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EDITORIAL

Anti-oxidized low-density lipoprotein antibodies in chronic heart failure

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Abstract

Oxidative stress may play a significant role in the pathogenesis of heart failure (HF). Antibodies to oxidized low-density lipoprotein (oxLDL Abs) reflect an immune response to LDL over a prolonged period and may represent long-term oxidative stress in HF. The oxLDL plasma level is a useful predictor of mortality in HF patients, and measurement of the oxLDL Abs level may allow better management of those patients. Antibodies to oxLDL also significantly correlate with the New York Heart Association score. Hypercholesterolemia, smoking, hypertension, and obesity are risk factors for atherosclerotic coronary heart disease (CHD) leading to HF, but these factors account for only one-half of all cases, and understanding of the pathologic process underlying HF remains incomplete. Nutrients with antioxidant properties can reduce the susceptibility of LDL to oxidation. Antioxidant therapy may be an adjunct to lipid-lowering, angiotensin converting enzyme inhibition and metformin (in diabetes) therapy for the greatest impact on CHD and HF. Observational data suggest a protective effect of antioxidant supplementation on the incidence of HD. This review summarizes the data on oxLDL Abs as a predictor of morbidity and mortality in HF patients.

Key words: Heart failure; Oxidized low-density lipoproteins; Antibodies; Antioxidants

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INTRODUCTION

Packer[1] described the clinical syndrome of chronic heart failure (HF) as "characterized by abnormalities of left ventricular function and neurohormonal regulation, which are accompanied by effort intolerance, fluid retention and decreased longevity." Endothelial dysfunction in patients with HF is a critical component in the characteristic systemic vasoconstriction and reduced peripheral perfusion. Endothelial regulation of vascular tone is mediated mainly by nitric oxide (NO)[2]. Oxidative stress is a general term that denotes the imbalance between factors that promote production of reactive oxygen spe-

cies (ROS) and the ability to oppose/scavenge and subsequently neutralize the byproducts of these reactive free radicals[3-5]. Thus ROS react with NO in the setting of decreased antioxidant defenses that would normally clear these radicals, culminating in attenuated endothelium-dependent vasodilatation in patients with HF[2,3-5].

Several lines of evidence suggested that oxidative stress could be involved in the pathogenesis of HF. Free radicals also have a pathogenetic role in the progressive deterioration of the decompensating myocardium[5,6]. Infusion of oxidized free radicals produces a marked decrease in myocardial contractility[2,3,6-10]. Immunoglobulins (Ig) to oxidized low-density lipoprotein (oxLDL) were discovered by chance by Beaumont[9] in a patient with multiple myeloma and hyperlipidemia. Antibodies (Abs) against oxLDL were found in many diseases other than atherosclerosis, among them HF, diabetes mellitus, renovascular syndrome, uremia, rheumatic fever, ankylosing spondylitis and lupus erythematosus[2,3,11,12]. Moreover, antibody levels of oxLDL antibodies were reported to correlate significantly with the clinical status of HF patients, as defined by their New York Heart Association (NYHA) score[8]. Measurements of oxLDL Abs also reflect the status of lipoprotein oxidation over a prolonged period[3,10].

Assessment of oxidative stress in humans is complex since there is no reproducible, standardized methodology[7,8,10]. The aim of this review is to acquaint the reader with the recent research on oxLDL Abs and their use and determination in clinical practice. We also cite current studies on antioxidants and review their implications in the treatment in HF from the view that these antioxidants may contribute to longevity[11-17].

