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Dyslipidemia and heart failure: current evidence and perspectives of use of statins

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Abstract. – Heart failure (HF) is a condition with growing morbidity and mortality. Dyslipidemia in HF is not concentrated around hypercholesterolemia as in coronary artery disease. As a corollary, the robust benefits seen with statins across the spectrum of CAD have not been replicated in HF. Multiple potential pleiotropic effects of statins include anti-inflammatory, antioxidant, endothelial stabilization, antiapoptotic, anti-thrombotic, and modulation of the autonomic system apart from lipid lowering. These benevolent actions need to be counterbalanced with the potential derangement of ubiquinone, selenoprotein and endotoxin pathways. While small randomized and non-randomized studies demonstrated a multitude of benefits in clinical and surrogate endpoints, two large RCTs failed to demonstrate unequivocal benefits. However, multiple large meta-analyses do demonstrate definite improvement in clinical endpoints including death and heart failure hospitalization. The clinical likelihood of benefit was higher in younger patients with less advanced HF and use of lipophilic statins.

Key Words:
Heart failure, Dyslipidemia, Statins, Inflammation, Cholesterol.

Introduction

Management of patients with heart failure (HF) has always been a challenging task for physicians despite recent advances in both pharmacological and device therapy. HF is associated with significant mortality and morbidity with a resultant high economic burden[1]. The standard drug treatment of HF includes beta blockers, renin angiotensin aldosterone system (RAAS) blockade, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and diuretics. Device therapies include implantable cardioverter defibrillators and cardiac resynchronization therapy, and their usage has brought down mortality by approximately 50%[2]. With the introduction of novel pharmacological therapies in the form of angiotensin-receptor neprilysin inhibitor (ARNI) and sodium-glucose co-transporter-2 (SGLT2) inhibitors, there has been a further reduction in morbidity and mortality[3,4]. Nevertheless, despite these advances, there is still a scope for improvement owing to the increase in the burden of HF patients.

The role of statins in reducing morbidity and mortality is well documented in patients with coronary artery disease (CAD) or those who are at risk of cardiovascular diseases[5]. Statins are frontline drugs in both primary and secondary prevention of cardiovascular diseases[6,7]. However, evidence of statins benefit in heart failure is not well documented and is debatable. Therefore, the role of this narrative review is to discuss the current evidence and perspectives on statin use in patients with heart failure.

Literature Search

We searched the PubMed database up to December 2020 with the keywords "Heart failure" OR "HF" OR "Left ventricular dysfunction" OR "Cardiomyopathy" AND "Statins" OR "Statin" OR " Lipid lowering therapy" OR "Lipids" OR "Rosuvastatin" OR "Atorvastatin" OR "Pravastatin" OR"Lovastatin". We excluded case reports, case series, editorials, original studies with a sample sizes of less than 20, those involving animals, and those published in languages other than English.

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Dyslipidemia in HF-An Epidemiological Primer

Dyslipidemia is a well-known risk factor for cardiovascular (CV) diseases. It has been demonstrated in various clinical trials of lipid-modifying therapy that treatment with statins decreases the incidence of HF[8]. This finding suggests that dyslipidemia is a risk factor for HF, although this association may be mediated by the occurrence of myocardial infarction (MI).

On the contrary, some scholars[9] have emphasized the effect of lipid abnormalities on myocardium independent of MI. In the Framingham heart study[10], there was a clear association between increased risk of heart failure with elevated non-high density lipoprotein cholesterol (non-HDL-C) levels and decreased HDL-C levels. This association was continuous and graded after adjustment for established risk factors for heart failure and persisted even after adjustment for interim MI[10]. Kannel et al[11] have shown that an elevated total to HDL-C ratio is associated with increased HF incidence. Meanwhile, elevated triglyceride (TG) levels were implicated in increased risk for HF. In a sub-study of Multi-Ethnic Study of Atherosclerosis (MESA), increased TG, low HDL-C, and increased TC/HDL-C ratio were predictors of HF in diabetic patients compared to non-diabetic counterparts[12].

However, in other studies[13], this relationship between hypercholesterolemia and HF has been challenged. It was first reported in 1998[7] that lower levels of cholesterol in HF are significantly associated with increased mortality. This phenomenon of 'reverse epidemiology' in CHF is observed not only for serum cholesterol levels but also for body mass index and blood pressure. Thus, low cholesterol could just be due to advanced CHF, without any causal role, or high cholesterol could be an indicator of a greater metabolic reserve to deal with the disease. On the other hand, any association between increased mortality and lipid lowering therapy has not yet been demonstrated[14].

Dyslipidemia in HF: Predicted Underlying Mechanisms for Association

It has also been demonstrated that elevated cholesterol level is associated with elevated blood pressure, increased arterial stiffness, decreased vascular compliance, and increased left ventricular (LV) mass and wall thickness. All these can lead to both systolic and diastolic dysfunction of LV, which will ultimately promote HF *via* elevation of LV end-diastolic volume and pressure and decreased myocardial perfusion[15]. Also, decreased HDL-C concentrations are associated with increased LV mass and impaired LV diastolic and systolic function in patients with or without CAD[10]. Treatment with statins in HF patients with dyslipidemia and without overt CAD has also been shown to improve outcomes. Apart from lipid modification, the protective effect of HDL-C may be mediated by its pleiotropic effects. It improves endothelial function and has anti-inflammatory effects, which may be beneficial[10].

