expected to produce antioxidant effect, but no-effect for 8-OHdG concentrations tendency and cumulative cell density ensued. Higher L/G (lactate to glucose ratio) means glucose turn to lactate through pyruvate, hence energy efficiency is low. High concentration Q-Media supplemented with 160 micromol/L indicated slight decline of L/G. Potential of improvement in electron transport chain by Q-media was speculated. CHO and NS0 are the common host cell-lines for manufacturing of Mabs. Ratio of enhancement was

different between cell-lines, but SPR enhancement was shown in each cell-line by Q-Media. Q-Media did not affect biological activity of Mab, such as antigen binding activity and ADCC. Tease results indicated quality of Mab has no influence by Q-media, which is a well known high ADCC Mab production by YB2/0. Q10 was found to be the enhancer for Mab production. Q-Media greatly improved the efficacy of animal cell lines: Case I: 66.3 per cent, Case II: 28.8 per cent, Case III: 31.9 per cent without impacting the biological function of the antibody.

Detection of Ubiquinone (Coenzyme Q) and a Profile of its Ramifications.

The identification of Coenzyme Q as a compound was a result of complex probing of the mechanism of the biological energy conversion. In 1950, David Green at the Enzyme Institute, University of Wisconsin embarked on a major program to determine how the enzymes of the fatty acid oxidation and citric cycle oxidation were organized and how this contributed to energy coupling in oxidative phosphorylation. For this, around a dozen beef hearts were homogenized per day in a large blender followed by centrifugation. The supernatant was then centrifuged in a large industrial size sharples machine to sediment the mitochondria as a brown paste which were suspended in a sucrose phosphate buffer prior to freezing. This provided an easy source of mitochondria for the study. With a good supply of mitochondria available, Green instituted a program to systematically separate parts of the electron transport system to see how they interacted and how this interaction was related to ATP formation. According to theories of membrane structure at that time, the components of the electron transport would be bound to the surfaces of the mitochondrial lipid bilayer. This led to a consideration of the possible functional role of lipid. These experiments led to two considerations: first that the electron transport proteins were remarkably resistant to denaturation by hydrocarbon solvents which laid the ground work for the use of these solvents to extract coenzyme Q in studies of its activity. In a comparison between the cauliflower mitochondria and the beef mitochondria, it was found that the beef mitochondria had carotenoids but lacked Vitamin A which was verified by a negative Carr-Price reaction. The quinone discovered was found to have a broad absorption peak after the carotenoids at 400 nm as well as a small peak at 275 nm. The evidence that the 400-275 compound was a quinone led to consideration of substitutions on the ring to modify the quinone spectra to shift the peak to 275 nm. An assay was developed for Q275 function in succinoxidase by extraction of beef heart mitochondria with heptane to remove some of the coenzyme Q. Q275 was reduced when incubated with mitochondria and the quinol was oxidized by the mitochondria. However, these oxidation-reduction reactions were subdued by certain mitochondrial inhibitors. To determine the specificity of mitochondrial electron transport for coenzyme Q the Merck group synthesized all combinations of dimethoxy benzoquinones and it was found that only the 2,3 dimethoxy quinone analog could

restore succinoxidase after extraction of coenzyme Q. The essential role of coenzyme Q in mitochondrial electron transport was challenged on the ground that the rate of oxidation- reduction was slower than the other electron carriers such as cytochrome. This was countered by Klingenberg's (1968) review that there were 10 times as much coenzyme Q as other carriers. Hence, reduction of each molecule of Q would be slackened by the less abundant carriers. The groundwork for broader functions of coenzyme Q in membranes other than mitochondria was laid at this time when Ramasarma and coworkers showed that coenzyme Q was present in other cellular membranes. It later was shown to be essential for photosynthesis with a role in chloroplasts like coenzyme Q in mitochondria. The finding of an essential quinone in mitochondria naturally led to consideration of a quinone derivative as an intermediate in oxidative phosphorylation. If the oxidation and reduction of coenzyme was oriented across the membrane it would provide a way to generate a membrane potential by proton gradient generation across the membrane. It was noted that when coenzyme Q is reduced it takes up two protons which are released when it is oxidized. So, the energy conversion role of coenzyme Q was in the protonation and not in the electron transport function. It was found that only 2-3% of crystalline coenzyme Q was taken up in the blood. Further study of absorption led to the development of gel capsules which gave a high percentage of uptake and led to significant increase in coenzyme Q in the blood. For many years the target of coenzyme Q research was on its aspect of energy transduction in mitochondria. However, it became known that it was widely distributed in cell membranes and could execute antioxidant function and proton transport in other membranes. A high concentration of coenzyme Q in Golgi membranes was found and that it functioned in a non-mitochondrial electron transport was also sighted (Crane and Morre,1977). The discovery of coenzyme Q in all membranes brought on a concept of coenzyme Q as an important antioxidant. Coenzyme Q could contribute to the generation of reactive oxygen radicals which might contribute to destruction of membrane lipids or be responsible for hydrogen peroxide signaling. Evidences have verified that it functions as a proton transferring redox agent in acidification of lysosomes. Indication of therapeutic effects in diabetes (Hodgson et al., 2002), Encephalomyopathy or ataxia (Quinzii et al. 2006), Parkinsonism and Huntingtons disease (Shults, 2003; Beal, 2004; Ryu and Ferrante, 2005), and Cancer were recognized. The full extent of its diversity remains to be explored and the search for medical or nutritional application continues. The first successful application of coenzyme Q to a medical problem was in Yamamura's treatment of congestive heart failure. All animals, plants, and bacteria synthesize their own coenzyme Q so a typical vitamin deficiency was not found until recently. Several instances of mitochondrial deficiency disease have been related to coenzyme Q. A mutation in a gene necessary for coenzyme Q synthesis has recently been found to explain a

deficiency. Nonetheless, various queries about coenzyme Q in medicine, nutrition, basic biochemistry, antioxidant-prooxidant balance, mechanism of uncoupled protein action, and control of membrane fluidity remain to be investigated.

Remedial Utilization of Coenzyme Q₁₀ and Coenzyme Q₁₀- related Compounds and Structures

The elucidation for the medicinal application of CoQ10 is converged on its fundamental role in cellular bioenergetics and mitochondrial activity. This technique is improved because CoQ10 has an impressive safety record and is well tolerated over long periods with few side effects at high doses. The distribution of CoQ10 is not consistent between organs, or even between different parts of the same organ. The regulation of the distribution of CoQ10, however, is uncertain. In order to facilitate absorption by peripheral tissues and likely even to cross the blood-brain barrier (BBB), plasma CoQ10 concentrations need to be high. In comparison, for multiple tissues, the plasma level for absorption tends to be different. Dietary CoQ10's bioavailability is particularly important for neurodegenerative diseases where higher plasmas are needed for therapeutic purposes. Nanoparticulated and solubilized preparation of CoQ10 are the better delivery systems, and the reduced CoQ10 is also better than the oxidised form. Bioavailability of CoQ10 depends on the formulation, which implies that it is hard to specifically relate the rise in CoQ10 concentration to the doses used in specific therapies. During clinical trials, plasma levels of CoQ10 should be controlled to enable the analysis of treatment outcomes. Oral CoQ10 supplement can be a promising solution for reduced CoQ10-related diseases. Many patients suffering from CoQ10 genetic defects displayed clinical progress during oral CoQ10 supplementation supervision. In the management of these patients as well as using CoQ10 formulations, early diagnosis is of crucial importance and enables increased plasma development. The majority of positive results on neurodependent generative disorder therapy in clinical trials have not been adequate to the advantage of patients and clinical effectiveness findings in CoQ10 have been inconsistent on the whole. Unfortunately, several studies neglected to record levels of CoQ10 and hence the clinical reaction relationship to CoQ10 levels in plasma is not often distinguishable. Relevant data included drug dosage, CoQ10 formulation, treatment duration, disease severity and the timing of the intervention, indicating the need for large multi-centre, closely monitored double-blind placebo-controlled trials. The level of CoQ10 was tracked closely. The use of CoQ10 is controversial for statin-related myopathies. In low-intensity patients, it is recommended to use atorvastatin that does not suppress CoQ10 in muscles CoQ10 basal requirements. As a result, the inclusion of CoQ10 could be relevant in statin intolerant patients and elderly people with normally low concentrations of CoQ10 which may provide an alternative to halting therapy with these essential drugs. The recommendation of CoQ10 care

and CoQ10 controls plasma levels and therapeutic response is therefore, not unreasonable for patients suffering from symptomatic heart failure. Preoperative oral treatment with CoQ10 may also enhance the clinical result following heart surgery. Plasma level and its redox status may be established as an independent indicator of certain diseases like chronic heart disease mortality, FRDA (Freidreich's Ataxia) reaction to CoQ10, male infertility, diabetes and early-stage PD (Parkinson's disease) pathogenesis. CoQ10 has not been completely tested for its efficacy in the enhancement of resistance of cancer therapies. Greater randomized clinical studies are needed to assess the appropriate CoQ10 dosage in people with cancer. Idebenone is an emerging drug, especially with regard to FRDA, in certain neurological disorders. As the treatment only stabilised the ICARS (International Cooperative Ataxia Rating Scale) scores in the paediatric population, the age of intervention in an important factor in the effectiveness of the therapy. Besides, idebenone has a very distinct effect on different mitochondrial enzymes and its particular effects on various mitochondrial dehydrogenases should therefore be taken into consideration in its theral application. The development of a new antioxidant analogue to mitochondria CoQ10 like MitoQ could enhance the efficiency of CoQ10 by removing its low intake in the brain in particular. Many genes currently involved in CoQ10 biosynthesis have been cloned, but there is little information regarding the post-transcript mechanisms governing CoQ10 endogenous synthesis, particularly in progression or senescence. In the long term, it will be important to design therapeutic agents that improve the CoQ10 endogenous synthesis. The higher oxidative concentrations of CoQ10 were correlated with ageing, stress and inflammation and oral supplementing with CoQ10 may be a promising antioxidant approach for certain neurodegenerational conditions, asthma, cancer, muscle and cardiovascular diseases including oxidative stress. With the powder form of CoQ10 consumed only minimally, new CoQ10 formulations were produced, increasing bioavailability, nanoparticulation, solubilisation, emulated oil as well as powder preparation of CoQ10 were developed in order of decreasing the bioavailability. The exogenous CoQ10 was not collectible into plasmas and tissues after the cease-fire and the observed CoQ10 level of protection was 1200mg/day/person with no major harmful impacts on humans. CoQ10 inclusion has a positive cardiac operative effect and is recommended for patients who suffer from symptomatic heart failure, increases fatigue symptoms and dyspnea without any noticed side effects. In comparison, patients on breast cancer receiving CoQ10 reported lower levels of serum tumor markers and a decreased risk for cancer recurrence and metastases, which showed positive prognosis and treatment effectiveness. Although the findings are unsatisfactory, a major slowdown in early HD (Huntington's Disease) and PD functionality has also ensued in some trials. Idebenone, which is better absorbed by the intestines than CoQ10 and passes by BBB, exhibits a great therapeutic potential for FRDA therapy. A further

CoQ10 analogue, Mitochondrial intended MitoQ agent, decreases the oxidative in vitro cell redox status of PD and FRDA systems and avoids the deleterious effects of ischaemia / hypoxia in rat-isolated hearts.