PATHOPHYSIOLOGY OF LDL OXIDATION

Oxidation of LDL is a complex process taking place in both the extra- and intracellular space[3,10,12-15]. It plays an important role in endothelial dysfunction as follows. Modification of LDL particles due to oxidation, glycation and binding of advanced glycation end-products (AGEs) or malondialdehyde (MDA, a final product of lipid peroxidation) is considered as being highly important in the process of atherogenesis[4,7]. Oxidatively modified LDL particles are distinguished by another receptor type, which was discovered on the surface of macrophages and termed "the scavenger receptor[3,10,13,14]. Uncontrolled intake of LDL converts macrophages to foam cells, and their accumulation under the vascular endothelium is involved in the initiation of atherosclerosis[7,13,14]. Modified LDL particles show chemotactic, cytotoxic and immunogenic properties at the end of this oxidative process. The oxLDL particles express a large number of epitopes and cause the production of a polyclonal mixture of Abs (isoantibodies IgA and IgG) caused by high-density lipoprotein (HDL) and LDL polymorphism against these products, especially the lipid phase of LDL, against apoB100 modified by MDA and 4-hydroxynonenal[3,12-14]. Immunoglobulins to oxLDL (Abs against oxLDL) can be demonstrated either directly in intimal lesions or as a component of circulating immune complexes[2,12-14]. Increased generation of ROS reportedly promoted exercise intolerance and diminished tissue perfusion due to increased peripheral resistance in patients with HF[2]. Moreover, oxLDL Abs levels correlated with the quality of HF control, as reflected by the number of hospital admissions recorded in the year prior to enrolment[4,8]. The changes and correlations of oxLDL Abs, anti-beta-2-glycoprotein I IgG and antiphospholipid Abs support the immunological link between thrombotic and atherosclerotic processes in the human body[3,13,14], thus indicating that the high concentration of oxLDL Abs correlates with the severity of HF.

CARDIOVASCULAR DISEASE: ANIMAL STUDIES

Experimental studies in animal models of cardiac dysfunction, such as those produced by myocardial infarction after left anterior descending artery ligation, doxorubicin administration and pressure overload, all exhibited increased production of free radicals[16-20]. Animal studies have addressed the potential importance of the generation of intracellular ROS in the cells that normally comprise the vessel wall. Superoxide anion O_2^- was increased in the aortas of rabbits who were fed high cholesterol diets for a period of several weeks, leading to impaired endothelial-dependent relaxation that was reversible by treatment with polyethylene-glycolated superoxide dismutase or probucol[2,19]. Antioxidant therapy was shown to attenuate myocardial damage induced by doxorubicin[19-21]. Increased expression of the antioxidative superoxide dismutase gene has been reported in rats without HF after endurance training that resulted in greater NO activity[15,20-22].

Depressed vascular endothelial function occurred in experimental HF in rats despite an increase in endothelial NO synthetase (*eNOS*) gene expression, and was attributed to increased vascular O_2^- production[17,23]. Dhalla *et al*[17] suggested that the mechanism by which oxidative stress is increased by hyperlipidemia could involve the renin-angiotensin system. Both endothelial dysfunction and lesion area were improved by treatment with an angiotensin Ⅱ receptor antagonist in a rabbit model[20]. Moreover, nicotinamide adenine dinucleotide phosphate oxidase subunit expression and O_2^- production doubled in rats made hypertensive by angiotensin Ⅱ infusion[22]. Because LDL upregulates angiotensin Ⅱ receptor type 1 (AT1) expression[24], the effects of angiotensin Ⅱ can be exacerbated by hypercholesterolemia. Finally, angiotensin Ⅱ causes hypertrophy of vascular smooth muscle in a ROS-dependent fashion, a process which can participate in arterial thickening[17,23].

CARDIOVASCULAR DISEASE: HUMAN STUDIES, ATHEROSCLEROSIS

Atherosclerosis is the main cause of HF and the most

frequent cause of death in developed countries. Cholesterol itself is neither toxic nor antigenic towards the LDL particles that transport cholesterol: they become harmful for the organism if they are altered. It is this modification due to oxidation, glycation and binding of AGEs or MDA, which is considered most important in the process of atherogenesis. The interaction of modified LDLs with scavenger receptors on the surface of the endothelium represents the first phase of the atherosclerotic process. Lipid peroxidation can be observed *in vitro* as a change in the lag phase of LDL oxidation stimulated by Cu^{2+} ions[2,3,7,11-14]. *In vivo* lipid peroxidation was especially apparent in tissue macrophages, endothelial cells and smooth muscle cells, and hemoglobin, hypochlorous acid, ceruloplasmin, lipoxygenase and peroxidase appeared to be effective oxidants[3,11,12].