Statins – The Lower, the Better

Over the last 60 years, multiple randomized control trials (RCTs) and meta-analyses have proven the beneficial role of statins in improving CV outcomes. In a meta-analysis of 27 RCTs involving 134,537 patients[16], each 1 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C) produced an absolute reduction in major vascular events of about 11 per 1000 over 5 years. This benefit was seen irrespective of age, sex, presence or absence of prior vascular disease[16]. Recent trials of high doses of statins with more LDL-C reduction have been shown to further reduce ischemic events and mortality. In ODESSEY outcome and FOURIER long-term outcome trials, it was seen that LDL-C lowering even up to 25-30 mg/dl was well tolerated with the benefits of CV event reduction[17,18]. Thus, the results of these two trials reinforce the norm that for atherosclerotic cardiovascular risk reduction, the lower the LDL-C levels, the better it is (Figure 1).

Role of Inflammation in HF

Inflammation is a pathophysiological mechanism common to both atherosclerosis and heart failure. It is well known that one of the pathophysiological factors causing HF is a chronic inflammatory process, causing elevated levels of circulating proinflammatory cytokines, such as interleukin-1(IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), and acute phase indicators, such as high sensitivity C-reactive protein (hs-CRP)[19]. It was found in the RE-

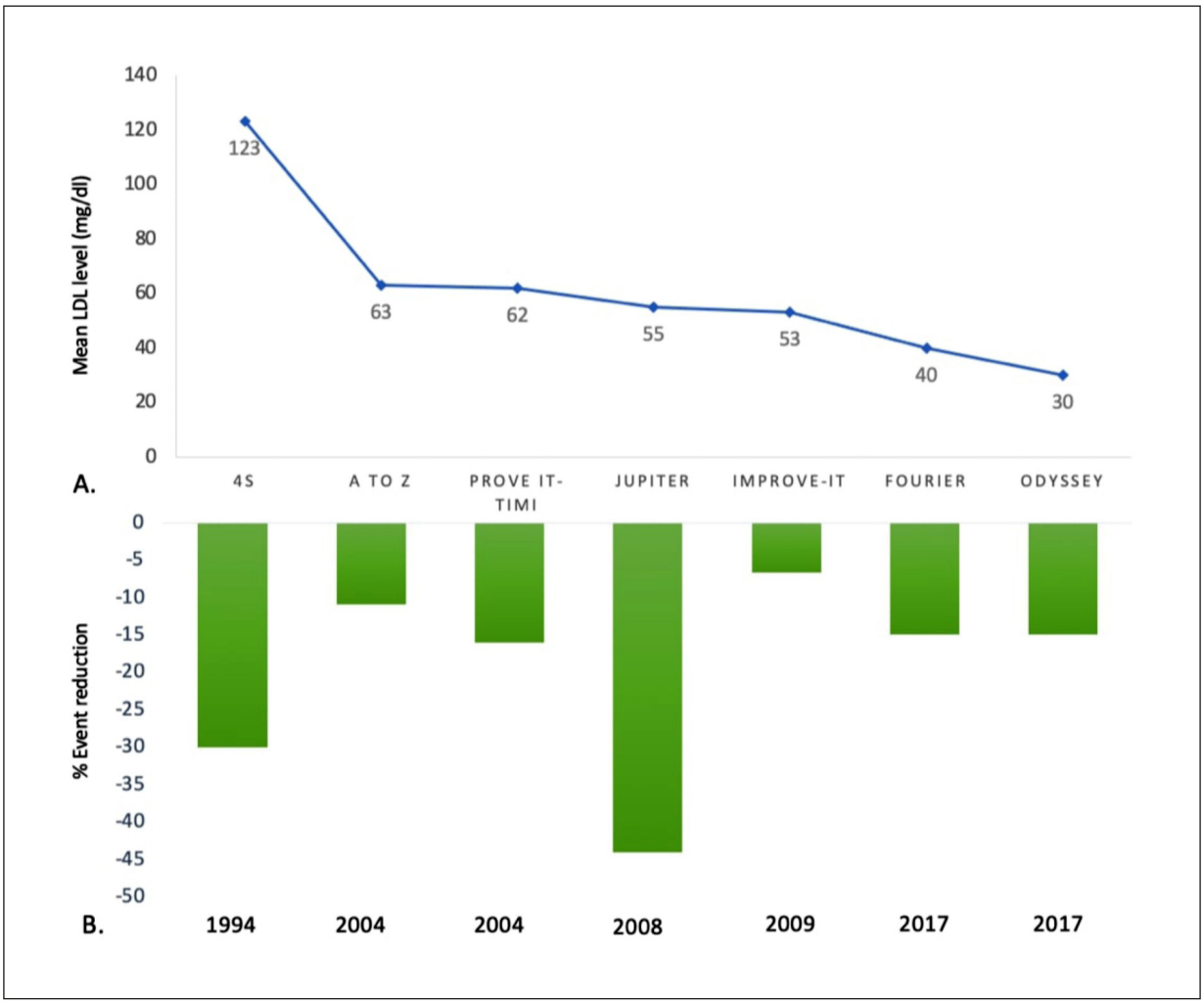

Figure 1. Low Density Lipoprotein (LDL) – lower is better. **A**, The mean LDL levels attained in large Randomized trials of lipid lowering stating from 4S trial (1994) till date. **B**, The corresponding relative risk reduction (%) in primary end point of each trial. [4S – Scandinavian Simvastatin Survival Study; A to Z – Aggrastat to Zocor; PROVE-IT TIMI 22 – Pravastatin or Atorvastatin evaluation and infection therapy TIMI 22; JUPITER – Justification for use of statins in prevention: An intervention trial evaluating rosuvastatin; IMPROVE-IT – Improved reduction of outcomes: Vytorin efficacy international trial; FOURIER – Further cardiovascular outcomes research with PCSK-9 inhibition in subjects with elevated risk; ODYSSEY Outcomes – Evaluation of cardiovascular outcomes after acute coronary syndrome during treatment with alirocumab].

