INTRODUCTION

Heart failure (HF) is a serious condition effecting five million people in the United Sates and contributes to 300,000 deaths each year. HF is a condition where damage to the heart causes it to be unable to provide significant blood flow to meet the body's needs. It results in fluid congestion, inadequate oxygen to tissues and organs, shortness of breath, and fatigue (1). Many supplements are commonly prescribed to patients with HF including Coenzyme Q_{10} (CoQ_{10}) also known as ubiquinone. CoQ_{10} plays a critical role in oxidation phosphorylation and is necessary for APT production. It influences the rate of energy released from the electron transport chain by regulating key enzymes. CoQ_{10} has antioxidant properties and protects cells from damage by free radicals by stabilizing the cell's membrane. Levels of CoQ_{10} are lower in patients with HF and replenishment may prevent oxidative stress and further myocardial damage. ATP bioavailability plays a central role in regulating myocardial contractibility. The less ATP available to the heart the harder it is for the heart to contract and keep up proper blood flow. Because CoQ_{10} is needed for ATP production a decrease in CoQ_{10} concentrations in myocardial cells leads to a decrease in energy supplied to the heart to maintain proper function. CoQ_{10} supplementation for patients with HF may increase concentration levels which may improve heart function. The purpose of this literature review is to analyze current research on CoQ_{10} supplementation and its effect on HF. After exploring major outcomes such as ejection fraction, exercise capacity, and New York Heart Association Classification a conclusion will be determined on what kind of effect CoQ_{10} supplementation has on HF.

EJECTION FRACTION

Ejection Fraction (EF) is a measurement of the percentage of blood leaving the heart each time it contracts. The left ventricle is the heart's main pumping chamber, which is why ejection fraction is usually measured only in the left ventricle. Left ventricle ejection fraction in people without HF is 55 to 70 percent while patients with HF tend to have an ejection fraction of 40-20 percent.

No change in Ejection Fraction

A randomized double blind crossover trail preformed by Watson et al. (2) found that EF in patients with chronic heart failure (CHF) supplemented with CoQ_{10} remained unchanged when compared to placebo. Thirty patients with a mean EF of 26 ± 6% received 100 mg/d of CoQ_{10} or placebo for three months then alternate treatment for three months. No change in EF was observed during the three months of CoQ_{10} supplementation and placebo. CoQ_{10} verses placebo resulted in P=0.98. Khatta et al. (3) studied EF in patients with congestive HF and observed no change in EF after CoQ_{10} supplementation compared to placebo group. Fifty five patients were randomly assigned to receive 200 mg/d of CoQ_{10} or placebo for six months. Baseline characteristics did not differ between the two groups. After treatments EF remained unchanged in both groups.

Significant increase in Ejection Fraction

A double-blind and double-crossover trial conducted by Langsjoen et al. (4) found EF in patients with HF treated with CoQ_{10} showed significant increase when compared to placebo. Patients were randomized to group A (n=8) or group B (n=11). Group A received 33.3 mg three times a day of CoQ_{10} for 12 weeks then placebo for 12 weeks, with only a one week washout in between treatments. Group B received placebo for 12 weeks then CoQ_{10} at 33.3 mg three times a day for 12 weeks, with only a one week washout in between treatments. There was not significant difference between group A and B at baseline. After CoQ_{10} treatment EF significantly increased when compared to placebo. Figure 1 shows EF in group A and B during CoQ_{10} treatment and placebo. Some patients in group A continued to show a slight increase in EF after CoQ_{10} supplementation was stopped. The study concluded this was due to left over CoQ_{10} in their blood, which indicates the washout period was too short.

Rango et al. (5) conducted a single-blind randomized study and found that EF in 60 patients with congestive HF significantly increased after supplementation of CoQ_{10} when compared to placebo group.