Plasma Coenzyme Q₁₀ Focus, Cell Reinforcement Status and Serum N-terminal Supportive of Cerebrum Natriuretic Peptide Fixation in Canines with Different Cardiovascular Illnesses and the Impact of Heart Treatment on Estimated Factors

Under normal conditions, the antioxidant system of aerobic organisms successfully limits the deleterious effects of ROS in a state called redox homeostasis, which can be disrupted by an excess of ROS, a decrease in antioxidant defense, or a combination of both, causing a state of oxidative stress. There is growing evidence that oxidative stress substantially impairs the function of organs and has a major role in the etiopathogenesis of several diseases, including a broad range of cardiovascular diseases, in humans and other animals. In human medicine, emphasis has been put on the role of oxidative stress in different cardiovascular diseases and oxidative stress mitigation strategies. However, a decreased concentration of CoQ10 in plasma and the myocardium seems to be a consistent finding in cardiovascular diseases in humans. In humans and most mammals, including dogs, the predominant form of CoQ is CoQ10. It was surmised that CoQ10 and antioxidant levels (plasma TAC, erythrocyte SOD and whole blood activities of GSH-Px) in dogs with cardiac disorders are lower than in healthy dogs, that these variables are decreased as heart disease progresses; and that CoQ10 and antioxidant variables are higher in canine cardiac patients receiving cardiac treatment than in untreated patients. The dogs were considered healthy on the basis of history, clinical examination findings, and the results of hematologic and biochemical analyses. In addition, hematologic and biochemical analyses were performed to exclude dogs with concomitant noncardiac diseases. The written consent of the owners was obtained for the dogs' study participation. Blood samples for assessment of serum biochemical variables and NT-proBNP concentration, plasma TAC, plasma concentration of CoQ10, whole blood GSH-Px activity, and erythrocyte SOD activity were collected into tubes containing the anticoagulant lithium heparin. Blood samples for determination of plasma TAC and plasma CoQ10 concentration were centrifuged immediately after collection at 1,500 X g for 15 minutes at 4 °C. Aliquots of whole blood with heparin were prepared and immediately frozen at 80 °C until analysis. Immediately after blood sample collection, hemolyzed RBCs were prepared following the manufacturer's instructions of a kit used for erythrocyte SOD activity determination, and stored at 80 °C until analysis. For all dogs, plasma TAC, whole blood GSH-Px activity, and erythrocyte SOD activity were determined spectrophotometrically with an automated biochemistry analyzer and commercial kits. Results for plasma TAC were expressed as millimoles per liter of Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-

carboxylic acid) equivalents. Lipid standardized CoQ10 was calculated as the ratio between concentrations of plasma CoQ10 and serum total cholesterol and was expressed as milligrams of CoQ10 per millimoles of total cholesterol. Serum NT-proBNP concentrations in samples obtained from dogs with cardiac diseases and from healthy dogs were measured with an ELISA method. Kruskal-Wallis analysis followed by post hoc multiple comparisons were used to test for significant differences in all measured variables and age between each of the 3 groups of dogs with cardiac disease and the group of healthy dogs. A Mann-Whitney U test was performed to test for significant differences in serum NT-proBNP concentration between the dogs with cardiac disease that were or were not receiving cardiac treatment. Spearman rank correlation coefficient analysis was performed to determine the correlation between disease severity (ie, serum NT-proBNP concentration) and antioxidant variables (level of plasma TAC, whole blood GSH-Px activity, and erythrocyte SOD activity) or plasma CoQ10 concentration in dogs with different stages of cardiovascular diseases and in dogs with cardiac disease that were or were not receiving cardiac treatment. The healthy dogs in the control group were significantly younger than dogs in the ISACHC I, II, and III groups. Mean ages of the dogs in the 3 ISACHC groups did not differ significantly. Compared with the value for the healthy dogs, the median plasma TAC for the ISACHC I group was significantly lower. Median plasma concentration of CoQ10 and CoQ10 were not significantly different between dogs with cardiovascular disease and healthy dogs or among groups of cardiac patients (the ISACHC I, II, and III groups). With regard to serum NT-proBNP concentration, there was a significant, negative correlation with plasma CoQ10 concentration and with plasma CoQ10 in the group of dogs receiving cardiac treatment. Treatment had no effect on SOD activity in dogs with cardiac diseases. The effect of cardiac treatment might be ascribed to the antioxidant properties of some cardiac medications used. The study had some limitations including the lack of sample size determination. Nonsignificant results may be the result of insufficient statistical power. The lower plasma CoQ10 concentrations were likely associated with greater severity of CHF. Further investigation into the possible effects of treatment on antioxidant variables is needed.

Therapeutic Uses of Coenzyme Q₁₀ in Cardiovascular Ailments

This inventory caters to the prospects of the utilization of CoQ10 in future with an overview of its effect on the health and quantity of life of patients in renal, cardiovascular and statin intolerant patients. Coenzyme Q10 (CoQ10) is an organic molecule that was identified for the first time by Frederick Crane of Wisconsin (USA) in 1957. CoQ10 concentration is particularly high in organs such as the kidneys, heart, and liver because they need it as an efficient energy transfer molecule supporting their high metabolic rate. 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. In vitro, it inhibits the oxidation of low-density lipoprotein more than other antioxidant molecules, such as α -tocopherol or β -carotene. Fatty fishes (salmon, sardin, and tuna), soya, spinach, and nuts contain high levels of this cofactor. Some factors may reduce plasma concentrations of CoQ10, such as aging, genetic factors, drugs (e.g., statins), certain diseases. supplementation could be efficient in the prevention and/or treatment of a number of pathogenic disorders.

A brief overview of the action mechanism and the scientifically confirmed effects and the most important note of tolerability were reported for each possible therapeutic indication. CoQ10 tends to have an effect on the endothelium directly, inducing blood pressure and vasodilations. This effect is connected with its ability to increase bioavailability of nitric oxides and induce vasodilation, especially in hypertension patients. When the blood pressure on the target is on, the CoQ10 supplement should not affect blood pressure in patients with type 2 diabetes mellitus and ischemic left ventricular systolic failure. On the whole, the antihypertensive role of CoQ10 in patients remains uncertain, despite some encouraging data. Main effect of CoQ10 on plasma lipids seems to be the increased LDL resistance to oxidative stress in healthy adults. In an RCT (Randomized Controlled Trial), 101 dyslipidemic subjects without taking any lipid-lowering drugs were administered 120 mg CoQ 10 or placebo daily for 24 weeks. At the end of the study, Co Q10 supplementation mildly reduced TG ($p = 0.020$) and LDL-C ($p < 0.001$) and increased apolipoprotein (Apo)A-I. Overall, the effect was quantitatively small and its clinical relevance has yet to be demonstrated. A variety of cardiovascular disorders were tested to determine their effect on the self-perceived quality of life, the instruments and, at times, clinical findings. CoQ10 deficiency could then play an etiopathogenic role in the development and progression of Heart Failure (HF). The Q-SYMBIO multicentre, randomized placebo-controlled trial was used to assess the impact of the daily intake of CoQ10 on total mortality. It has been shown that the administration of CoQ10 reduces mortality, improves exercise capacity and reduces MACE (Major Adverse Cardiac Events) rate. However, no significant difference was observed in the endpoints of left ventricular ejection fraction (LVEF) between the "active group" and placebo. The diversity of plasma concentrations of this molecule are extremely variable in relation to pharmaceutical form and administered dosages but were reported in few RCTs. Treatment with CoQ10 in HF could prevent myocardial cell damage and could restore tissue CoQ10 deficiency. CoQ10 is an ATP-sparing agent and regenerable antioxidant. In a recent RCT of 55 patients with LVEF $< 50\%$ after AMI (Acute Myocardial Infarction), 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. CoQ10 administered early after AMI

may be protective against left ventricular remodelling. However, long-term RCTs are needed to confirm preliminary data. Patients of Atrial Fibrillation (AF) treated with CoQ10 were significantly less likely to develop ventricular arrhythmias. 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). Statin-associated myopathy pathogenetic mechanisms are still not fully understood. Statins inhibit hydroxyl-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate limiting enzyme that is essential for CoQ10 biosynthesis. No study has yet been designed to demonstrate that CoQ 10 supplementation could prevent statin-related myalgia. However, it has been clinically proven that CoQ10 supplementation could improve self-perceived fatigue in healthy subjects, in obese patients, and in patients affected by fibromyalgia. CoQ10 is a molecule with relatively high molecular weight (MW = 863) and is insoluble in water. Most of the CoQ10 integrated is eliminated through the faeces and only a fraction of that supplement reaches the blood and thus the tissues and organs. The key to effective supplementation is therefore the improvement of its bioavailability. The absorption efficiency is well known to be dose dependent and occurs through a "simple passive facilitated diffusion" process. The results of pharmacokinetic studies conducted using deuterium-labeled CoQ10 demonstrated slow absorption in the gastrointestinal tract ($T_{max} = 6$ h). CoQ10 exerts many mild positive effects on different tissues and metabolism. U ubiquinol form is the most available compared to ubiquinone. The improvement of bioavailability with CoQ10 + β -cyclodextrins and with ubiquinols have already been demonstrated in humans, with satisfactory results. Most of the orally supplemented CoQ10 is eliminated via faeces. In order to improve the cardiac health in patients with coronary heart disease and heart failure, scientific data confirms the inclusion of large doses of bioavailable-CoQ10 (always 200 mg/day), partially modulating many hazards for certain conditions and partially acting directly on myocardial cellular metabolism. Long-term RCTs are also needed for a significant number of patients and for CV diseases to validate and better understand the effectiveness and safety profile of this molecule.

Clinical trials: extracted from clinicaltrials.gov

Firefighter Aged Garlic Extract Investigation With CoQ10 as a Treatment for Heart Disease (FAITH) NCT00860847

Patients randomized to placebo had a greater Agatston score change (44.8% greater) than patients randomized to oral Aged Garlic Extract (AGE) and Coenzyme Q10. No significant secondary outcome measure data was reported.