LAX-HF (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure with Preserved Ejection Fraction) study that approximately 57% of patients with HF had elevated C-reactive protein (CRP) levels[20]. Also, in the Trial of Intensified *vs.* Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF), the median hs-CRP levels were 6.6 mg/l and 8.5 mg/l in patients with reduced and preserved ejection fractions, respectively[21]. An abnormal inflammatory response is thought to have contributed to various aspects of the HF phenotype, such as abnormal left ventricular reconstruction, endothelial dysfunction, inadequate erythropoiesis, and peripheral myopathy. Elevation of proinflammatory cytokine levels in response to myocardial injury is a factor which could increase mortality among CHF patients[22] (Figure 2).

Role of Statins in HF

Statins have been used for primary and secondary prevention of atherosclerosis for the past two decades. They reduce the risk of MI in pa-

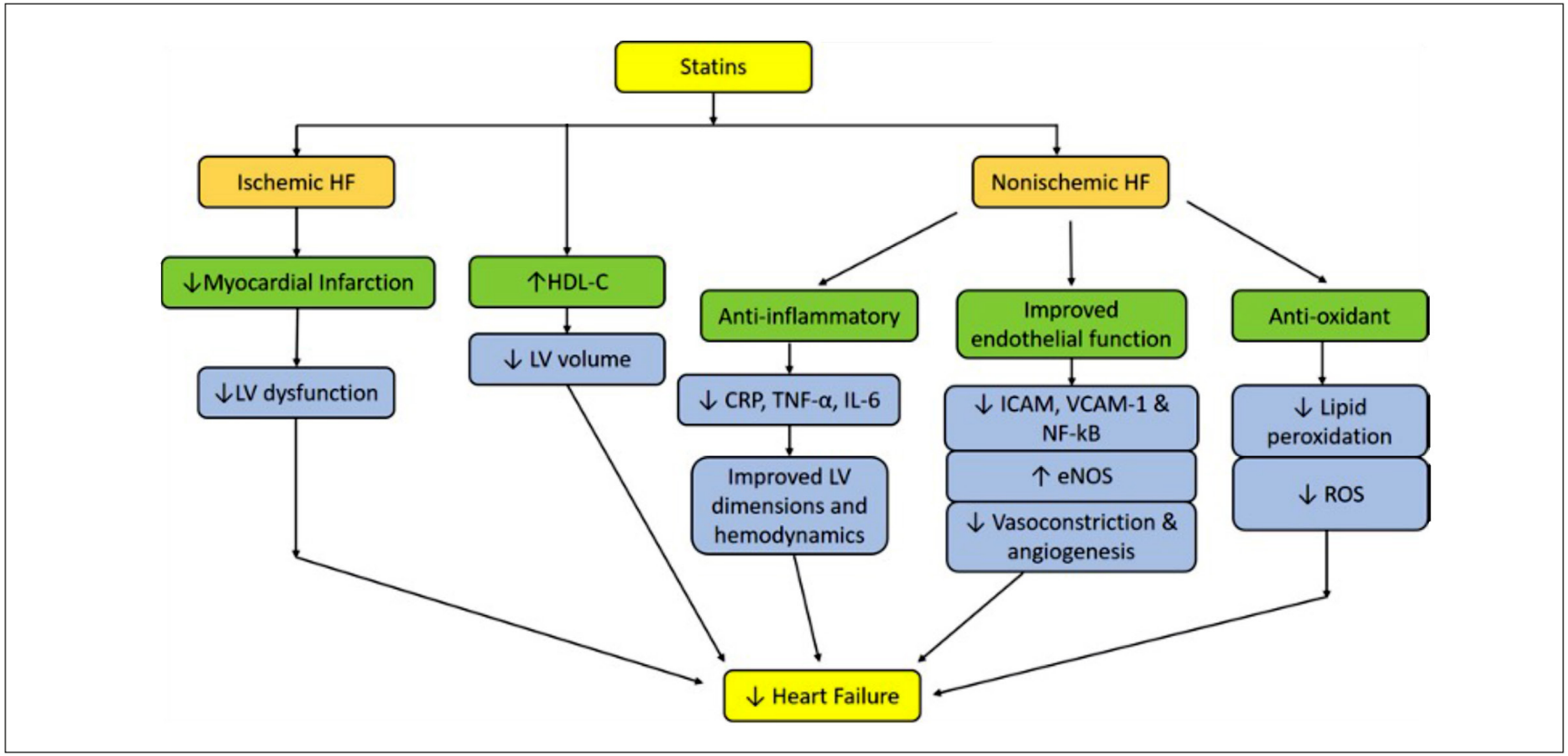

Figure 2. Mechanistic benefits and harms of statin use in patients with established heart failure. [HF – Heart failure; LV – left ventricular; HDL-C – high density lipoprotein cholesterol; ROS – Reactive oxygen species; CRP – C reactive protein; eNOS – endothelial nitric oxide synthase].

tients with well-established CAD or those who are at risk for CV disease, thus reducing CV morbidity and mortality. The relationship between serum cholesterol concentration and mortality in HF is a subject of debate. It has been postulated on the basis of meta-analysis of two observational studies that there is a decreased risk of hospitalization or death resulting from CV causes. This benefit was independent of the initial level of cholesterol, disease etiology, or the clinical condition of the patient[23]. Vrtovec et al[24] showed that statins reduce the risk of sudden death in patients with advanced HF. They found that in patient with LVEF <30% and cholesterol levels >150 mg%, atorvastatin reduced the cholesterol levels along with a reduction of all-cause mortality during the 1-year follow-up in comparison to the control group.