Figure 1. Ejection Fraction in group A and B during placebo and CoQ_{10}

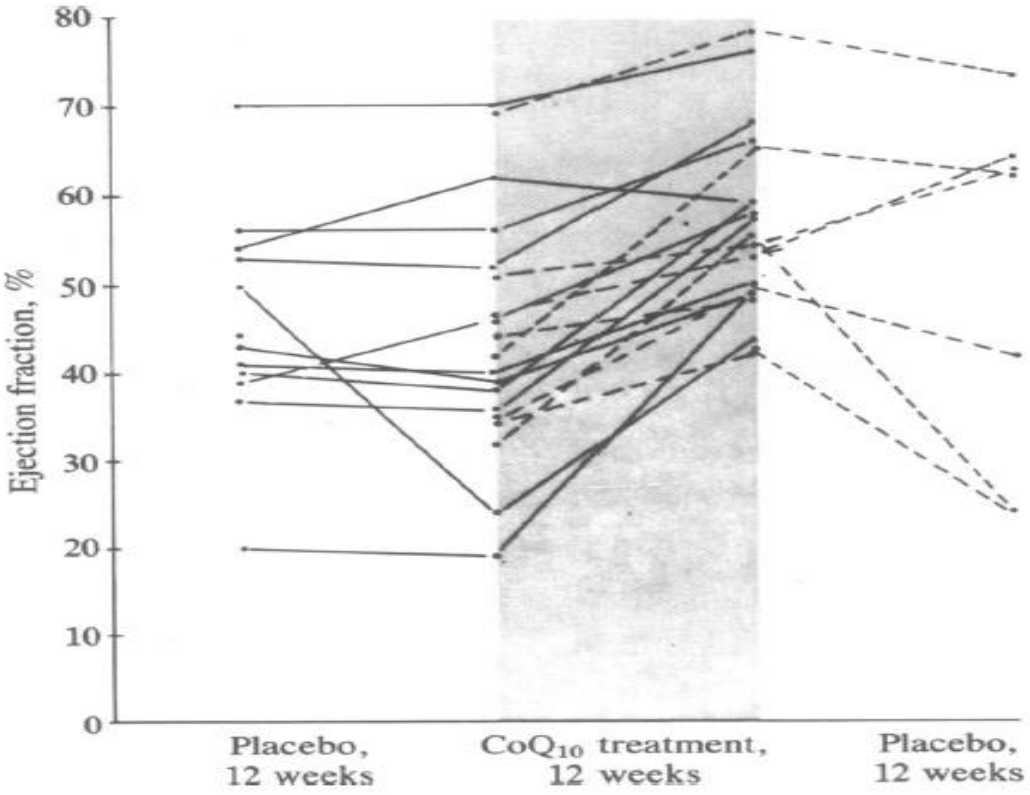

FIG. 4. Data on ejection fraction (%) for group A (----) and group B (—).

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Langsjoen P, Vadhanavikit S, Folkers K. Response of patient in class III and IV cardiomyopahty to therapy in a blind and crossover trail with coenzyme Q_{10}. *Proc. Natl. Acad. Sci.*1985;82:4240-4244.

Patients were treated with 150 mg two times a day CoQ_{10} or placebo for seven months. A 16% increase in EF was observed in the CoQ_{10} group and when compared to placebo group the difference resulted in P=0.001.

Another study done by Belardinelli et al. (6) looked at EF in patients with CHF and found a significant increase after treatment of CoQ_{10} when compared to placebo. According to a double-blind, placebo controlled, crossover design patients were randomly supplemented with CoQ_{10} at 100 mg three times a day or placebo for four weeks then the alternate treatment for four weeks. Mean EF was 37 ± 8.3% at baseline and after supplementation of CoQ_{10} increased to 43 ± 8.7% with no change during placebo.

Witte et al. (7) found EF in 28 patients with CHF treatment of CoQ_{10} significantly increased when compared to placebo group. Patients were randomized to 150 mg/d CoQ_{10} (n=14) or placebo (n=14) for nine months. All patients had EF ≤ 35%. At baseline the CoQ_{10} group had a mean EF of 25.6% and placebo group had a mean EF of 26.6%. There was no significant difference between groups. After nine months of treatment EF in CoQ_{10} group increased to 30.9% with no change in placebo group. This resulted in a P=0.03 between the two groups.