ANTI-OXLDL ABS - PREDICTOR OF MORBIDITY AND MORTALITY IN CORONARY ARTERY DISEASE

Oxidized LDL is present in atheromatous plaques and correlates with the extent of atherosclerosis[4-6,12-17,20,22-24]. Assessment of oxLDL Abs may more reliably reflect the level of oxidative stress than plasma oxLDL. These Abs have already been shown to correlate with the extent of atherosclerosis and predict future myocardial infarction[12,14-17,19-24]. Elevated levels of Abs against oxLDL were found in many investigations to be predictive of myocardial infarction[3, 6,7,9, 22,23]. The correlation was independent of LDL cholesterol levels, though oxLDL Abs had an additive predictive effect. The mean Ab level, as expressed in optical density units, was significantly higher in cases of myocardial infarction than in controls (0.412 *vs* 0.356, $P = 0.002$). After adjustment for age, smoking, blood pressure, and HDL cholesterol level, there was a 2.5-fold increased risk (95% confidence interval, 1.3-4.9) of a cardiac endpoint in the highest tertile of Ab level compared to the lowest tertile ($P = 0.005$ for trend)[19]. Thus, elevated Ab levels added to the predictive effects of classic coronary risk factors[5,15-17].

MYOCARDIAL INSULIN RESISTANCE

Recent human studies strongly support a link between insulin resistance and non-ischemic HF[25]. The occurrence of a specific insulin-resistant cardiomyopathy, independent of vascular abnormalities, is now recognized. Cardiac insulin resistance is characterized by reduced availability of sarcolemmal Glut4 transporters and consequent lower glucose uptake. A shift away from glycolysis towards fatty acid oxidation for adenosine triphosphate supply is apparent and is associated with myocardial oxidative stress.

The pathophysiology of cardiovascular disease in diabetes involves traditional and novel cardiac risk factors, including hypertension, dyslipidemia, smoking, genetic factors, hyperglycemia, insulin resistance/hyperinsulinemia, metabolic abnormalities, oxidative/glycoxidative stress, inflammation, endothelial dysfunction, a procoagulant state and myocardial fibrosis. Specific vascular, myopathic and neuropathic alterations have been suggested to be responsible for the excessive cardiovascular events and mortality in diabetes[25]. These alterations manifest themselves clinically as coronary heart disease (CHD) and HF. In order to contain the emerging epidemic of cardiovascular disease, diabetic patients should have excellent glycemic control, a low normal blood pressure and low levels of LDL cholesterol, and be taking an angiotensin-converting enzyme inhibitor and aspirin, which may prevent cardiovascular disease[25]. Metformin stimulates production of endothelial NOS, increases plasma NO levels, and improves myocardial insulin resistance.

HF

Tsutsui *et al*[23] measured the plasma level of oxLDL by sandwich enzyme-linked immunosorbent assay with a specific monoclonal antibody against oxLDL, and showed that plasma levels of oxLDL had a good correlation with HF severity and mortality. In that study, the plasma oxLDL level was significantly higher in patients with severe HF than in patients with mild HF and healthy subjects. Others found a significant negative correlation between the plasma level of oxLDL and left ventricular ejection fraction (LVEF), and a significant positive correlation between the oxLDL plasma level and circulating norepinephrine levels[16,24]. In another study most patients (mean age 71.5 years) had systolic HF, with mean NYHA functional class of 2.7 and mean LVEF of 39.7%. Mean IgG oxLDL Abs levels in patients with hospital admissions were 3.4 times higher than those in subjects not hospitalized over the previous year[8]. Assessments of oxLDL IgG levels, were able to discriminate between patients with clinically controlled HF and patients requiring hospital admission[7,8,10].

Levels of oxLDL Abs also correlated with the presence of chronic atrial fibrillation, a finding that could be related to more severe HF or to the possible involvement of oxidative stress in the pathogenesis of atrial fibrillation[3,12-16].

Anti-oxLDL Abs and B-type natriuretic peptide

Several studies found that the discriminative power of anti-oxLDL Abs was even better than that obtained for serum n-terminal pro-B-type natriuretic peptide (Nt pro-BNP) in patients admitted for worsening HF[8,24,26,27]. These results support the observation of elevated oxidative stress in patients with HF. Importantly, no association was found between Nt pro-B-type and anti-oxLDL Ab levels, suggesting that determination of the latter may have an incremental value over that provided by the former[8]. Plasma levels of oxLDL Abs were shown in many investigations to be increased with the severity of

HF in patients with different etiologies, e.g., systolic, diastolic, ischemic and valvular diseases[2-4,8,14-17,20,21-24].