Statins as an Anti-Inflammatory Agent for HF

Zhang et al[19] performed a meta-analysis of 10 randomized studies incorporating 6,000 patients randomly assigned to receive either statin or placebo. The analysis revealed that statin treatment was associated with a significant reduction of hs-CRP concentration, but there was no influence on the concentrations of IL-6 or TNF-α. The benefit was most significant in patients in patients over 60 years of age, with LVEF >30%, with HF of ischemic etiology, and those who continued their treatment for at least 12 months[19]. On the other hand, Yamada et al[25] demonstrated that atorvastatin reduced the concentration of interleukin-6 and CRP. They also observed that there was a significant improvement in cardiac hemodynamic parameters with a reduction of left ventricular dimensions and an increase in LVEF. The results suggest that statins exert anti-inflammatory actions and inhibit cardiac muscle cell apoptosis. In another study by Nakagomi et al[26], it was demonstrated that in HF patients, the concentration of TNF-α and IL-6 was significantly higher than in healthy persons. There was a significant reduction in these circulatory cytokines by statin therapy owing to their anti-inflammatory actions with reduction in atherosclerotic plaques. Thus, it was concluded that statins contribute to a significant improvement in prognosis in patients with HF and concomitant dyslipidemia. Statins have been shown to decrease median CRP concentrations by 15% to 30% which is largely independent of lipid reduction[27]. There is data from observational studies and post-hoc subgroup analyses of statin trials in CAD patients suggesting improvement of HF outcomes by the use of the drug[28,29].

Statins have also been shown to reduce HF hospitalization in patients with stable CAD and those with post-MI. However, the data regarding HF hospitalization and death in patients without CAD is unclear[28,30]. In contrast, in the randomized UNIVERSE study involving HF patients, rosuvastatin use led to a significant increase in the serum levels of procollagen I and III amino terminal pro-peptides in the study arm. In these patients the authors also found a reduction in coenzyme Q^{10} levels. The authors of this study hypothesized that the anti-inflammatory action and cardiac remodeling benefits of statins in heart failure patients may have been negated by the increase in collagen turnover markers and the reduction in plasma coenzyme Q^{10} levels in these patients.

Effect of Statins on Endothelial Function

The endothelium plays a pivotal role in maintaining normal body homeostasis. It is involved in the anticoagulation mechanism by inhibiting the interaction of platelets and leucocytes with the vascular wall and maintains the vascular tone by releasing various active substances. Endothelial dysfunction has an important role both in the pathogenesis and the clinical course of HF, arterial hypertension, and atherosclerosis[32]. In HF patients, there is accentuation of endothelin-1 (ET-1), which is a vasoconstrictive agent, and statins reduce its expression. The inhibition of matrix metalloproteinases by statins may also play a significant role in the inhibition of HF progress[33]. Statins induce endothelial nitric oxide synthase enzyme, which leads to improvement of endothelial function. In addition, they decrease the expression of adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1, attenuate NF-kB, proinflammatory cytokine, and chemokine expression, thus blocking T cell activation[33]. Erbs et al[34] found that rosuvastatin therapy significantly increases the number of endothelial progenitor cells, thus facilitating the repair of damaged endothelium. It also leads to a significant elevation of the number of CD34+ stem cells, inducing angiogenesis.

Anti-Oxidant Action

Oxidative stress has an important role in the pathophysiology of HF. The increased produc-

tion of reactive oxygen species (ROS) with the concurrent decrement in antioxidant mechanisms culminates in the diminution of nitric oxide secretion and the development of an inflammatory response. Moreover, high levels of ROS have been observed in the venous blood of HF patients[35]. Statins primarily exert a favorable effect by enhancing the production of endothelial nitric oxide synthase and inhibiting nicotinamide adenine dinucleotide phosphate activity[36]. In addition, they also stimulate the production of antioxidant enzymes catalase and superoxide dismutase.

Cholesterol Lowering Beyond LDL-C

In the Framingham heart study[10], it was demonstrated that low levels of HDL-C and high levels of non-HDL-C are linked to increased risk of HF. The population-attributable risk for dyslipidemia was found to be around 22%. So, the focus of treatment should not only be limited to LDL-C[10]. However, the studies of HDL-C-increasing drugs are largely negative as far as patients with CAD are concerned[37]. Instead, we should focus on therapies lowering non-HDL-C.

In a meta-analysis of 35 RCTs encompassing 42,151 individuals, PCSK-9 inhibitors have not been shown to affect HF hospitalization38. In the HIJ-PROSPER trial, HF hospitalization was reduced in patients with ACS with dyslipidemia treated with Pitavastatin and ezetimibe combination compared to Pitavastatin alone[39]. On the other hand, the ACCORD and ACCORDIAN trial of fenofibrate showed no significant effect on patients of HF[40]. There is dearth of data for niacin in HF[37].