Langsjoen et al. (8) conducted another study which looked at EF in seven patients with end-stage CHF and found a significant increase after treatment of ubiquinol when compared to baseline. This study is unique because all seven patients were already receiving CoQ_{10} supplementation and were changed to ubiquinol, which is an active form of CoQ_{10} and believed to be more easily absorbed. All patients received varying doses of ubiquinol in order to maintain plasma CoQ_{10} levels ≤ 2.5 µg/ml. CoQ_{10} at this concentration or greater has shown significant clinical and echocardiography improvement in patients with HF. The average dose of ubiquinol was 580 mg/d. Months of treatment also varied from three to twenty months, due to personal reasons, with an average of 12 months. Significant increase in EF was observed in five out of the seven patients. The two patients that were reported to have no change in EF did in fact experience an increase in EF after ubiquinol supplementation but developed the flu which resulted in EF returning to baseline levels. Overall this study found that mean EF increased from 22% at

baseline to 39% after supplementation and concluded that ubiquinol supplementation that maintains plasma $CoQ_{10} \leq 2.5$ μg significantly increases EF.

Ejection Fraction Conclusion

The majority of studies that found a significant increase in EF supplemented patients with higher doses of CoQ_{10} compared to the two studies that found no change in EF. Watson et al. (2) used 100 mg/d of CoQ_{10} and Khatte et al. (3) used 200 mg/d of CoQ_{10} and found no change in EF, whereas both Langsjoin et al. (4) and Berardinelli et al. (6) supplemented patients with a total of 300 mg/d and in the second study done by Langsjoin et al. (8) supplemented patients with a average CoQ_{10} at 580 mg/d and found a significant increase in EF. However, Rango et al. (4) supplemented patients with a total of 100 mg/d and Wittle et al. (7) used 150 mg/d and doth observed significant increase in EF.

Doses of $CoQ_{10} \geq 300$ mg/d seem to be more likely to show an increase in EF. Looking at the data presented it can be concluded that CoQ_{10} at doses ≥300 mg/d may increase EF in patients with HF. A low EF directly affects a patient's ability to pump adequate amount of blood to their body, which effect's their ability to exercise. Supplementation of CoQ_{10} has seen to lead to increases EF, which improves the pumping capabilities of the heart and may directly improve patients exercise capacity. Many studies have looked at the correlation between exercise capacity and supplementation of CoQ_{10}.

EXERCISE CAPACITY

CoQ_{10} is found in skeletal muscle and because of its role in ATP production when levels are low it can decrease patients exercise capacity. Muscles become fatigue quickly because the heart cannot pump adequate blood to all tissues, resulting in a limited supply of oxygen. Patients with HF tend to becomes fatigued quicker and may experience dyspnea, angina, or discomfort during physical activity. Supplementation of CoQ_{10} may increase concentration levels in myocardial cells, which may lead to increased ATP production and energy supplied to the heart. Current research has studied COQ_{10} supplementation and its effect on exercise capacity in patients with HF.

No change on Exercise Capacity

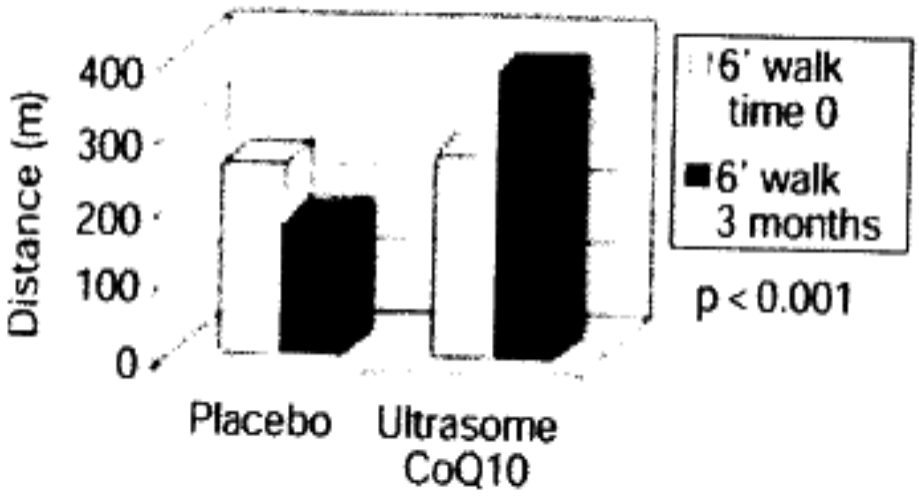
Premanetter et al. (9) looked at cardio output in patients with CHF and found no change in exercise tolerance after supplementation of CoQ_{10} and when compared to placebo. Twenty five patients were randomized into two groups. Group I (n=10) received a placebo three times a day for four months followed by CoQ_{10} 33.3 mg three times a day for four months. Group II (n=15) received CoQ_{10} 33.3 mg three times a day for four months followed by placebo three time a day for four months. Patients preformed an exercise test on a bicycle ergometer, which is a stationary bike with an ergometer attached to measure the work load done by the exerciser. Resistance was added gradually in 25 watt steps at intervals of 5 minutes. Patients were directed to exercise until max work load was reached or when fatigue or discomfort was experienced. Each patient preformed this exercise test at baseline under controlled conditions, after CoQ_{10} supplementation, and after placebo. Both groups showed no change in exercise tolerances after treatment of CoQ_{10} and placebo.