BNP is an established surrogate follow-up marker for patients with CHF[7,8,24,27]. The results of a study by our group[8] demonstrated that NT pro-BNP plasma levels, oxLDL Abs, LVEF and NYHA class were of prognostic value in terms of outcome in HF patients as assessed by multivariate analysis. However NT pro-BNP was a better predictor of all-cause mortality, and oxLDL Abs plasma levels were a significant independent predictor of long-term morbidity and mortality in HF.

Abs to oxLDL significantly correlated with the mean NYHA score[8]. The apparent differential predictive power of oxLDL Abs and NT pro-BNP may be attributable to the different mechanisms leading to their elevated levels. Thus, NTpro-BNP represents the neurohormonal axis, whereas oxLDL Abs mirror oxidative stress. These two mechanisms governing HF progression can predict different endpoints in the management of patients with HF.

CLINICAL IMPACT OF OXLDL ON REHABILITATION AND PROGNOSIS

Oxidized LDL Abs could prove to be a useful marker for predicting the clinical course and outcome of many patients with HF of different etiologies. There is an urgent need to develop simplified assays that are applicable for high-throughput analysis. The patient's oxidant status can be assessed and the true efficacy of antioxidant therapies can then be established so that effective therapy can be provided selectively. Refinement of clinical trial designs to incorporate such indices would ensure recruitment of appropriate patients, identify the most efficient antioxidant dosing regimens and perform controlled analysis. Better monitoring and prognostic predictors are required in order to achieve further improvement in the management of patients with HF[8,28].

Vascular endothelial function and, particularly, NO-mediated vasodilation are clearly enhanced by physical training among HF patients[12,26,29-32]. The molecular basis for this improvement is unclear, although animal studies support either of two (nonexclusive) mechanisms. One attractive hypothesis is that training induces NO production by increased expression of the gene encoding eNOS[2,3,5,32]. The NOS promoter contains a cis-acting shear-stress response element[32], and so its expression could be regulated directly by periodic increases in blood flow that occur during physical training. Alternatively, vasodilatation could be enhanced indirectly after training by a distinct mechanism that decreases oxygen free radicals that otherwise can inactivate NO.

Rehabilitation programs involving immersed exercises are more and more frequently recommended for even severe cardiac patients. Laurent *et al*[33] studied one group of 24 male stable CHF patients and 24 male coronary artery disease (CAD) patients with preserved left ventricular function who participated in a rehabilitation program performing cycle endurance exercises on land. They also performed gymnastic exercises either on land (first half of the participants) or in water (second half). Resting plasma concentration of NO metabolites (nitrates and nitrites) and catecholamines were evaluated, and a symptom-limited exercise test on a cycle ergometer was performed before and after the rehabilitation program[33]. The plasma concentration of nitrates in the groups that performed water-based exercises was significantly increased (P = 0.035 for CHF and P = 0.042 for CAD), whereas it did not significantly change in the groups that performed gymnastic exercise on land. Plasma catecholamine concentration levels did not change but the cardiorespiratory capacity of all patients was significantly increased after rehabilitation. The water-based exercises seemed to effectively increase the basal level of plasma nitrates. Such changes may be related to an enhancement of endothelial function and may be of importance for the patient's overall health status[33].

ANTIOXIDANTS

As mentioned earlier, free radicals have a role in the progressive deterioration of the decompensating myocardium[7,8]. Antioxidants terminate these chain reactions by removing free radical intermediates and inhibiting other oxidation reactions. They do this by being oxidized themselves, therefore antioxidants, e.g., thiols, ascorbic acid, or polyphenols, often act as reducing agents[33-35]. Overall, these low molecular mass antioxidant molecules add significantly to the defense provided by the enzymes superoxide dismutase, catalase and glutathione peroxidase. However, antioxidant vitamin therapy has not been convincingly demonstrated in randomized trials as being beneficial[35]. The data are, however, entirely consistent with the alternative hypothesis, that reduced oxidative stress may account for the increase in vascular NO-mediated vasodilation. An insight into the mechanism of this process may be relevant when considering therapies for exercise-intolerant HF patients[5,6,11,34]. A critical review of the role of dietary antioxidants suggested that vitamins A and E along with coenzyme Q10, flavonoids, and resveratrol show promise in extending human life. That review examined current studies on antioxidants and their implications in the aging process, with the conclusion that these antioxidants may contribute to longevity[11,35-45].