Coenzyme Q-10 and Pulmonary Arterial Hypertension NCT01148836

After taking CoQ-10 for 3 months, Left Ventricular End Diastolic Volume decreased by 13.5% , Right Ventricular Outflow increased by 16.3%, Right Ventricle Myocardial

Performance decreased by 22.22%, Tricuspid Regurgitation Grade decreased by 14.28%, Right Atrial Pressure decreased by 20%, Haemoglobin increased by 3.42%, Hematocrit increased by 1.82% in the RBCs, Mean Corpuscular Hemoglobin increased by 3.6%, RBC distribution width decreased by 3.33% and no alterations were observed in the volume of RBCs of the pulmonary hypertension subjects analyzed for the study.

Coenzyme Q10 as a Symptomatic Treatment in Parkinson's Disease

NCT00180037

No study results were posted for this clinical trial.

Coenzyme Q10 in Relation to the Antioxidative Vitamins, Oxidative Stress and Inflammation in Coronary Artery Disease Patients During Statin Therapy.

NCT01424761

No study results were posted for this clinical trial.

3.3 Rosuvastatin with cq10²¹⁻²⁸

Sr. No.	Title of Paper	Year Published
1	Decreased ubiquinone availability and impaired mitochondrial cytochrome oxidase activity associated with statin treatment	2009
2	Role of coenzyme q10 and statins in heart failure: the dog that didn't bark	2010
3	A significant increase in Hdl-c, rosuvastatin combined with regular exercise preserves cq10 levels in patients with coronary artery disease	2011
4	Low cq10 levels, unaffected mitochondrial ATP synthesis in children with familial hypercholesterolemia upon the use of rosuvastatin	2011
5	Genetics of the coenzyme q10 pathway and rosuvastatin-induced muscle effects	2011
6	A systematic review and meta-analysis of placebo-controlled trials on statin therapy and plasma coenzyme q10 concentrations	2015
7	To Ameliorate Trastuzumab Cardiotoxicity by targeting proinflammatory cytokines, oxidative stress, TGF-β1 and STAT-3 by Rosuvastatin and Ubiquinone.	2017
8	Standard meta-analysis and bayesian network analysis on efficacy of statin treatment based on cardiovascular events in elderly patients	2020

Decreased ubiquinone availability and impaired mitochondrial cytochrome oxidase activity associated with statin treatment: 2009

As statins are inhibitors of the enzyme 3-hydroxy3-methylglutaryl-coenzyme A (HMG-coA) reductase, a rate-limiting enzyme of cholesterol biosynthesis pathway in turn results in mitochondria dysfunction by affecting the electron transport chain. The side effects of this statin treatment also included myotoxicity, hepatotoxicity and rhabdomyolysis in fewer cases (Thompson *et al.* 2003; Farmer and Torre-Amione 2000; Weber 2001). These side effects are due to the blockage of an important precursor molecule for various other compounds such as steroid hormones, protein prenylation and ubiquinone (Hargreaves

et al. 2005). As ubiquinone is a part of electron transport chain and helps in oxidative phosphorylation, deficiency due to statin therapy causes various complications similar to the inborn effects of metabolism. Of two patients with myopathy, one was treated with simvastatin (40mg/day) and cyclosporine and the other was given simvastatin (40mg/day) and itraconazole. The skeletal muscle biopsies from the patients 1 and 2 were found to have decreased complex IV activity. The determination of ubiquinone was done using HPLC analysis of samples from human skeletal muscles, blood mononuclear cells and primary rat astrocytes using UV detection at 27nm. The complex II+III and complex I activities were within reference limits. The results indicated a positive correlation between the statin treatment and reduced ubiquinone levels and also loss of ETC IV activity. The present study was insufficient to determine the reason for reduction of ubiquinone level and complex IV activity occurrence is coupled with the blockage of MVA pathway by statins or the unavailability of a necessary precursor leading to the loss of other. Bruckert *et.al.*, (2002) concluded that treating hypercholesterolemia with statins are more effective.

Role of coenzyme q10 and statins in heart failure: the dog that didn't bark- 2010

CQ10 is an important cofactor that acts as antioxidant inside mitochondria. 3-hydroxy3-methylglutaryl-coenzyme A (HMG-coA) reductase is a rate limiting enzyme in the synthesis of CQ10 pathway and inhibition of this enzyme by statins may cause myopathy and also increase cases of heart failure. Many articles have shown the adverse effect of statin use on cardiac related risks. And avoiding statins and supplementing CQ10 having a beneficial effect. The data obtained from the Controlled Rosuvastatin Multinational Study in Heart Failure study concluded that the low levels of CQ10 had a large impact on heart failure events and can be used as an important biomarker. On contradiction to this, Soukoulis *et.al.*, stated that 'the efficacy and safety of micronutrients such as CQ10 in heart failure remains unproven and continues to be a subject of debate'. Further studies by Marcof *et.al.*, on the systematic review on depletion of CQ10 and myopathy induced by statin had no strong evidence to prove the therapeutic benefits from supplementation of CQ10.

A significant increase in high-density lipoprotein cholesterol, rosuvastatin combined with regular exercise preserves coenzyme q10 levels in patients with coronary artery disease: 2011

Patients with coronary artery disease (CAD) often suffer from low Coenzyme Q10 levels and the current study focuses on increasing or preserving coenzyme Q10 level as it is a beneficial strategy. Though statins inhibit the biosynthesis of coenzyme Q10 but a combination of statins with coenzyme Q10 supplementation increases high-density lipo-protein cholesterol (HDL-C) levels compared to statins alone. Regular exercise and statins are known to increase HDL-C levels and the combination also could help further reduce the residual cardiovascular risk. 28 CAD patients

were selected randomly and the study was performed by dividing them into two groups. One group was administered with Rosuvastatin at doses from 2.5 to 20 mg/day and the other group with atorvastatin from 10 to 40 mg/day without any other lipid-lowering drugs to lower low-density lipoprotein cholesterol (LDL-C) levels. The patients were strictly instructed to perform daily home exercise by a registered exercise rehabilitation instructor for 20 weeks. In CAD patients, rosuvastatin in combination with regular exercise showed significant results by preserving coenzyme Q10 levels along with increase in HDL-C levels than atorvastatin. Present article showed there were no significant difference in the two groups selected for the study. And also in both the groups no patients were identified having other cardiovascular drugs, analgesics, dietary and vitamin supplements. The baseline lipid profile, serum ubiquinol and cardiac function on echocardiography were not significantly different between the two groups. During the study, both the statins were well tolerated, and they significantly decreased LDL-C levels, the rosuvastatin group showed a 30% increase in HDL-C levels and an increase in apolipoprotein A1 along with the preservation of serum ubiquinol levels. No correlation was seen between the change in HDL-C levels and exercise intensity. Serum ubiquinol decreased significantly in the atorvastatin group, but not in the rosuvastatin group. Furthermore, the change in ubiquinol levels correlated significantly and positively with the increase in apolipoprotein A1 and HDL-C. The study demonstrated that there was a significant increase in HDL-C levels along with preservation of coenzyme Q10 in the patients suffering from coronary artery disease when treated with rosuvastatin in combination with regular exercise, compared to atorvastatin. In addition to increase HDL-C levels, a well-established strategy to reduce cardiovascular events is through the reduction of LDL-C levels by means of statins which reduces the chances of residual cardiovascular risk. Unlike atorvastatin, rosuvastatin- a hydrophilic statin helped in preserving serum ubiquinol levels as it had very minute effects on HMG-CoA-mevalonic acid pathway. As it was not a potential inhibitor of CoQ10 production, it helped to synthesize ATP for cellular mitochondrial respiration with the help of regular exercise for a long term. The study on precise mechanism of action of hydrophilic statin and increase in HDL-C needs to be further investigated.

Low coenzyme q10 levels, unaffected mitochondrial atp synthesis in children with familial hypercholesterolemia upon the use of rosuvastatin- 2011

Statins are widely prescribed to prevent cardiovascular diseases in at-risk patients and is highly recommended for children with Familial Hypercholesterolemia. Although side effects like myalgia and fatigue are reported in a small proportion of the patients, statins are remarkably well tolerated. HMG-CoA reductase inhibition by statins helps lower the levels of plasma total cholesterol and low-density lipoprotein cholesterol. HMG-CoA reductase is also involved in the coenzyme Q10 biosynthesis which is an

electron carrier mitochondrial ATP synthesis. The reduced form of coenzyme Q10 acts as an anti-oxidant as well. Hence, statin therapy might reduce energy metabolism and reduce cellular anti-oxidant capacity. To study the true effects of statin on coenzyme Q10, effect of rosuvastatin therapy in children with familial Hypercholesterolemia is studied. Children of age 10-17 with heterozygous FH were subjected to a two phase study: a double blind, placebo controlled phase where patients were randomized to either placebo or 5, 10 or 20mg of rosuvastatin. A 40-week open label phase where LDL-C concentration of 110mg/dL was achieved through titration of rosuvastatin. Blood samples were collected after an overnight fasting and after rosuvastatin treatment and stored with EDTA at -80°C. Plasma and PCMBs Coenzyme Q10 level, mitochondrial ATP synthesis level were measured. Primary outcome was to measure the change in coenzyme Q10. And if found outside range (37-103), Pearson co-relations were made with CPK, ALT, AST, mitochondrial ATP synthesis, plasma total cholesterol and low-density lipoprotein cholesterol levels. There is evidence to suggest a decrease in the co-enzyme Q10 level but no decrease in the level of mitochondrial ATP biosynthesis. 17 of the 29 samples from patients were assessed for mitochondrial ATP synthesis level. 5 patients with placebo, 9 with 5mg, 7 with 10mg and 8 with 20mg of rosuvastatin were treated. In the open phase, max dose was administered for a mean period 29 weeks. No trend for a dose-related effect of rosuvastatin on PBMC CoQ10 level was observed. No correlation between changes in PBMC CoQ10 level and changes in CPK, ALT, or AST level for CoQ10 level outside range. For the mitochondrial ATP biosynthesis, no significant change was observed from the baseline. The corrected plasma CoQ10 levels are the same as the baseline results. Total cholesterol and LDL-C levels were significantly decreased but no change in HDL-C. Correlation was observed between Plasma TC, plasma LDL-C and CoQ10 enzyme level. For mitochondrial ATP synthesis to decrease, CoQ10 levels must fall below a threshold and in the study, there is evidence to suggest that statin treatment does not decrease the CoQ10 levels enough to reduce the mitochondrial ATP synthesis. The decrease in the CoQ10 levels in the plasma is due to the reduction of the plasma lipoproteins. Children of age 10-17 with heterozygous FH were chosen because they were clinically healthy otherwise. This reduces confounding by comorbidity. Also, the recommended age to start statin treatment is age 8. In this study decrease in CoQ10 levels were observed by the end of 40 weeks but no reduction in the mitochondrial ATP synthesis. There is data suggesting myotoxicity due to statin treatment but it is scarce and contradictory. Lack of statistical power due to less subjects and few subjects dropping out, resulted in no placebo comparison and no dose response trend was possible. Rosuvastatin is a hydrophilic statin, different results can be expected with lipophilic statins.