Significant increase in Exercise Capacity

A study done by Berman et al. (10) observed exercise capacity in patients with end stage HF awaiting heart transplantation and found that supplementation of CoQ_{10} significantly increase their exercise capacity when compared to baseline. Thirty two patients were randomly assigned to receive 60 mg U/ day of Ultasome-$CoQ_{10,}$ a special preparation to increase intestinal absorption, or placebo for three months. Patients completed a 6 minute walk test at baseline and three months after treatment. Distance walked was measured. Figure 2 shows that patients treated with placebo showed no change in the 6-minute walk test from baseline, whereas patients treated with CoQ_{1o} showed a significant increase in meters walked compared to baseline. Patients supplemented with CoQ_{10} walked an average of 269.5 meters in six minutes at baseline and an average of 382.2 meters in six minutes after supplementation, which resulted in a P vale of 0.001.

Rosenfeldt et al. (11) observed exercise capacity in 35 patients with HF significantly increase after treated with CoQ_{10} when compared to baseline and placebo group.

Figure 2. Six-minute walk test at baseline and three months after placebo and CoQ_{10}



Berman M, Erman A, Ben-Gal T, Dvir D, Georghiou G, Stamler A, Vered Y, Vidne B, Aravot D. Coenzyme Q_{10} in patients with end-stage heart failure awaiting cardiac transplantation: A randomized, placebo-controlled study. *Clin Cardiol.*2004;27:295-299.

Patients were asked to walk for six minutes on a treadmill. Distanced walk at baseline and after three months of treatment with 150 mg/d of CoQ_{10} or placebo was measured. There was no change in distanced walked in placebo group. There was a significant increase in distance walked in the group treated with $COQ_{10,}$ P=0.047. The difference in distance walked between the CoQ_{10} and the placebo group resulted in a p value of 0.024.

Kamikawa et al (12) studied exercise performance in 12 patients with CHF and found a significant increase after CoQ_{10} supplementation when compared to placebo. This double-blind, placebo-controlled, randomized, crossover trial supplemented patients with 150 mg/d CoQ_{10} for four weeks or placebo then switched patients treatments for four weeks. Exercise test were completed on a treadmill after each treatment phase. Patients walked until leg fatigued or dyspnea was observed. Exercise time increased from 345 ± 102 seconds after placebo to 406 ± 114 seconds after CoQ_{10} treatment which the study concluded shows a significant increase in exercise performance. .

Another study by Hofmain-Bang et al. (13) found that maximal exercise capacity in patients with chronic congestive HF significantly increased after treated with COQ_{10} when compared to placebo. Seventy-nine patients were randomly assigned to double blind therapy of CoQ_{1o} 100 mg/d or placebo for three months then switched to alternative treatment for three months. System-limited exercise test were performed on a bicycle ergometer. The workload was increased by 10 watts each minute. Symptoms of angina, dyspnea, and leg fatigue were scaled during the last 15 seconds of every second workload and at the last workload. Patients preformed exercise test at baseline, after the months of treatment, and after three months of alternative treatment. The study shows that maximal exercise tolerance increased by 6% from 94 ± 31 W after placebo to 100 ± 34 W after CoQ_{10}, resulting in P=0.05.

Morison et al (14) studied cardio output in patients with CHF and found a significant increase after supplemented with CoQ_{10} when compared to placebo. This randomized, double-blind, placebo controlled, cross-over trial supplemented seven patients with CoQ_{10} 50 mg three times for a week or placebo. After four weeks of treatment patients received alternative treatment for four weeks. An exercise test using a bicycle ergometer was performed by patients at baseline, four weeks after first

treatment, and fours weeks after alternative treatment. Patients began exercise test with a two minute warm up at 20 W, 60 rpm, followed by a 1 W increase every 3-6 minutes until symptom-limiting end-points such as leg fatigue or dyspnea was reached. The cardio output was higher during CoQ_{10} treatment than in placebo treatment. When patients received CoQ_{10} cardio output at rest increased from 19 ± 2 to 33 ± 5 and also increased at peak exercise from 24 ± 3 to 41 ± 8. There was no change in cardio output after placebo.