However, the possibility of translating the patient's oxidant status into use of effective antioxidant drugs is not supported by current evidence. Notwithstanding promising observational data, prospective, double-blind, placebo-controlled trials did not support a causal relationship between antioxidant therapy, mainly vitamin supplements, and lowering of CAD risk[46].

We reviewed recently published basic research on the protective cardiovascular effects of antioxidants, especially resveratrol, because they may lead to the development of new treatment in patients with HF[37]. Vitamin A has been called the "anti-infective" vitamin because of its role in supporting the immune system. Carotenoids,

which are pre-formed vitamin A found in plants, turned out to be determinants of longevity[40]. Vitamin A supplementation led to an improvement in the lifespan of mice only when its use was initiated at the beginning of life[40]. One of the most widely researched antioxidants, vitamin E, was similarly found to extend life in mice when initiated in the early years. Vitamin E may protect older healthy individuals against atherogenesis (formation of thick plaque of cholesterol and other lipids in arterial walls), improve relearning ability, and reduce cancer formation[35]. However, vitamin E supplementation might be associated with an increase in total mortality, HF, and hemorrhagic stroke[35]. Vitamin E has been shown to increase oxidative resistance *in vitro* and prevent atherosclerotic plaque formation in mouse models[40]. Consumption of foods rich in vitamin E has been associated with a lower risk of CHD in middle-aged to older men and women[35]. However clinical studies have not demonstrated a benefit of vitamin E in the primary and secondary prevention of cardiovascular disease[35]. The American Heart Association does not support the use of vitamin E supplements to prevent cardiovascular disease, but it does recommend the consumption of foods abundant in antioxidant vitamins and other nutrients[35,47].

Coenzyme Q10 is the only known antioxidant synthesized in the body[48]. It extends life by reducing oxidative damage, thereby lowering cardiovascular risk and inflammation. The Q10 is the primary homologue found in longer-living mammalian species, including human beings. There were non-significant trends towards increased LVEF and reduced mortality in nine randomized trials of Q10 in HF published up to 2003[48]. Q10 decreases proinflammatory cytokines and decreases blood viscosity, which is helpful in patients with HF and CAD. It also improves ischemia and reperfusion injury of coronary revascularization. Q10 decreases proinflammatory cytokines and decreases blood viscosity, which is helpful in patients with HF and CAD. It also improves ischemia and reperfusion injury of coronary revascularization[48]. It was recently found to be an independent predictor of mortality in congestive HF. Coenzyme Q10 has also been found to be helpful in vertigo and Meniere-like syndrome by improving the immune system[48]. There is ongoing research aimed at firmly establishing its role in the treatment of cardiovascular diseases[40].

Flavonoids are the most common group of polyphenolic compounds in the human diet and are found mostly in plants. Flavanol-rich chocolate acutely improves vascular and platelet function in patients with HF[45]. Green tea supplementation has been found to protect against oxidative stress, and it increased antioxidant ability in the rat brain[37]. Another flavonoid, anthocyanin, has also been shown to be protective against vascular disease[37,45]. Resveratrol is a polyphenolic compound found in grapes, red wine, purple grape juice, peanuts, and some berries. Evidence from the "French Paradox" and from controlled studies point to its effectiveness in extending life[37]. It has also been associated with improved bone density, motor coordination, cardiovascular function, and in delaying cataracts. Other studies also show that it offers protection against Alzheimer's disease and prolongs the human lifespan as well as retarding aging[37]. The cardiovascular protective capacities of resveratrol are associated with multiple molecular targets and this may lead to the development of novel therapeutic strategies for atherosclerosis, ischemia/reperfusion, metabolic syndrome, and HF[37].