Genetics of the coenzyme q10 pathway and rosuvastatin-induced muscle effects: 2011

An evaluation on the study by Avis *et al.*, the impact of rosuvastatin treatment on coenzyme Q10 (CoQ10) status in children with heterozygous familial hypercholesterolemia. In children with FH, though the reduction in CQ10 without affecting mitochondrial ATP synthesis was an important finding obtained, the mechanism was found to be insufficient to induce muscular intolerance. Hence the contradiction of no improvement in muscle tolerability even after supplementing CQ10 was a major concern. The muscle side effects are triggered by statins is also associated with the CQ10 pathway. In children with FH, each statin should be studied in detail to analyse the CQ10 involvement in putative muscular intolerance.

A systematic review and meta-analysis of placebo-controlled trials on statin therapy and plasma coenzyme q10 concentrations: 2015

A study on the relation between statin therapy and reduction of plasma coenzyme10 as most mitochondrial dysfunction is due to the deficiency of CQ10. Fixed-effect or random-effect models of I2 statistics were meta-analysed, a reduction in plasma CQ10 followed by treating with statins were conducted for 8 placebo-controlled treatments. The impact of the statin therapy duration, change of LDL-C in plasma concentration, and also concentration of CQ10 at baseline treatment were assessed by a weighted random-effects meta-regression using unrestricted maximum likelihood model Comprehensive Meta-Analysis (CMA) V2 software. From the results obtained by studying 8 placebo-controlled treatments, there was a significant reduction observed in plasma CQ10 concentration because of statin therapy. It was supported by the conclusion given by Sirvent *et.al.*, (2008) as the precursor is inhibited by the statin resulting in decreased mevalonic acid production and thus ubiquinone. This statin induced CQ10 also results in onset of diabetes. As there is interference with the complexes of electron transport chain in mitochondria in turn inhibiting the synthesis of geranyl-pyrophosphatase which is an important precursor of CQ10. This may result in mitochondrial impairment in pancreatic beta cells.

To ameliorate trastuzumab cardiotoxicity by targeting proinflammatory cytokines, oxidative stress, TGF- β 1 and STAT-3 by Rosuvastatin and Ubiquinone

The study aims to evaluate the possible enhancing effects of rosuvastatin and/or ubiquinone on cardiotoxicity induced by trastuzumab and its mechanism of action in mice. Trastuzumab is a monoclonal antibody used in treating breast cancer, as it acts as both inhibitor of proangiogenic factors and enhancer of antiangiogenic factors thus suppressing angiogenesis. But the major drawback is the feasible progress of cardiotoxicity. Rosuvastatin being a member of statin, possess pleotropic effects that is used to treat hypercholesterolemia and also reduces cardiac risks. Ubiquinone, a fat-soluble substance acts as both antioxidant and anti-inflammatory agent inhibit the expression of the proinflammatory cytokines such as tumour necrosis factor alpha (TNF-a), interleukin-1 beta (IL1b) and IL-6

(Mirmalek *et.al.*, 2016). 120 mice were divided into 6 equal groups including control. TRZ group; TRZ + carboxymethyl cellulose group; TRZ + rosuvastatin group; TRZ + Ubiquinone group and TRZ + rosuvastatin + Ubiquinone group. Serum creatine kinase, lactate dehydrogenase, troponin I and N-terminal pro-B-type natriuretic peptide, tissue malondialdehyde (MDA), catalase, glutathione peroxidase, interleukin 6, transforming growth factor beta-1 and signal transducers and activators of transcription-3 (STAT-3) were determined. Along with determination of various factors, echocardiography was performed. Histopathological, immunohistochemical and electron microscopic examination were performed for different parts of heart. The antioxidant activity of the enzymes were suppressed by TRZ and increased MDA production thus having a possible cardiotoxicity effects as there was a considerable increase of reactive oxygen species. Compared to TRZ- treated group, the administration of RSV and ubiquinone had a beneficial effect in increasing the antioxidant activity thereby reducing the MDA levels and promoting the growth of cardiac function biomarkers. Both RSV and ubiquinone administration triggered the expression of STAT-3 compared to TRZ- treated group. Nuclear factor kappa B (NF-kB) is a protein complex that controls DNA transcription, production of pro-inflammatory cytokines and cell survival (Zhang *et. al.*, 2015), is inhibited by both RSV and CQ10. The combined effect of RSV and CQ10 had a significant effect on TRZ-induced cardiotoxicity in mice than usage of individual drugs. This is due to the preservation of antioxidant effect and anti-inflammatory properties by RSV and CQ10 combined action in mice. The morphology of cardiomyocytes were also preserved by the combined action of the drugs.

Standard meta-analysis and bayesian network analysis on efficacy of statin treatment based on cardiovascular events in elderly patients

CVD is one of the leading causes of mortality and high LDL content is a major risk factor especially in the elderly population (age 65 years or higher). Statin is widely prescribed to reduce the level of LDL to prevent CVD. Due to the age-related changes in the pharmacokinetics of elderly population, very limited number of studies exist. Meta-analysis of previous studies lacks certain aspects like assessment of quality levels, recommendations. In another study a comparison between statins to provide rankings was not established which is crucial. Current study comprises of a Bayesian network analysis and a standard meta-analysis to summarize the effectiveness of the use of statin in the elderly population. RCTs for CVDs were searched in MEDLINE, Embase, and the Cochrane Central database. Inclusion criteria includes age, comparison of statin with control and other statins, outcome: primary endpoint CVD, secondary end point all-cause mortality. Exclusion criteria includes overlapping information, review articles, size less than 100, follow up period 6 months or less. 2 or more authors extracted the data, assessed the quality of the study,

reviewed the inclusion criteria. RevMan software v 5.1 and STRATA software v 15.1 was used for statistical analysis. Heterogeneity was investigated using Q statistic and Trial Sequential Analysis was used to check reliability. Aggregate Data Drug Information System (ADDIS) v 1.16.5 for Bayesian network analysis, Markov Chain Monte Carlo (MCMC) for ranking the probability of each treatment group and SUCRA for probability of each outcome in each treatment in the network. 2167 articles were identified of which 1438 were eliminated. In 13 trials effects of statin in preventing the cardiovascular events were studied and Atorvastatin 80mg proved to be most effective. 11 trials regarding all-cause mortality comparing different statins had no significant difference among statins. 11 trials on cardiovascular mortality also found no significant differences among statins for primary prevention and in 4 trials 80mg atorvastatin was most effective for secondary prevention. From 7 and 4 trials, no significant difference was observed for secondary prevention and primary prevention of myocardial infarction. From 7 trials, 80mg atorvastatin was most effective for secondary prevention of revascularisation and no reliable results for primary prevention. For secondary prevention of stroke, no significant difference was found between statins and statins failed to prevent stroke. TSA suggests the data on secondary prevention were reliable except myocardial infarction. Data for primary prevention was not reliable since z-line did not cross the conventional and trial sequential boundary. Heterogeneity sensitivity revealed that there was statistically significant reduction for stroke in primary prevention and myocardial infarction in secondary prevention. Due to comorbidities, the elderly population are not part of trials for statins in prevention of CVDs. This meta-analysis indicates that the elderly population could significantly benefit from statin therapy especially, secondary prevention which is supported by TSA and heterogeneity sensitivity test which eliminated high bias studies. However, prevention of risk of stroke and myocardial infarction had varied results. This could be due to different types in MI and stroke. A similar study to the current one concluded that statins have therapeutic potential in preventing ischemic strokes and transient ischemic attacks and no significant difference was found between statins. The inhibition of CYP3A4BY by drugs can increase plasma atorvastatin leading to morbidity, muscular toxicity or rhabdomyolysis. Current study supports the feasibility of prioritizing a drug over another, especially for elderly. Late prognosis and early treatment will prove beneficial. More studies are necessary on effects of statins for primary prevention. TSA stands as a strong point for this study. Due to lack of data sub group analysis on LDLC reduction was not performed and to an extent, heterogeneity was not resolved completely. Evidence suggests statins reduce mortality related to CVD. However, primary prevention is low. There are differences among statins in secondary prevention.

Clinical evidences: extracted from clinicaltrials.gov, PMC and JACC

The effect of Q10 and Selen supplementation on muscular adverse events in statin therapy NCT00113477

Statins are well known inhibitors of HMG CoA reductase enzyme, thus reducing the cholesterol synthesis and several other compounds of mevalonate pathway, like CQ10. Though statins help to reduce intracellular cholesterol by increasing the number of the LDL-C receptors in the liver thereby increasing the metabolism of LDL-C, the depletion of CQ10 has adverse effects such as reduction of high energy phosphates, anaerobe metabolism and mitochondrial dysfunction. One of the study reported the reduction of CQ10 in the blood-platelet during statin therapy. Several reports have shown supplementation of CQ10 resulting in diminished muscular adverse events.

Coenzyme Q10 in older athletes treated with statin medication NCT01026311

The study showed there were no uniform effectiveness of CQ10 supplementation in elderly athletes. The study showed a trial of 200mg of CQ10 helps in low toxicity risk and promising treatment for statin induced-myopathy in elderly population. In the detailed review by Marcoff and Thompson, due to insufficient evidences recommended further studies on supplementation of CQ10 for statin-induced myopathy.

Does coenzyme Q10 supplementation reduce muscle pain caused by statins NCT02415114

The study showed 50mg of CQ10 supplementation daily for a period of 30 days reduced muscle pain in 75% of patients with statin-induced myopathy. The study mainly focused on the clinical effects of CQ10 supplementation but not on its mechanism or anti-inflammatory and anti-oxidative effects.

The role of coenzyme Q10 supplementation with statin drug use and chronic diseases DOI: 10.4172/2329-8731.1000157

A randomized trial of CQ10 supplementation to patients with statin myopathy demonstrated the reduction of the intensity of muscular pain and significant enhancement of antioxidant activity of enzymes. Studies on rat model showed that CQ10 supplementaion reduces toxicity of statins along with protecting hepatocytes. Pek et.al, (2016) stated that ubiquinol supplementation at the microRNA level may provide beneficial change to CQ10 liver deficiency

The effect of statin treatment on circulating coenzyme Q10 concentrations: an updated meta-analysis of randomized controlled trials DOI: <https://doi.org/10.1186/s40001-018-0353-6>

The study on randomized control trials evaluated on 1776 participants showed a significant decrease of circulating CQ10 levels during statin therapy and was independent of the duration of treatment, intensity and statin solution. A potential mechanism for statin-associated muscle symptoms was provided by the study along with suggesting

supplementation of CQ10 as a complementary approach for the condition.