Conclusion on Exercise Capacity

Most studies presented resulted in a significant increase in exercise capacity after treatment of $CoQ_{10.}$ Duration of treatment varied from one month to four months with varying does of CoQ_{10} from 60-150 mg of CoQ_{10}. However, the most significant variation among studies was exercise test performed by patients. Studies used different methods to measure exercise capacity. Some studies such as Berman et al. (10), Rosenfeldt et al. (11), and Kamikawa et al (12) used distance walked on treadmill to measure exercise capacity while others studies such as Premanetter et al. (9), Hofmain-Bang et al. (13), and Morison et al (14) used bicycle ergometer. Researches also used different characteristics to assess when patients maximum work load was reached. The difference in exercise test performed and the varying assessments used to determine maximum work load may be responsible for the difference results. Exercise tolerance is used to classify New York Heart Association Classification which classifies the extent of HF. Degree of limitations during physical activity is a criteria for determining which class patients fit into.

NEW YORK HEART ASSOCIATION CLASSIFICATION

New York Heart Association (NYHA) classification is a simple way of classifying the severity of HF. It places patients in one of four categories based on how much patients are limited during physical activity in regards to degree of shortness of breath, fatigue, palpitation, and angina pain. Classes range from class I (mild HF) to class VI (serve HF). Table 1 further explains criteria for classification. It is important to asses patient's stage of HF in order to determine the best course of therapy (15). Current

Table 1. The Stages of Heart Failure-NYHA Classification.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Heart Failure Society of America. "The Stages of Heart Failure" Available at http://www.abouthf.org/questions_stages.htm. Assessed on 11/21/2010

research has studied CoQ_{10} supplementation as an option for treatment to determine its effects on decreasing NYHA class.

No Change in NYHA

Mumkholm et al. (16) studied NYHA in 22 patients in class II and III and observed no change in classification after CoQ_{10} supplementation when compared to placebo group. Patients were randomized into two groups using a double-blinded, placebo controlled design. Patients received 100 mg CoQ_{10} twice a day or placebo for 12 weeks. To asses limitations during physical activity patients performed an exercise test on a bicycle ergometer at 30 Watts for three minutes at baseline and after 12 weeks of treatment. There was no change from baseline in cardio output in CoQ_{10} group and or placebo group. NYHA class remained unchanged in CoQ_{10} group with no significant difference between placebo group after treatment. Table 2.

Significant Increase in NYHA

Baggio et al. (17) looked at NYHA in patients with CHF and found a decrease in NYHA class when compared to baseline. One hundred seventy three hospitals were involved in this study and a total of 2,379 patents concluded the trail. All patients were in NYHA class II or III. Patients were supplemented with 50-150 mg/d of CoQ_{1o} with the majority (78%) receiving 100 mg/d for three months. To determine if there was an increase, decrease, or no change in NYHA class a two-seven point scales was used to assess the following clinical signs and symptoms: cyanosis, edema, pulmonary rates, enlargement of the liver area, jugular reflux, dyspnea, palpitation, insomnia, sweating, subjective arrhythmia, vertigo, and nocturia. All signs and symptoms were measured at baseline and after treatment.

There was a total of 664 (27.3%) patents in NYHA class III. One hundred four patients (28.6%) decreased to NYHA class II after supplementation of CoQ_{10}. Three hundred ninety one patients (60.4%) did not change their score or improved it but not enough to switch classes and 69 patients (10.8%) experienced an increase in score to class IV. There was 1,715 patents (72.2%) in NYHA class II and after receiving CoQ_{10} 1,538 patients (89.7%) decreased to class I. One hundred forty two patents (8.3%)

Table 2. NYHA at baseline and after 12 weeks of placebo or CoQ_{10}.