Benefits and Harms of Lowering Cholesterol in HF

Statins have a variety of pleiotropic effects that might contribute to benefits of statins in HF. These include:

– Antiatherogenic and plaque stabilization along with improvement in endothelial function. These altogether decrease the risk of acute coronary syndrome (ACS) and the ischemic burden on the failing ventricle. However, the frequency of ACS or MI is low in patients with HF, so it is difficult to demonstrate the benefit from statin therapy in them[41].
– Statins inhibit proinflammatory cytokine activity, modulate the autonomic nervous system favorably, and have an antiarrhythmic effect[42].
– Statins improve endothelial function and demonstrate antithrombotic and antiplatelet in some studies[36].

Statins use may be harmful in patients with HF due to the following reasons:

– The bacterial endotoxins (lipopolysaccharides) that enter the circulation are removed by lipoproteins. Lowering lipoprotein levels by statins may predispose HF patients to infection causing increased morbidity and mortality[43].
– Statins reduce the plasma levels of ubiquinone (coenzyme Q^{10}) are reduced. Ubiquinone is a coenzyme in mitochondrial respiration, and its decrease might adversely affect cardiac muscle activity. It has been seen that serum ubiquinone levels are inversely related to mortality in HF patients[44].
– Statins interfere with the enzymatic isoprenylation of selenocysteine transfer RNA (tRNA) inhibiting its maturation to functional tRNA molecules, thereby reducing selenoprotein levels. Severe selenoprotein deficiency have been found to be associated with statin induced myopathy[45].

RCTs and Observational Studies of Statins in HF

It has been observed in some studies that low serum cholesterol is associated with poor prognosis in HF. It might be due to the fact that lipids are known to be a marker of nutritional status in HF[46,47]. In general, statins have been shown to reduce the mortality in HF. However, some studies have been equivocal. The first one was done in 1998, in which lower cholesterol was a predictor of increased HF mortality[13]. They demonstrated that the best cut-off for cholesterol level in HF is around 190-200 mg/dl by Receiver Operating Characteristic (ROC) curve analysis. They found that for each mmol/l decrease in total cholesterol, mortality increased by 25%[13]. This phenomenon was later confirmed in some other studies that involved patients of both ischemic and non-ischemic heart failure, where low TC and LDL were associated with lower LVEF[48].

A prospective study of 96 patients[49] of HF with an LVEF < 40% with NYHA II-IV done at Duke Heart Failure Clinic did not show any benefits on CRP levels and there was no improvement in HF outcomes without any worsening.

Several non-randomized studies show evidence in support of statin use in HF. These studies evaluated the effects of statins on outcomes in HF patients. In a prospective study of HF patients with renal insufficiency, statins significantly improved the outcomes and the benefit was seen even in those with advanced renal dysfunction[50]. Go et al[51], also found that statin therapy was associated with 24% lower risk of mortality and 21% lower rates of hospitalization. In another study by Foody et al[52] on 54,940 patients, there was a significant reduction in HF mortality at 1 year. So according to these non-randomized studies and those described in Table I statins reduce the HF hospitalization[42,50-54].

The study by Laufs et al[55] in patients of dilated cardiomyopathy showed that there was an improvement in the brachial artery flow mediated dilation, quality of life score, functional ability along with the reduction in the levels of plasminogen activator inhibitor-1 (PAI-1), CRP, and TNF-α. In another study by Tousoulis et al[56], on 60 patients of both ischemic and non-ischemic HF with LVEF < 40%, patients were randomized to receive atorvastatin 10 mg or matching placebo for 4 weeks. The endpoints were levels of various biomarkers and flow-mediated vasodilation at baseline and 4 weeks. There was a significant improvement in the flow-mediated vasodilation with a reduction in inflammatory cytokines like VCAM-1, IL-6, and TNF-α, suggesting the benefits of statins in both ischemic and non-ischemic HF.

Table II summarizes in brief the small randomized clinical trials for statins in HF with clinical outcomes or cardiac function as end points[57-59].

CORONA and GISSI-HF Trials

The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study was a large randomized, placebo-controlled trial of rosuvastatin 10 mg *vs.* a placebo in patients with chronic symptomatic systolic HF of ischemic aetiology[60]. The study encompasses 5,011 patients of HF with LVEF <35% and NYHA class II symptoms and LVEF <40% with NYHA class III-IV symptoms. The patients were aged >60 years and were followed for 3 years. Rosuvastatin did not affect the primary outcome, which was a composite of cardiovascular (CV) death, non-fatal MI, and non-fatal stroke. However, it reduced the HF hospitalization, especially in older patients. The various reasons for these results have been contemplated. One may be that the study cohort was elderly with various other comorbidities and there might be interaction with complex medical therapy in geriatric patients, thus counteracting the benefits of statins in them. Of 5,011 patients recruited, 30% had died during follow-up indicating recruitment of sicker patients. Almost 11% had sudden cardiac death indicating advanced HF. Moreover, as the CORONA study recruited

Table I. Non-randomized studies of statin therapy in HF.