3.4 Cq10 with Rosuvastatin ²⁹⁻³⁷

Sr No.	Name of the Paper	Year published
1	Rosuvastatin: Characterization of Induced Myopathy in the Rat	2008
2	Coenzyme Q10, Rosuvastatin, and Clinical Outcomes in Heart Failure: A Pre-Specified Substudy of CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure)	2010
3	Rosuvastatin, inflammation, C-reactive protein, JUPITER, and primary prevention of cardiovascular disease – a perspective	2010
4	Effect of rosuvastatin on plasma coenzyme Q10 in HIV-infected individuals on antiretroviral therapy	2016
5	CoQ10 Augments Rosuvastatin Neuroprotective Effect in a Model of Global Ischemia <i>via</i> Inhibition of NF- κ B/JNK3/Bax and Activation of Akt/FOXO3A/Bim Cues	2017
6	Coenzyme Q10 in the treatment of heart failure: A systematic review of systematic reviews	2018
7	Effect of CoQ10 Supplementation on Oxidative Stress and Muscle Bioenergetics in Type II Diabetes: A Pilot Study	2020
8	Effects of statins on mitochondrial pathways	2021
9	Toxicity of statins on neuronal cells: Possible reversibility by Mito-Q	2021

Induced myopathy in rat by rosuvastatin application

Rosuvastatin, a drug used to treat hypercholesterolemia, is a member of statin family. It acts as an inhibitor of 3-hydroxy-methylglutaryl CoA (HMG-CoA) reductase enzyme. This enzyme helps in catalyzing the conversion of HMG-CoA to mevalonate and therefore it inhibits a major step in the sterol pathway. Rosuvastatin is considered to have lipid-lowering effects. It is found to be associated with the risk of myopathy. The alterations in the muscle-fibre type sensitivity were directly related to the inhibition of HMG-CoA reductase enzyme. The study aimed to characterize myopathy in rat due to very high doses of rosuvastatin and the comparison of results with other statins, simvastatin and cerivastatin. The study was performed Female Wistar Hannover rats [substrain Crl:WI(Glx/BRL/Han)]. Samples used were from kidneys, liver, stomach and selected muscle tissues. Necrosis in muscle sections was graded minimal, mild, moderate or severe when 10, 20, 50, and more than 50% fibers in the section were affected respectively. 3 rats dosed with 160mg/kg/day were observed to have thin appearance, weight loss and hunched posture. Most of the muscle samples were affected and a few were spared consistently. The study, therefore, showed rosuvastatin was required in higher doses to achieve consistent muscle necrosis in comparison to simvastatin and cerivastatin.

Several observations were made where 1 rat showed weight loss when dosed with 120mg/kg/day while 2 of the three rats with 140 and 3 rats with 160 mg/kg/day doses were found to show hunched posture, weight loss, piloerection and thin appearance. The observations indicated that these were the MTD doses and they would be considered above

MTD if administered without periods of rest. No significant observations were found in rats who were dosed 150 mg/kg/day rosuvastatin along with mevalonic acid. Increase in creatinine kinase levels were not apparent in first 10 days but returned to control values on days 14 and 16. There was epithelial hyperplasia along with some keratosis and subepithelial mixed inflammatory cell infiltration in the forestomach. No changes were observed in hearts of animals by rosuvastatin administration. Minimal necrosis was observed in control rats. There was clear observation of muscle necrosis in 1 of the rats dosed with 120 mg/kg/day, 2 dosed with 140 and all three dosed with 160 mg/kg/day. Most muscles which were taken as samples were affected, sparing a few. These few consistently spared muscles included soleus, masseter, and tongue. Flexor carpi ulnaris and the diaphragm were also spared predominantly. The time-course study showed no evidence of induced muscle necrosis in the rats which were dosed with mevalonic acid and rosuvastatin. Acute muscle necrosis was observed which was characterized by cytoplasmic eosinophilia with loss of cytoplasmic structure, vacuolation and negligible inflammatory infiltrate. Changes seen in ultrastructure in control samples were restricted to glycolytic type II fibres which showed few mitochondria and abundant sarcoplasmic glycogen deposits. Type I fibers were considered to be slow oxidative fibers and type II, the fast oxidative fibers. The muscle fiber type is generally determined on the basis of the expression of a particular myosin heavy chain isoform. Substantial portion of type II fibers were found to be necrotic while the type I fibers were normal. Several studies have been performed to understand the mechanism of statin-induced myopathy but it is still uncertain in humans and animals. Myopathy has been directly related to the HMG-CoA reductase inhibition as mevalonate precludes its occurrence. The study showed statin-induced muscle necrosis in rats. A high necrosis was observed by using high doses of rosuvastatin. This was in contrast to comparatively lower doses of simvastatin (80mg/kg/day) and cerivastatin (0.5 mg/kg/day) in earlier studies. The continuum of muscle fiber type from slow to fast twitch is: I \leftrightarrow IC \leftrightarrow IIC \leftrightarrow IIA \leftrightarrow IIAD \leftrightarrow IID \leftrightarrow IIDB \leftrightarrow IIB (in slowest to fastest twitch order). Type I, IIC, and IIA have been consistently shown to be insensitive to the statin-induced damage. Fast glycolytic fiber muscles, type IIB, were shown to have reproducible induced necrosis in presence of rosuvastatin and therefore we consider type IIB fibers to be most sensitive. Therefore, the effects of rosuvastatin were considered consistent with those of other types of statins. Rosuvastatin inhibited HMG-CoA reductase and therefore has lipid lowering effects as it directly inhibits the pathways of synthesis of mevalonic acid. The oral doses were to be supplemented were found to be maximum per day in case of rosuvastatin and then simvastatin and cerivastatin.

Clinical outcomes in heart failure in treatment with coenzyme Q10 and rosuvastatin

CoQ10 is an essential cofactor involved in mitochondrial oxidative phosphorylation. It acts as an electron transporter. CoQ10 acts as an antioxidant in its reduced form. Half of the CoQ10 in the body is synthesized endogenously. The pathway for this synthesis is the mevalonate pathway. Myopathy has been related to the deficiency of CoQ10. Ubiquinone deficiency might occur due to muscle energy starvation which is a major concern in heart failure cases. Studies have suggested that statins might be dangerous in heart failure cases but the role of CoQ10 in the effect of statins is uncertain. The patients were provided with 10mg of rosuvastatin and corresponding placebo was given once daily. Serum creatinine, creatine kinase, thyroid stimulating hormone (TSH), alanine transferase, high sensitivity CRP and lipid/lipoproteins were measured. A pre-specified CORONA study analysis plan was used to study the subjects in order to know whether baseline serum CoQ10 concentration was associated with the clinical outcomes and was evident that the treatment with rosuvastatin increased the risk in patients with low CoQ10 concentration. The study found out that CoQ10 was not the independent variable in heart failure cases and rosuvastatin was not significantly related to worst outcome but led to reduced CoQ10 concentration. Patients with lowest CoQ10 concentration tertile had more atrial fibrillation, lower plasma lipids and low left ventricular ejection fraction (LVEF). NT-proBNP concentration was found to be higher in patients with low CoQ10 tertile. Post completion of 3 months, a follow up visit was done in which it was observed that the whole group of patients had reduced LDL to 76 mg/dl from mean of 142 mg/dl at baseline (48% net difference; $p < 0.0001$). No change was observed in the placebo group. The difference in different tertiles of CoQ10 were 51%, 48% and 45% for tertiles 1, 2 and 3 respectively. CoQ10 concentration also declined at 3 months with rosuvastatin (39% difference; $p < 0.0001$). While, no effects were observed in placebo group. There was reduction in plasma concentration of CoQ10 due to rosuvastatin in all 3 tertiles. The patients in placebo group had numerically higher risk of cardiovascular death, myocardial infarction, or stroke. CoQ10 was not considered to be independent predictor of all-cause mortality. No significant interaction was observed between treatment effect and CoQ10 tertiles. There was no significant interaction between treatment and CoQ10 tertile with all-cause mortality and the composite mortality-morbidity outcomes. The tertile with lowest CoQ10 showed excess of 11 deaths with rosuvastatin group as compared to placebo group. Although insignificant, there were 9 nonfatal myocardial infarctions in rosuvastatin group in CoQ10 tertile1. NYHA functional class on rosuvastatin treated patients showed no significant results. The study found that patients who had low serum CoQ10 concentration were older in age and had severe evidences of heart failure. The lipid levels of such patients were expected to be lower than normal. This was also associated with higher risk of death. The enzyme CoQ10 was not observed as independent predictor of mortality in a multivariate analysis. Study of fatal and nonfatal events was also

examined including death or admission to hospitals for heart failure and it was observed that low CoQ10 levels might lead to worsening of the heart failure. CoQ10 was not an independent predictor of mortality in any of the outcomes. Rosuvastatin drug reduced the levels of CoQ10 in the serum which might be harmful in heart failure cases. In one tertile, there was numerically higher rate of statin-treated as compared to placebo with respect to low CoQ10 concentration. While other two CoQ10 tertiles showed that rosuvastatin was associate with numerically lower event rate as compared to placebo. No expected clinical events in the trials, as death, were at increased risk in rosuvastatin group as compared to placebo group. The study did not find any evidence of the predicted CoQ10 enzyme in effect with rosuvastatin such as muscle symptoms or increased creatine kinase. Although statin treatment reduced CoQ10 concentration but the therapy was not related with any worse outcome that was significant. No consistent pattern of the relation of rosuvastatin with CoQ10 was observed.