Table 3

Noninvasive parameters

	Q_{10} baseline	Q_{10} 12 weeks	Stat.	Placebo baseline	Placebo 12 weeks	Stat.
LVEF	26 ± 8	26 ± 11	ns	32 ± 9	35 ± 8	ns
NYHA	3A	2B	ns	2B	2B	ns
BP mean rest	93 ± 11	91 ± 13	ns	90 ± 7	94 ± 9	ns
BP mean work	118 ± 15	113 ± 13	ns	109 ± 7	112 ± 9	ns
HR rest	75 ± 9	71 ± 11	ns	65 ± 10	66 ± 11	ns
HR work	109 ± 12	104 ± 12	ns	97 ± 14	94 ± 15	ns

Munkholm H, Hansen H, Rasmussen K. Coenzyme Q_{10} treatment in serious heart failure. *BioFactors*. 1999;9:285-289.

experienced no change in class and 35 patents (2%) increased their score to class III. Baggie et al (14) concluded that CoQ_{10} supplementation tends to decrease NYHA class but these results were not supported by statistics.

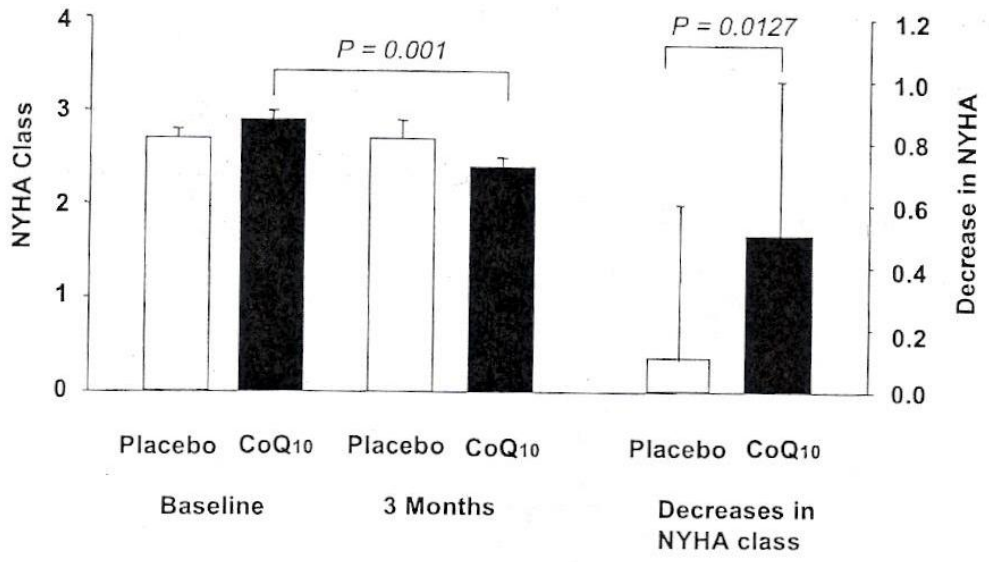
Berman at el. (10) a study perversely mentioned, evaluated NYHA classification in patients in NYHA classes III or IV and found that patients supplemented with CoQ_{10} experienced a significant decrease in NYHA class when compared to baseline. After three months of 60 mg U/d of Ultrasome CoQ_{10} or placebo there was no change in NYHA classification in placebo group and a decrease in class of 0.7 in CoQ_{10} group. Their NYHA class decreased from 3.1 to 2.5, resulting in P=0.01. Patents performed a six minute walk test to determine limitations during physical activity and other signs and symptoms were evaluates such as fatigue, nocturia, and dyspnea to determine changes in NYHA classification.

Another study, perversely mentioned, by Rosenfeldt et al. (11) observed NYHA class in patients in class II or III experienced a significant decrease in class when compared with placebo group. After three months of 150 mg/d CoQ_{10} or placebo NYHA class in CoQ_{10} group (n=17) showed a significant decrease of 0.5 class compared to placebo (n=18) group, P=0.001. Figure 3. Patients performed a six minute walk test to determine their limitations during physical activity.

Conclusion on NYHA

All trials lasted for three months and CoQ_{10} dose ranged from 60 mg/d to 200 mg/d. Mumkholm et al. (16) supplemented patients with the highest CoQ_{10} levels at 200 mg/d and was the only study presented that found no change in NYHA classification. Variations in exercise tests to determine patient's limitations during physical activity in order to classify NYHA class may have affected results. The criteria for NYHA class are subjective measures, which relies on patient's reporting their signs and symptoms. In addition other characteristics can limit exercise ability such as age, weight, and history of physical activity which may affect their performance and affect NYHA classification. After looking at the data presented it can be concluded that supplementation of CoQ_{10} may decrease NYHA classification.