Study	Year	Sample size	Follow-up (months)	Inclusion criteria	Drug used	Parameter	Outcome
Hognesta et al[53]	2004	5301	25	Ischemic HF	Statin and beta blocker *vs.* placebo	Mortality	Improved mortality
Ray et al[54]	2005	28828	96	Age 66-85 years with at least 90 days survival post HF diagnosis. Cancer free	Statin *vs.* placebo	All-cause Mortality Non-fatal MI & Stroke	Improved mortality
Sola et al[42]	2005	446	24	Non-ischemic HF, LVEF ≤ 35%	Atorvastatin 20 mg *vs.* placebo	Mortality/ hospitalization	Improved outcomes
Go et al[51]	2006	24598	29	All adults > 20 years with HF. Statin naive	Statin *vs.* placebo	Mortality/ hospitalization	Improved outcomes
Foody et al[52]	2006	54960	36	Age ≥ 65 Years. HF hospitalization	Statin *vs.* placebo	Mortality	Improved mortality

HF – Heart failure; MI – Myocardial infarction; LVEF – left ventricular ejection fraction.

Table II. Randomized trials of statin therapy in HF.

Study	Year	Inclusion criteria	Sample size	Follow-up	LDL-C levels	Statin used	End points	Outcomes
Vrtovec et al[24]	2008	Stable HF, EF<30%, (59% ischemic)	110	12 months	2.45 mmol/l	Atorvastatin 10 mg *vs.* placebo	SCD	Decreased SCD
Yamada et al[25]	2007	Stable HF, NYHA I-III, (53% ischemic)	38	31 months	3.02 mmol/l	Atorvastatin 10 mg *vs.* placebo	LVEF/ BNP	Increased LVEF Decreased BNP
GISSI-HF Trial[66]	2008	CHF, all LVEF, (40% ischemic)	4574	46 months	Not reported	Rosuvastatin 10 mg *vs.* placebo	Mortality/ SCD/HF admission	No benefit
CORONA Trial[60]	2007	All ischemic HF, Age >60 years. EF<40%	5011	32 months	3.55 mmol/l	Rosuvastatin 10 mg *vs.* placebo	Mortality/ SCD/ HF admission	No effect on mortality Reduced HF hospitalization
Wojnicz et al[57]	2006	Stable HF, DCM	76	6 months	4.18 mmol/l	Atorvastatin 40 mg *vs.* placebo	LVEF/ NYHA class	Increased LVEF Decreased NYHA class
Rq et al[58]	2008	Ischemic HF, LVEF <45%	119	12 months	3.64 mmol/l	Atorvastatin 10-20 mg *vs.* placebo	LVEF 6MWD	↓ both QT and QTC. ↑ 6MWD ↑ LVEF by 5%
Takano et al[59]	2013	LVEF <45%, (27% Ischemic)	577	35 months	3.24 mmol/l		Mortality, stroke, worsening HF	No difference in mortality and stroke ↓ in worsening of HF in LVEF >30%
Node et al[71]	2003	Non-ischemic DCM with LVEF < 40%	63	3 months	3.85 mmol/L	Simvastatin 5/10 mg *vs.* placebo	NYHA class, LVEF, BNP	Statin improved NYHA class, LVEF and BNP levels.

HF – Heart failure; MI – Myocardial infarction; LVEF – left ventricular ejection fraction; BNP – B type Natriuretic peptide; DCM – Dilated cardiomyopathy; 6 MWD – Six minute walk distance; NYHA – New York Heart Association; SCD – Sudden Cardiac death.

ischemic HF patients, so there are chances of development of statin tolerance due to its prolonged exposure. Such patients might require a higher dose or another statin to elicit the desired effect to reduce mortality. Coenzyme Q^{10} depletion is one of the putative mechanisms implicated regarding statin-induced muscle dysfunction/myopathy. This could be of more concern in heart failure where cardiomyocytes are already damaged or at risk. However, lowering of Coenzyme Q^{10} was also insufficient to explain the failure of rosuvastatin therapy in CORONA study in a prespecified sub-analysis[61]. In the multivariate analysis, Coenzyme Q^{10} was not shown to be an independent predictor of clinical outcomes.

Although the primary endpoint was not met, a discussion regarding the reduction of HF hospitalization is warranted. In the prespecified analysis, there were fewer total hospitalizations in rosuvastatin arm. However, only hospitalization from any cause and cardiovascular cause were significantly reduced (p=0.007), while those for

worsening HF and unstable angina were not significant. Another study[62] included both first and recurrent hospitalization events during the study to assess the impact of rosuvastatin on hospitalization for HF. Over a follow-up of 33 months, rosuvastatin decreased hospitalization for HF by 15% -20%, which translated to 8 lesser admissions per 100 patients treated. Only 54% were first hospitalized, while the rest were repeated. The effect of rosuvastatin was robust on both first and recurrent hospitalization for HF. Moreover, the benefits of rosuvastatin therapy for reduction in HF appeared much later, around 1 year (curves started to diverge). This is in contrast to early benefits achieved by ivabradine (SHIFT) and eplerenone (EMPHASIS-HF).