A review on prevention of cardiovascular disease by rosuvastatin

Coronary heart disease is the major concern for public health worldwide. Dyslipidaemia is considered to be the major risk factor. The family of drugs, statins, are known for prevention of cardiovascular diseases. Rosuvastatin is a widely accepted drug for treatment of atherosclerosis due to its efficacy, potency and safety profile. CRP is considered as a non-specific marker of inflammation. Rosuvastatin is shown to lower CRP levels and has been used to treat patients and achieve evidence based lipid targets while using the drug. Justification for use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER) trial has been designed on account of the observation that LDL reduction leads to better life in patients. The study aimed to understand the effect of statins on healthy individuals with high CRP values but normal lipid profiles. CRP levels are significant and altered by genetic factors and environment both. They are associated with many risk factors including obesity cancer, atherosclerosis, PCOS and several others. High levels of CRP are considered poorer prognosis in coronary heart disease patients. Rosuvastatin is a drug known to inhibit HMGCR enzyme and thereby reducing the cholesterol synthesis. Galaxy program, by AstraZenca investigated the use of rosuvastatin in improving cardiovascular events. Several studies have been performed including JUPITER, ASTEROID, AURORA, METEOR and CORONA. The review article aimed to understand the effects of rosuvastatin with inclusion of CRP and JUPITER studies in cardiovascular disease patients. Lifestyle and behavioral changes may reduce obesity which drives diabetes and coronary heart disorders. CRP polymorphisms exist in different populations. The concentrations are 16% lower in Asians but 26% higher in black people than in white. An association of large genome wide study ($n = 17,967$) and replication study ($n = 13,615$) showed the association of genetic loci with plasma CRP concentrations. There was a risk of coronary heart disease observed in the patients. This study showed genetic variants

were expected to lower the CRP expression by 20% but did not reduce coronary heart disease risks by the predicted amount of 6%. The synthesis of CRP is shown to be regulated by IL-6. A study concluded that the association of CRP with coronary artery disease depended upon fibrinogen levels and other conventional risk factors. Rosuvastatin drug is an important role player in reduction of risks in case of cardiovascular diseases. This is due to its lipid-lowering effect. Rosuvastatin inhibits an enzyme, HMGCR, which catalyzes the rate limiting step in the synthesis of mevalonate. This is an important pathway of cholesterol biosynthesis. Therefore, application of rosuvastatin showed a significant reduction in lipid levels and hence prevents the risk of enhancing of cardiovascular diseases. JUPITER studies demonstrated that within the population of persons accounted, those with higher levels of CRP benefited from the treatment with rosuvastatin drug. There have been observations that account for the prevalence of metabolic syndrome in JUPITER participants. Rosuvastatin treatment has been considered effective in the study when CRP levels elevated. Inflammation played a critical role in pathogenesis of metabolic syndrome and evidenced that it is of high quality. A meta-analysis showed that metabolic syndrome was associated with a 2-fold increased risk of cardiovascular diseases, related mortality and stroke and led to 1.5-fold rise in all-cause mortality. This was performed as a compilation of 87 studies which involved 951,083 patients. Although the statins are known for lowering lipid levels, there have been several side effects of the drug. They tend to cause statin myotoxicity. The spectrum of myopathy or myotoxicity includes several symptoms. These are myalgia, myositis, and rhabdomyolysis. Less than 3% myalgia have been observed in randomized statin trials. Vigorous exercise might lead to increasing of myalgia up to 25%. Several factors may be involved which lead to myopathy. These are increasing age, diabetes, polypharmacy, etc. Apoptosis of muscle cells or direct myotoxicity has been observed after acute statin exposure. As the effects, the side effects of statin treatment are also pleiotropic. The incidence of myopathy outweighs the benefits of statins and thereby the drug is not ultimately predicted clinically. Several studies have been done on the effectiveness and application of rosuvastatin along with coenzyme Q10 also.

How plasma coenzyme Q10 is affected by rosuvastatin in HIV-infected patients on antiretroviral therapy?

Statins are widely used in lowering serum cholesterol levels as they are HMG-CoA inhibitors and therefore inhibit the mevalonate pathway. They also help in lowering plasma CoQ10 concentration which is an important enzyme in the mitochondrial ETC. As a consequence of CoQ10 deficiency, statin-induced myopathy might also occur. CoQ10 lowers inflammatory markers according to some of the studies. Chronic HIV infection has been characterized by residual inflammation, immune activation, endothelial dysfunction and increased cardiovascular risk. CoQ10 may improve neurotoxicity and endothelial dysfunction with use

of antiretroviral therapy (ART). The study aimed to examine rosuvastatin effects on CoQ10 and CoQ10 /LDL ratio in SATURN-HIV trial for over 24 weeks. Also, CoQ10 levels were analysed to know the anti-inflammatory effects of statin therapy. SATURN-HIV, a randomized, double-blind placebo-controlled trial, was designed to measure effect of rosuvastatin with markers as cardiovascular risk and skeletal bone health in well treated HIV infected patients. A secondary analysis of SATURN-HIV trial was done for a span of 96 weeks. The trial required providing doses of 10mg rosuvastatin daily versus placebo group to HIV-infected patients on antiretroviral therapy. The results showed borderline significant associations between changes in CoQ10 and myalgia symptoms. The study concluded that 10mg daily dose of rosuvastatin was able to decrease the concentration of CoQ10 and increased CoQ10 /LDL ratio in HIV-infected patients on ART.

The study found no baseline differences between treatment and the placebo group ($p < 0.05$). The male patients constituted 78% and 68% were African-American. CoQ10 concentration positively correlated the LDL cholesterol levels ($r = 0.208$, $p = 0.012$) and negative relations were found between CoQ10 /LDL ratio and LDL levels ($r = -0.441$, $p < 0.0001$). Both the observed ratios were negatively correlated in the Caucasian race. No baseline correlations were observed with soluble markers of systematic inflammation or immune activation. Carotid distensibility was negatively correlated with both. Median CoQ10 concentration was borderline higher in placebo group [0.77(0.60–1.04) vs. 0.89(0.67–1.12) mg/L, statin vs. placebo; $p = 0.06$] but LDL ratio was similar [0.008(0.006–0.012) vs. 0.009(0.007–0.012); $p = 0.27$]. Statistically significant correlation was found between changes in CoQ10 and LDL ($r = 0.341$, $p < 0.001$). This was borderline significant when statin treatment arm was analyzed. There was no association of change in biomarkers of inflammation and CoQ10 ($p = 0.86$ for IL-6 and $p = 0.79$ for hs-CRP). Clinically significant myalgia was observed in only one of the four patients who experienced low grade myalgia symptoms within the 24 weeks of study. It was concluded that 24-week alterations in CoQ10 were not related to changed in creatine kinase or aspartate transaminase concentrations ($p > 0.4$). The study did not evidence any association between changes in CoQ10 on statin therapy and alteration in inflammation markers. Both CoQ10 and CoQ10/LDL ratios were considered. Changes in both CoQ10 and its ratios with LDL were found consistent with the ones observed in HIV-negative individuals. The study showed a 24% change over 24 week period in the CoQ10 concentration. Decrease in CoQ10 leads to inhibition of HMG-CoA enzyme and therefore the sterol biosynthesis, mevalonate pathway. The reduction of CoQ10 was comparatively lower than approximately 45% decrease in case of rosuvastatin group with 10mg doses in the general population. CoQ10 /LDL ratio still increased in this study. 10mg daily doses of rosuvastatin led to sustained reductions in several immune activation biomarkers such as soluble CD14 in the SATURN-HIV trial. The study showed

very small effects of CoQ10 supplementation in HIV infected patients which have anti-inflammatory effect of statin therapy. No relationship was observed between baseline CoQ10 and odds of developing muscle related symptoms. Therefore it was concluded that 10 mg of rosuvastatin dosage daily could reduce CoQ10 concentrations and modestly increases CoQ10 /LDL ratio in HIV infected patients on antiretroviral therapy.

Augmentation of rosuvastatin neuroprotective effect by CoQ10 in model of global ischemia

Statins act by inhibiting HMG-CoA reductase enzyme and lower the CoQ10 concentrations. Both the effects are known to possess neuroprotective potentials. The mechanisms which lead to ischemia reperfusion (I/R)-induced neuronal death are complexed with formation of ROS, release of inflammatory mediators, calcium overload, and upregulation of apoptotic genes. Overproduction of ROS via NOX and RNS play an important role in delayed neuronal death (DND). Oxidative stress is also activated apart from which increased neuronal expression of NF-kB also occurs. Several signaling pathways together augment to neuronal damage. One of such pathways is PI3K/Akt signalling pathway. This pathway abates cell death through inactivation of several downstream substrates. Among these, FOXO family, and FOXO3A, specifically regulates neuronal apoptosis by induction of Bcl-2. ROS also lead to activation of JNK3 pathways which initiate apoptotic signaling. CoQ10 is well known in regulation of mitochondrial ETC and therefore ATP production and also acts as an antioxidant. Statins reportedly deplete or reduce the levels of CoQ10 which ultimately leads to oxidative stress. The study aimed to nominate CoQ10 as an add-on therapy along with statins. It experimented the possibility of used of rosuvastatin and CoQ10 on rat model of transient global ischemia. The treatment regimens were administered for 7 days (rosuvastatin = 10 mg/kg, CoQ10 = 10mg/kg, rosuvastatin + CoQ10) and I/R was induced on the eighth day. Statistical analyses were done through ANOVA followed by Turkey's post hoc multiple comparisons among treatment means. It was concluded that rosuvastatin had neuroprotective potentials against the I/R injury by reducing hippocampal oxidative stress, inflammation and apoptosis. This involved several signalling cues as, NFκBp65/TNF-α/gp91^{phox} and p47^{phox}, Akt/FOXO3a/Bim, and JNK3/c-Jun/Bax. All these impacts were analogous to CoQ10 but in combination with rosuvastatin there were effects that surpasses either of the treatments.

When rosuvastatin was administered in pre-ischemic conditions, there were notable hindrances as compared to I/R group. Similar observation was seen in CoQ10 which hampered injurious insult of CA1 neurons but rosuvastatin + CoQ10 treated group showed better effects. The study showed that rosuvastatin protected against oxidative stress by reducing MDA, NO and replenishing GSH and SOD. Upregulation of NOX subunits was observed in the examination that were markedly mitigated due to pre-administration of rosuvastatin and CoQ10. a notable

increase was seen in hippocampal activity of TNF-α, ICAM-1 and MPO when compared to sham group. The combination group showed better effects and lessened the protein expression of Bim and nuclear FOXO3A. Best effects of phosphorylation of JNK3 and c-Jun were observed in the combination group. Elevation of these signaling cues led to increased apoptotic activity in hippocampal tissues. The outcomes of the study showed suppression in oxidative and nitrosative stress and inflammation which was chiefly due to NF-kBp65. statin was shown to reduce hippocampal MDA and elevated GSH and SOD which was in consistence with the effects of rosuvastatin in diabetic patients. Inhibition of NOX may represent as a mechanism of neuroprotective damage of rosuvastatin in case of global cerebral I/R injury. CoQ10 has the capacity to reduce oxidative stress in hippocampal tissues. Rosuvastatin in combination with CoQ10 leads to down regulation of hippocampal iNOS expression and elevation of NO which supported previous findings. Downregulation of NF-kB leads to upregulation of TNF-α. Therefore, combination of both can significantly show neuroprotective capacity. Increased oxidative stress also leads to reduction in p-Akt expression to inhibit its phosphorylation. Neuronal apoptosis is prevented via downregulation of FOXO3A/Bim in response to hypoxic/ischemic brain injury. CoQ10 has the bailability to attenuate angiotensin II- induced upregulation of p-JNK and rosuvastatin has been reported to have inhibitory effect on p-JNK. Selective neuronal degeneration occurs in hippocampal CA1 area due to I/R insult according to several studies. The study confirmed the anti-apoptotic characters of rosuvastatin and CoQ10 by reduction in neuronal death, pro-apoptotic mrkers and increase in Bcl-2 expression.. Neuronal salvage may be suppressed through the rosuvastatin and CoQ10 treatment since the radicals are responsible for the same. Therefore, neuroprotective potentiats of rosuvastatin again I/R injury may be due to suppression of oxidative stress, inflammation and apoptosis with involment of several signaling cues. Combination treatment of rosuvastatin and CoQ10 had better effects which made the conclusion that CoQ10 could be used alongside the treatment with statins.