The pleiotropic effects of statins appear to result from improvements in endothelial function, a reduction in inflammatory mediators, a decline in the development of atheroma through the stabilization of atheromatous plaques, and the inhibition of cardiac hypertrophy through an antioxidant mechanism[38]. Long-term statin use may reduce morbidity and mortality rates in a broad range of patients[38]. However, lower LDL cholesterol levels appear to predict a less favorable outcome in patients with HF, particularly those taking statins, raising questions about the need for an aggressive LDL-cholesterol-lowering strategy in patients with HF, regardless of its etiology[35,49]. Clopidogrel treatment in patients with CAD not only inhibits platelet activation but also improves endothelial function and NO bioavailability. HF is associated with endothelial dysfunction and increased platelet activation. Hu *et al*[50] investigated whether treatment with clopidogrel modified endothelial function in HF following myocardial infarction and concluded that endothelial dysfunction and vascular oxidative stress have a positive prognostic impact on cardiovascular events.

Nitrates are very effective anti-ischemic drugs used for the treatment of patients with stable angina, acute myocardial infarction and chronic congestive HF. There are new data on the protective properties of the organic nitrate pentaerythrityl tetranitrate, which, in contrast to all other organic nitrates, is able to upregulate enzymes with a strong anti-oxidative capacity thereby preventing tolerance and the development of endothelial dysfunction[40]. Carvedilol is a beta-blocker with antioxidant properties. In several large clinical trials on patients with mild to severe HF, treatment with carvedilol improved mortality, especially in severe cases with the worst prognosis[2,41]. The beta-blocker nebivolol has been used in Europe for almost 10 years[42]. Like carvedilol, it belongs to the third generation of beta-blockers which possess direct vasodilator properties in addition to their adrenergic blocking characteristics[42]. Nebivolol has the highest beta (1)-receptor affinity among the beta-blockers and, most interestingly, it substantially improves endothelial dysfunction *via* its strong stimulatory effects on the activity of e-NOS and *via* its antioxidative properties. Because impaired endothelial activity is considered a major causal role in the pathophysiology of congestive HF, the endothelium-agonistic properties of nebivolol suggest that this drug might provide additional benefit beyond beta-receptor blockade. Clinically, this compound has been proven to have antihypertensive and anti-ischemic effects as well as beneficial effects on hemodynamics and prognosis in

patients with chronic congestive HF[41,42]. Further studies are required to compare the benefit of nebivolol in terms of its prognostic impact in patients with HF[42]. Spironolactone is an aldosterone receptor antagonist that has been shown to decrease mortality in patients with severe HF when added to conventional therapy[43]. Treatment with spironolactone resulted in a significant increase in the forearm blood flow response to acetylcholine ($P < 0.001$)[43]. This demonstration of improvement in endothelial function (caused by oxidative stress) provides a novel mechanism for the beneficial effect of spironolactone in HF patients[43]. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers are widely used drugs for HF to prevent hypertrophy of the myocardium and vascular smooth muscle caused by angiotensin II in a ROS-dependent fashion, which can contribute to arterial thickening[39,44]. Treatment of patients with HF, CAD and other conditions associated with endothelial dysfunction induced by oxidative stress with an ACEI (especially quinaprilate) has been shown to improve endothelium-dependent vasodilation and contribute to increased exercise capacity[39,44].

Some studies have shown that metformin activates AMP-activated protein kinase and has a potent cardioprotective effect against ischemia/reperfusion injury as result of oxidative stress. Both left ventricular fractional shortening and left ventricular end-diastolic pressure were significantly improved in dogs treated with oral metformin. As a result of these effects, metformin decreased apoptosis and improved cardiac function in failing canine hearts. Therefore, metformin may be a potential new therapy for HF[51,52].

CONCLUSION

The OxLDL Ab level is a useful predictor of morbidity and mortality in HF patients. Assessment of oxidative stress in humans is complex. Since there is no reproducible, standardized methodology, additional prospective data with further determination of oxLDL Ab levels may prove oxLDL Abs as a useful marker for predicting exacerbations in patients with HF.

Therapies that improve endothelial function caused by oxidative stress have been shown to improve exercise tolerance and outcomes in patients with HF. Dietary antioxidants such as vitamin A along with coenzyme Q10, flavonoids, and resveratrol, and medicines such as spironolactone, pentaerythrityl tetranitrate, nebivolol, quinaprilate, clopidrogel and metformin show promise in extending human life in patients with HF.

Further research will be needed to elucidate therapies based on this biology that could increase NO production, interrupt the pathologic cascade that results in generation of free radicals, and augment antioxidant defenses in patients with HF.

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