Despite the overall neutral results, two subsets of population benefited from statin therapy. In a post-hoc analysis of the CORONA trial, there was significant interaction between baseline Galectin-3 levels and the occurrence of adverse cardiovascular events among patients administered rosuvastatin[63]. Interestingly, in patients with lower levels of Galectin-3 (<19.0 ng/ml), rosuvastatin use led to lower rates of the composite primary endpoint (35%), lower total mortality (30%), and combined total mortality with HF hospitalizations (28%↓). Similarly, another analysis evaluated the baseline NT-pro BNP values for predicting outcomes with rosuvastatin therapy in CORONA trial[64]. Among patients with HF on rosuvastatin therapy, those with the lowest tertile of NT proBNP values (< 868 pg/ml) had a higher reduction in the primary endpoint point (HR-0.65; p=0.0192) *vis-a-vis* those patients in the higher tertile. Patients with simultaneous low galectin-3 and low NT-proBNP attained maximal benefits from statin therapy (HR-0.33; p=0.002) (Figure 3). Collectively, we can conclude that these observations possibly argue against the benefits of statin therapy in advanced HF (as evidenced by elevated galectin-3 and NT-proBNP levels) and signal to start lipid-lowering in the early stages of HF (NYHA I-II). These observations also complement those of the Heart Protection Study (HPS), wherein there was a reduction in BNP from simvastatin treatment which benefited HF outcomes[65]. However, this was a retrospective analysis and needs confirmation by a prospective study.

The GISSI-HF trial was a multi-center, randomized, double-blind study that studied the effect of n-3 polyunsaturated fatty acids and rosuvastatin 10 mg *vs.* placebo on CV morbidity and mortality in patients of symptomatic and chronic HF[66]. It encompassed 4,574 patients of HF with NYHA class II to IV symptoms, irrespective of etiology. In this trial, there was no signifi-

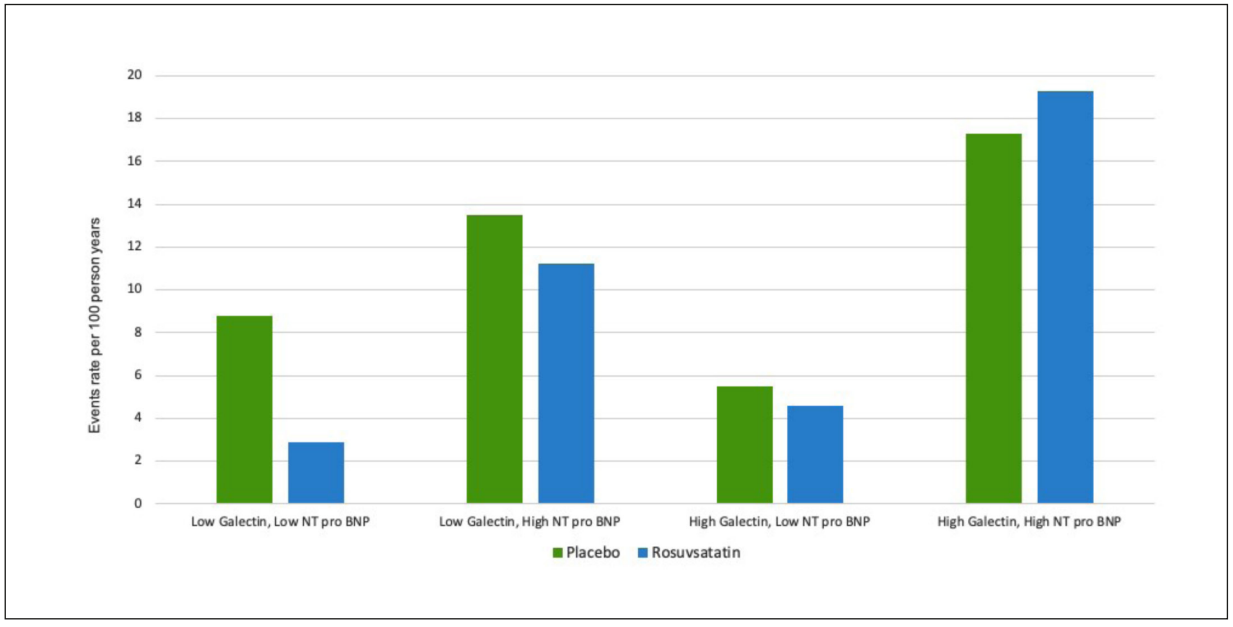

Figure 3. One-year event rate in subjects of CORONA trial among Placebo and rosuvastatin arms stratified by baseline Galectin -3 and N terminal pro B type natriuretic peptide (NT-proBNP) levels. As seen in the Figure, maximum benefit with rosuvastatin therapy was observed in the strata with both low galectin and low NT-pro BNP levels. Low galectin level was defined as levels < 19.0 mg/ml while low NT-pro BNP level was taken as 102 pmol/L.

cant effect of rosuvastatin on clinical outcomes in patients with chronic HF of either ischemic or non-ischemic etiologies after 3 years of follow-up. Although both in CORONA and GISSI-HF patients, there were no adverse effects of statins, and thus statins were safe in HF patients. The study drug discontinuation rate was high at 31% and it remains speculative whether the study results were affected as a consequence.

A recent study[67] assessed the effect of statin on all-cause mortality in a large cohort of 10,510 consecutive patients of both ischemic or non-ischemic HF (mean age 72 years) from the Veterans Affairs Health System. They also assessed the effect of increasing statin dose on mortality. It was seen that statins significantly reduced the mortality among the veterans. The statin used was either simvastatin or atorvastatin. The study cohort was comparable to GISSI-HF and CORONA trial, but there was a nonsignificant 29% decrease in mortality compared with the placebo group. The benefit was seen in those who used statins for more than 25% over 3 years duration, suggesting compliance as a confounding factor. Differences in revascularization rates, compliance, aggressive lipid control, and other comorbid conditions may have accounted for the disparity in mortality rates. The CORONA and GISSI-HF studies used rosuvastatin at a low dose, thus the results were inconclusive for the class effect of drug in HF. On the other hand, the majority of patients in the Veteran Affairs Health System study used simvastatin and atorvastatin, suggesting differential effect of different statins in HF.