A review on treatment of heart failure with the help of coenzymeQ10

CoQ10 has been observed to be deficient in myocardial tissues of patients with cardiovascular diseases and also in patients with congestive heart failure, angina pectoris, cadiomyopathy and hypertension. CoQ10 is associated with lowering the risk of heart failure by reducing the symptoms. CoQ10, produced endogenously, has two forms, oxidized and reduced. It as an important enzyme involved in mitochondrial respiratory chain and also acts as an antioxidant. CoQ10 is shown to have various actions which involve increase in ATP generation, reduction in oxidative stress, and stabilizing calcium dependent ion channels in the myocardium. Several databases were searched and systematic reviews of clinical trials were taken into account

excluding non-clinical investigations. AMSTAR tool was used to assess methodological quality of the included reviews which was applied to both Cochrane and non-Cochrane reviews. Methodological quality of the reviews and risk of bias was also assessed.

Final overview included a total of seven systematic reviews out of initially identified 1266 records. One of the systematic reviews reported that CoQ10 supplement led to higher plasma Q10 level (mean difference of 1.44 mg/dL, 95% confidence interval (CI) 1.16–1.73 mg/dL, $p < 0.001$) and another showed that CoQ10 had no significant effect on left ventricular ejection fraction (MD 2.26; 95% CI 15.49 to 10.97). Also, the results showed that the use of CoQ10 increased its concentration in the blood (MD 1.46; 95% CI 1.19, 1.72). An improvement of 3.7% was observed in ejection fraction (1.59 to 5.77; $p < 0.00001$) in subjects who were provided CoQ10 supplementation. Observations showed that the cardiac output increased by an average of 0.28L/min (0.03–0.53; $P = 0.96$) while no significant increase was observed in Cardiac Index. There was an increase in stroke index by an average of 5.68 ml/m² (1.02–10.34; $P = 0.28$) for statistical heterogeneity. NYHA class in CoQ10 group ($n=17$) patients showed a significant improvement of 0.5 class compared to placebo ($n=18$) ($p=0.01$). The data showed that CoQ10 might benefit the more severe form of heart failure (NYHA Class IV). A study showed less hospitalization of those given CoQ10 as compared to placebo (hazard ratio = 0.39 95% CI 0.29–0.53, $p < 0.001$). A meta-analysis reported improvement in ejection fraction, stroke volume, cardiac index and end diastolic volume index. This was the consequence of CoQ10 supplementation. CoQ10 is an important member of mitochondrial respiratory chain. It is found in Golgi, lysosomes and plasma membranes as well. It acts as an antioxidant as it reacts directly with free radicals or regenerates tocopherol and ascorbic acid from their oxidized state. CoQ10 has different effects on different types of heart failures. Two of the studies taken into account showed benefits from CoQ10 versus placebo. Q-SYMBIO, the first PRCT, showed that there were 10% deaths in CoQ10 group as compared to 18% in placebo group. This corresponded to a 42% relative reduction ($p=0.036$). There were reductions in hospitalizations of CoQ10 group compared to placebo group. Therefore, it was observed that treatment with CoQ10 along with standard therapy is safe for patients with moderate to severe heart failure. It is associated with reduction in symptoms. Combining CoQ10 with standard therapy is shown to reduce mortality according to one of the meta-analysis. Other three meta-analyses showed positive results in improvement in ejection fraction and cardiac outputs. The Q-Symbio trials showed that CoQ10 could be used in patients with moderate to severe heart failure and is safe and tolerable. Therefore, it is suggested that CoQ10 can be used as an important part in supplementation in order to manage patients with heart failure.

A study on effects on oxidative stress and muscle bioenergetics by CoQ10 supplementation

Type 2 diabetes (T2D) is one of the major types of diabetes among diabetic population in US. Glucose metabolic pathways may be altered in T2D patients which lead to formation of by-products like reactive oxygen species (ROS). These ROS are harmful to the body and cause oxidative stress. One of the T2D complications is Peripheral Arterial Disease (PAD). There has been increased mortality in the cases where T2D is associated with PAD. T2D also leads to mitochondrial dysfunction. Defects in fatty acid metabolism lead to its accumulation which is prone to lipid peroxidation increasing ROS. CoQ10 deficiency may occur in T2D which can diminish metabolic efficiency. CoQ10 is a part of respiratory chain and an antioxidant too. If provided in the form of supplements, it can improve functional capacity of T2D and might reduce progression of diabetes. The study aimed to test various parameters in T2D patients who were provided CoQ10 supplementation. The patients were previously diagnosed with T2D. Both T2D patients and control subjects went through 2 weeks of placebo treatment which was then followed by CoQ10 treatment at 200 mg a day. Malondialdehyde levels were measured to estimate oxidative stress. For this purpose, blood samples were drawn before and after exercise. Dynamic changes of phosphate metabolites, intracellular pH and total Hb/Mb-oxy saturation were observed through exercise protocols. The experiment exhibited positive effect of CoQ10 supplementation in lower oxidative stress. Resting Response: There were no significant differences found in heart rate and blood pressure measures. The resting ³¹P spectra of T2D patients showed significantly smaller PCr ($p = 0.04$), PCr/Pi ($p = 0.01$) and larger Pi ($p = 0.04$). Exercise Response: The end exercise PCr, its depletion rate and ipH were not observed to be significant. ipH was above 6.5 which showed that aerobic conditions prevailed during exercise. Hb/Mb-oxy ratio was not statistically significant. There was a larger and significant increase in change in blood volume in case of control group, while the change remained same in T2D patients. Recovery Response: Time constant and phosphocreatine resynthesis rate was observed to be lesser in T2D when compared to control ($p = 0.02$). A significant delay in HbO₂ recovery was observed in ($p = 0.02$). Resting Response: No significant reduction in MDA was observed after CoQ10 trial in T2D (1.31 ± 0.19 vs. 1.47 ± 0.36 uM, $p > 0.05$) while a significant reduction was observed in control subjects (1.29 ± 0.41 vs. 0.88 ± 0.35 uM, $p < 0.05$). The results were found to be similar to the resting responses. MDA levels showed significant reduction in control subjects but there was no significant change in T2D patients' results. Phosphocreatine resynthesis rate did not show any statistical difference among both the groups. Intracellular pH was slight improved in T2D but the difference was not statistically significant. The Hb/Mb-oxy ratio was also not significant during recovery with CoQ10 treatment.

The study found a significant decrease in PCr, PCr/Pi and higher Pi in T2D as compared to the control subjects. Some studies have reported lower PCr/Pi in patients with

mitochondrial or COPD disease. On the other hand higher Pi/PCr ratio is observed in case of T2D patients. The reason could be due to constant metabolic stress at rest and a reduced phosphorylation potential. This also leads to accumulation of metabolites besides over production of ROS. Low phosphocreatine synthesis rate in T2D patients in case of exercise and recovery responses could be due to compromised mitochondrial capacity. Insufficient oxygen supply to the mitochondria could also be the reason. Reduced change in Blood Pressure indicated reduced oxygen supply to the muscles which may further lead to impairing of oxidative phosphorylation capacity of the mitochondria. Intracellular pH of T2D patients was lower than control and the recovery was delayed significantly. After CoQ10 trial, there was a significant reduction of MDA in control subjects. This suggests that CoQ10 may have reduced oxidative stress due to its antioxidant effects. Reduction of MDA was also reported in studies of autism spectrum disorder and multiple sclerosis. The reason of insignificant change in MDA in case of T2D patients may be due to the amount and duration of CoQ10 which might not have been sufficient. The results in exercise and recovery responses in T2D patients were inconclusive. The reason might be attributed to the dosage of CoQ10 in the patients. Another possibility could be the greater effect of CoQ10 on mitochondria rather than the microvasculature. The study suggested that the limitations in results could be due to the small sample size which decreases the statistical accuracy. CoQ10 supplementation was shown to be significant in reduction of MDA in control subjects while in T2D patients, it had marginal effect on oxidative phosphorylation.

Mitochondrial pathways and effects of statins on them

Statins are a family of drugs that have pleiotropic effects. This family of drugs have been used to treat hyperlipidaemia with the capacity to prevent cardiovascular diseases. Statins inhibit β -hydroxy β -methylglutaryl-coenzyme A (HMG-CoA) reductase which is involved in the rate-limiting step of mevalonate pathway. Cardiovascular diseases (CVDs) which are associated with high plasma cholesterol, LDL and reduced HDL include myocardial infarction, angina, heart failure and cerebrovascular accidents. These CVDs lead to significant amount of mortality. Reduction in LDL by 1 mmol/L reduces the CVD risk by 22%. Statins are considered to be the most effective lipid-lowering agents. They are reversible and competitive inhibitors of HMG-CoA reductase and reduce serum and tissue levels of total cholesterol, LDL, apoB, and triglycerides. Statins also stabilize atherosclerotic plaques, immunomodulations and improvement of endothelial dysfunction. Statins may interfere with mitochondrial activity by impairing electron transport chain. The review article aimed at providing statin-driven molecular mechanisms which interfere with mitochondrial function. The data suggested that mitochondrial functions were affected by statins and some of the adverse effects might mediate through the pathways.

These are muscle symptoms associated with statin treatment. They correspond to decrease in creatine kinase levels. A severe side effect of statin treatment is a rare complication, rhabdomyolysis, which is characterized by 50 fold increase in upper normal limit of creatine kinase. Mitochondrial dysfunction plays an important role in SAMS pathogenesis. Statin-treated patients are known to have high blood lactate/pyruvate ratio. SIM is characterized by lipid aggregation in mitochondria and accumulation of ragged red fibers in subsarcolemmal region. Depletion of CoQ10: Coenzyme Q10 is a hexameric quinone ring which has high antioxidant activity and plays an important role in mitochondrial ETC. CoQ10 deficiency has been observed in diseases like heart failure, nephrotic syndrome and muscular and neurological disorders. Inhibition of mevalonate pathway by statins might reduce CoQ10 levels by 16-54% which leads to mitochondrial dysfunction. A randomized trial showed 80 mg/day of simvastatin, not 40 mg/day of atorvastatin, was significant to reduce muscle ubiquinone concentration. Oxidative stress in relation to mitochondrial depletion: dosage of 80 mg/day was shown to reduce mtDNA/nuclear DNA ratio. The drug majorly led to mitochondrial depletion due to its lipophilic nature. Exercise training markedly enhanced the oxygen uptake by approximately 10% and also enhanced citrate synthase activity. Toxicity by statins might also be due to reduced phosphorylation of protein kinase B which has an important role in mitochondrial health. The toxicity could also be related to production of ROS and oxidative stress. The ROS accumulation stimulates PGC-1 α activity which leads to mitochondrial biogenesis and improvement of its function. Inhibition of ETC complexes: statins lead to direct inhibition of complexes. They are known to interfere with exercise training which basically rely on functioning of mitochondria.