Figure 3. Effect on CoQ_{10} and placebo on NYHA class.



l. Effect of CoQ_{10} treatment on NYHA class. Left side: NYHA class at base line and three months in placebo and CoQ_{10}
). Right side: Difference in improvement in NYHA class between the CoQ_{10} group and the placebo group.

Rosenfeldt F, Hilton D, Pepe S, Krum H. Systematic review of effect of coenzyme Q_{10} in physical exercise, hypertension and heart failure.

Table 3. Summary Table of Data.

Authors	Number of participant	Duration	Dosage of CoQ10	Ejection Fraction	NYHA	Cardio Capacity
Watson et al.	30	3 mo	100 mg/d	No change	n/a	n/a
Khatta et al.	55	6 mo	200 mg/d	No change	n/a	n/a
Langsjoen et al. (4)	19	12 wk	100 mg 3xd	Significant Increase	n/a	n/a
Rango et al.	60	4 mo	50 mg 2xd	Significant Increase	n/a	n/a
Belardinelli et al.	21	4 weeks	100 mg 3xd	Significant Increase	n/a	n/a
Witte et al	28	9 mo	150 mg/d	Significant Increase	n/a	n/a
Langsjoen et al. (8)	7	Varied average of 12 mo	Varied average of 580mg	Significant Increase	n/a	n/a
Permanetter et al.	25	4 mo	33.3 mg/3xd	n/a	n/a	No change
Berman et al.	32	3mo	60 mg/d	n/a	Significant Improvement	Significant Increase
Rosenfeldt et al	35	3mo	150 mg/d	n/a	Significant Improvement	Significant Increase
Hofmain-Bang et al	79	3 mo	100 mg/d	n/a	n/a	Significant Increase

Kamikawa et al	12	1 mo	150 mg/d	n/a	n/a	Significant Increase
Morisco et al	6	1 mo	50 mg 3 x day	n/a	n/a	Significant Increase
Mumkholm et al.	22	3 mo	100 mg 2 x day	n/a	No change	n/a
Baggio et al.	2,379	3 mo	50-150 mg/d 75% 100 mg/d	n/a	Significant Improvement	n/a

CONCLUSION/IMPLICATIONS FOR PRACTICE

Current research presented has shown that CoQ_{10} may improve certain characteristics of HF and improve the heart's ability to pump blood and supply tissues and organs with adequate oxygen. Supplementation of CoQ_{10} tends to increase plasma concentrations which may increase ATP production and energy supplied to the heart. Many studies observed an increase in ejection fractions after CoQ_{10} treatment meaning that the percentage of blood leaving the heart each time it contracts increased. The more blood leaving the heart helps deliver more oxygen to tissues and organs and causes them to become fatigue less quickly. This directly impacts patient's ability to perform physical activity and many studies have seen an increase in cardio tolerance after supplementation. Physical activity level is used as a criteria to place patients in NYHA classes. A decrease in limitations during physical activity may result in a decrease NYHA class.

The majority of studies presented show that supplementation of CoQ_{10} has benefits. Supplementation of an average of 150 mg/d has shown to increase ejection fraction, exercise capacity and decrease NYHA classification. Most studies had limited number of participants with the exception of Baggio et al (16) and varying criteria to measure exercise capacity and change in NYHA class. After evaluating all data presented there is evidence to support that CoQ_{10} provides beneficial outcomes. This literature review concludes that supplementation of CoQ_{10} in patients with HF may increase ejection fraction, exercise capacity, and decrease NYHA classification.

CoQ_{10} is safe with no side effects except occasional stomach upset. Recommended dose of CoQ_{10} is 60-250 mg/d. Studies with higher doses were more likely to show benefits. Supplementation should be taken with meals to enhance absorption. CoQ_{10} is inexpensive and readily available over the counter. Patients can buy a 60 capsule bottle of 100 mg CoQ_{10} for approximately $30. There are also natural food sources of CoQ_{10} such as oily fish including salmon and tuna, organ meat such as liver, and whole grains. Eating these foods along with supplementation may be beneficial to patients with HF.

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