Calcium metabolism dysregulation: Statin-treated patients were observed to have decreased frequency of calcium sparks in symptomatic but not in asymptomatic patients in comparison to placebo. Statins have been observed to increase the cytosolic and sarcoplasmic calcium iron concentrations. There is abnormal opening of mitochondrial transition pore and Na²⁺-Ca²⁺ exchanger which may be due to reduction in mitochondrial membrane potential and depolarization of IMM. Lactone toxicity: Lactone is the inactive prodrug form of statins. Higher circulating levels of lactones were observed in individuals affected by SIM. They have higher capacity to impair ETC complex III activity. Apoptosis: An abnormal activation of apoptosis pathway occurs as a consequence of decrease in the Bcl-2/Bax ratio which is related to be statin-induced. Calpain is a considered to be an upstream effector for statin-induced initiation of intrinsic apoptotic pathway. Accumulation of ROS might also be the reason of inducing apoptosis. Administration with quercetin leads to inhibition of apoptosis in fast glycolytic skeletal muscle fibres while atorvastatin treatment down regulated Bax/Bcl-2 ratio and caspase-3 activation. Statins are considered to have effect

of alteration of phosphorylated state of Akt by interfering in pathways of cell survival.

Polymorphisms in COQ gene have been associated with SAS and SAMS. GATM gene, encoding mitochondrial glycine amidinotransferase enzyme, was found to be in reduced levels by statin treatment and therefore lead to reduced creatine synthesis. Statin treatment studies also show reduction in mitochondrial number or volume due to CoQ10 deficiency which might cause mitochondrial encephalopathy, lactic acidosis and stroke like symptoms. CPT-2 deficiency is a disorder related to lipid metabolism. Statin treatment in patients could cause reduction in lipid due to impairment of CPT-2 activity. JUPITER trial showed a significant increase in the onset of diabetes in rosuvastatin group in comparison to placebo group. A significant increase of 9% was observed as the risk of T2DM in patients. Mitochondrial dysfunction causes impairment of insulin secretion in beta cells. This is could be likely due to decrease in ATP production which is ultimately due to inhibition of complexes of ETC due to statin treatment. Atorvastatin has been related to increased levels of ROS which is due to oxidative stress and beta cell dysfunction. T2DM patients show reduced expression of UCP-3 which helps in beta-oxidation.

Hypercholesterolaemic patients showed an increased risk of Alzheimer's and vascular dementia in a study. Although, recent analyses fail to demonstrate any such effect of statin treatment. Simvastatin in higher dose showed an increase in hypoxia induced factor 1 α and β -site amyloid precursor protein protein cleaving enzyme which suggests that statins in higher doses may affect neuronal function. Statins are therefore known to have effects on CVD as they may induce adverse effects like myopathy. Mitochondrial dysfunction due to CoQ10 depletion, inhibition of mevalonate pathway, induction of intrinsic apoptosis, fatty acid oxidation and dysregulation of calcium metabolism are therefore some of the vast effects observed in patients of statin-induced treatment. An increased risk of T2DM has also been observed and cognitive impairment are also associated with chronic treatment of statins.

Possible reversibility of statin toxicity in neuronal cells by MitoQ

Statins have been prescribed as the most common drug for the patients with cardiovascular diseases due to their lipid lowering effects. They inhibit HMG-CoA reductase competitively which is the rate limiting step in the mevalonate pathway. Statins show pleiotropic effects on several organs and tissues. Several studies have showed neuronal, liver and muscle related toxicities due to statin induced treatments. Statins also inhibit CoQ10 enzyme which is an important part of mitochondrial electron transport chain. Neuroprotective effects of statin toxicity are being unexplored and controversial. The study aimed to compare the effects of five different statins on neuronal cell lines of rat PC12 and human SH-SY5Y. The cells were treated with statin 1-15 micromolar concentrations for 24 and 48 hours. NBT and luciferase assays were used to

detect the changes in reactive oxygen species (ROS) and levels of ATP in the cells that were treated with statins. The study analyzed the protective effect of pre-/ or co-MitoQ treatment with statins. Rat PC12 was found to be insensitive to statins so human SH-SY5Y cell line was continued. The study concluded the effect of statin in the order fluvastatin > pitavastatin > atorvastatin > rosuvastatin with fluvastatin being most potent.

A significant dose and time dependent decrease in viability (85-90% at 48 hours), increase in ROS (50-75%) and decrease in ATP (60-99%) was observed in statin treated cells of human cell line SH-SY5Y. Pre- and co-treatment MitoQ with statins did not exhibit any protective effect. No protection to cell death was being done by catalase. Statins led to decrease in the viability of the SH-SY5Y cells and induced ROS production. Extended exposure to statins caused enhancement in ROS levels with different type of statins. Mevastatin lead to maximum 65% increase at the highest tested concentration of 10 micromolar. Statins often cause an increase in oxidative stress due to increased production of ROS. The enzyme catalase helps in reduction of ROS. But there was no observation of restoration of viability in catalase pretreated cells as compared to statin-treated cells. This indicated that neuronal cells were independent of cytotoxicity of statins. A reduction in ATP level was observed in human neuronal SH-SY5Y cells which is directly related to inhibition of HMG-CoA and subsequently ubiquinone also. 24 hour treatment showed decreased ATP levels (17-35 % from different statins). 48 hour treatment further reduced the levels of ATP by 10-15%. therefore, it was concluded that each of the statins reduced the ATP levels to different extent. There was no effect on MitoQ against statin-induced cell death. Statins showed alteration in cholesterol content with maximum reduction seen through application of pitavastatin after treatment of cells for 24 hours. Statins are anti-atherosclerotic due to their inhibiting action on HMG-CoA. This decrease also leads to decrease in ubiquinone and other biomolecules. The neurological effects of statins are attempted to be observed in this study. Five different statins were used to be tested on human and rat cell lines. All statins were shown to cause dose and time- dependent cell death which was more frequent and observable after 24 and 48 hours of treatment. Decrease in ROS and consequently ATP levels by statins was observed to be in order: fluvastatin > pitavastatin > atorvastatin > rosuvastatin. Pre-treatment with catalase or MitoQ did not result in any significant viability. Fluvastatin and pitastatin were found to be most potent in the study. The reason could be due to their lipophilicity and smaller size such that they permeate the plasma membrane easily. Toxicity of statins was not limited to cholesterol levels but also decrease in downstream molecules was observed. This affected cell signaling, cell growth and ubiquinone. Mitochondrial respiration is also affected. Some statins are known to inhibit different complexes of mitochondrial ETC. Chronic treatment with statins might be related to mitochondrial dysfunction. As progression of diseases such as

Alzheimer's disease is considered due to increased ROS, statin induced cell death was observed in the study. Mitoquinone, an analog of ubiquinone can get oxidized by ROS and has been used for their antioxidant effects. MitoQ treatment singly or in combination with statins could not protect the statin induced cell death. The order of toxicity of statins was observed to be fluvastatin > pitavastatin > atorvastatin > rosuvastatin. Therefore, structural differences might have different effect of the drugs on central nervous system.

Clinical evidences: as extracted from clinicaltrials.gov

A study comparing CoQ10 Levels while taking 3 different statins (SPARQ)

NCT01660191

Pitavastatin showed reduction in total CoQ10 levels which was lesser as compared to other two statins. (With mean values -464.85 for pitavastatin, -642.43 for rosuvastatin and -721.09 for atorvastatin.)

Evaluation of Ubiquinol on Mitochondrial Oxidative Capacity in Statin patients using 31PMRS

NCT01702987

PCr recovery showed a mean of 7.7 in statin + ubiquinol patients while -18.9 in statin + placebo group. PCr recovery is primary measure of mitochondrial oxidative capacity.

Ubiquinol in Parkinson's Disease: Safety, Tolerability, and effects upon Oxidative Damage and Microtubule Biomarkers

NCT03061513

Number of adverse events were higher (27) in Parkinson's disease patients with ubiquinol supplementation and less (12) in patients in placebo group. Lactate levels showed a mean change of -11.98 in ubiquinol group and 6.23 in placebo group.

Ubiquinol (Reduced CoQ10) for patients with Sepsis

NCT01948063

Total CoQ10 levels had a higher median of 0.87 (IQR = 0.57 to 1.26) in patients with ubiquinol supplementation having sepsis while median of 0.38 (IQR = 0.26 to 0.66) was seen in placebo group.

Clinical trial of CoQ10 for Mild-to-Moderate Statin-Associated Muscle Symptoms

NCT01032993

53% of participants observed pain reduction in statin + ubiquinol group while 65% were seen in statin + placebo group.

A Phase 3 Study Measuring the Effect of Rosuvastatin 20mg on Carotid Intima-Media thickness in Chinese Subjects with subclinical Artherosclerosis

NCT02546323

Annualized rate of change in mean of the maximum CIMT measurements from each of 12 carotid artery sites showed a mean value of 0.0038 in rosuvastatin group (272 patients) and 0.0142 in placebo group (271 patients) over a 104-week treatment period in a phase 3 trial.

A study of Lanabecestat (LY3314814) in Healthy Participants when taken with Rosuvastatin

NCT03019549

Pharmacokinetics of rosuvastatin analyzed with a geometric mean of 80 in rosuvastatin group (31 patients) and 78 in Rosuvastatin + Lanabecestat group.

4. Conclusion:

This research review's purpose is to help the reader understand different aspects posed by the research on the Analeptic properties of Rosuvastatin and cq10 combination. This is significant because it gives insights about Rosuvastatin and cq10 (Ubiquinone) individually and in combination. There has been much research and discussion these opinions of Rosuvastatin and cq10 (Ubiquinone) and the Analeptic properties of Rosuvastatin and cq10 combination. Most of the research found was on the ability of two combinational drugs Rosuvastatin and cq10 to treat human disorders/ diseases by lowering cholesterol and displaying antioxidant activity respectively. The research also sheds light on rosuvastatin, cq10 and their individual and combined effects to treat Dyslipidemia, Cardiovascular diseases, Ischemia and most importantly cardiovascular diseases. More research and testing is required to gain a better understanding of the Analeptic properties of Rosuvastatin and cq10 combination.

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6. Human and animal rights

No Animals/Humans were used for studies that are base of this research.

7. Availability of data and materials

The author confirms that the data supporting the findings of this research are available within the article.

8. Funding acknowledgement and conflict of interest

The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in

speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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