A pooled analysis of both the above-mentioned landmark trials GISSI-HF and CORONA studies was performed to improve the statistical power to detect any effect of rosuvastatin on atherothrombotic events[68]. The analysis revealed that incident MI were attenuated with rosuvastatin therapy compared to placebo (HR-0.81; p= 0.49) in ischemic HF patients who were statin naive. However, in absolute numbers, the MI events were infrequent in both studies. This has to be understood in the context of higher tendency for Non-MI related deaths in the above subgroups. A Number Needed To treat (NNT) of 94 was derived for prevention of one myocardial infarction with rosuvastatin therapy.

Additional support for stain use can be obtained from post-hoc analysis of a few large HF trials. In the Val-HeFT trial, two-year mortality was lower with statin use compared to placebo (17.9% *vs.* 20.3%)[29]. Baseline statin use was also associated with a lower hazard of death in the CIBIS-II study[69]. Similarly, ELITE-2 statin use at baseline was associated with attenuated hazard of death (HR -0.61; 95% CI 0.45-0.83; p=0.0007)[70]. Interestingly, in this analysis, statin therapy improved survival irrespective of etiology of HF (ischemic or non-ischemic), age, sex, betablocker use, baseline LVEF and cholesterol levels. In the same paper, the authors describe additional multicenter observational data of 2,068 HF patients. Statin therapy lowered mortality in the observational arm, too, and this was again irrespective of etiology. These results align with a small RCT (n=63) demonstrating improvement in NYHA class and LVEF in non-ischemic cardiomyopathy with short-term simvastatin therapy by Node et al[71].

Meta-Analysis and Systematic Reviews

In a meta-analysis of 13 studies which involved 11 retrospective studies and two prospective studies, authors found that statin treatment was favorable for HF with a significant 26% reduction in relative risk of mortality[72]. These benefits were observed irrespective of the etiology of HF (ischemic or non-ischemic). However, the analysis was limited by a meager number of prospective studies and high heterogeneity.

Lipinski et al[73] in their meta-analysis of 10 studies, did find a reduction in worsening HF admissions with statin therapy. Additionally, they were also able to demonstrate an improvement in LVEF by 4% with follow-up. However, there was no significant effect on total or cardiovascular mortality. The benefits, though modest, have the potential to attenuate the morbidity and the financial burden of HF.

Subsequently, Zhang et al[74] performed a meta-analysis of 13 trials involving 10,447 patients. There was no significant benefit of statin therapy on either total mortality, cardiovascular mortality or HF hospitalizations although the numbers were numerically lower with statin therapy. However, younger people (<65 years) did derive significant benefit from statin therapy (all-cause mortality: RR=0.48, 95% CI: 0.29-0.77, p=0.003 and hospitalization for worsening HF RR=0.52, 95% CI: 0.33-0.82, p=0.004, respectively). Elderly patients with calcified arteries and more advanced

heart failure may not achieve same amount of improvement of endothelial function and immunomodulation. Interestingly, with the omission of GISSI-HF and CORONA studies from the analysis, the results were strongly in favor of statin therapy for all endpoints. However, in a separate analysis, the researchers were able to demonstrate improvement various echocardiographic parameters like LVEF (+3.3%), LV end systolic diameter (-3.57 mm) and LV end diastolic diameter (-3.77 mm) with statin therapy[75]. Improvements in serum BNP and NYHA class were also noted in the paper which included data from 11 trials.

A more recent meta-analysis of 15 studies involving 45,110 individuals with HF (22,471 patients received statin and 22,639 did not received statin) showed a reduction in all-cause mortality (RR = 0.71; 95% confidence intervals [CI] 0.61-0.83) and rehospitalization for HF (RR = 0.84, 95% CI 0.74-0.96) in patients who received statins over and above evidence-based therapy for HF[76]. However, there was little or no effect on cardiovascular mortality, sudden deaths, and pump failure mortality. The strengths of the study were the inclusion of only prospective studies and a large population database. The omission of GISSI-HF and CORONA studies did not alter the final outcomes, bolstering the applicability in real-world practice.

Finally, Bielecka-Dabrowa et al[77] performed the largest meta-analysis till date of 17 studies, including 88,000 patients with a median follow-up of 36 months. The yielded results indicate that statin use is associated with a reduction in all-cause mortality (23%), CV mortality (18%), and CV hospitalizations (22%↓; Figure 4). When the results were stratified according to baseline LVEF > 40%, there was no difference in results.

In contrast, a meta-analysis based on 24 RCTs did not any show benefit of statins on sudden cardiac death and all-cause death[78]. Nonetheless, there was a significant but modest reduction in hospitalization for worsening HF (HR 0.79; 95% CI 0.66 to 0.94). A sensitivity analysis was performed to assess the impact of the two large RCTs – CORONA and GISSI-HF on the results. The exclusion of these trials led to significant difference in favor of statins for sudden death, all-cause death, and worsening HF hospitalization. Interestingly, almost half of the RCTs included in the meta-analysis were based on surrogate endpoint like inflammation, pleotropic effects, endothelial dysfunction, and autonomic nervous system. Ten studies had a sample size less than 50, and only 7 had a sample size > 100. The authors acknowledge the possible presence of publication bias and heterogeneity.

However, the precise reason for this divergence of results is unclear, it may be due to the reason that the benefit of statin therapy depends upon the stage of HF at which they are initiated.

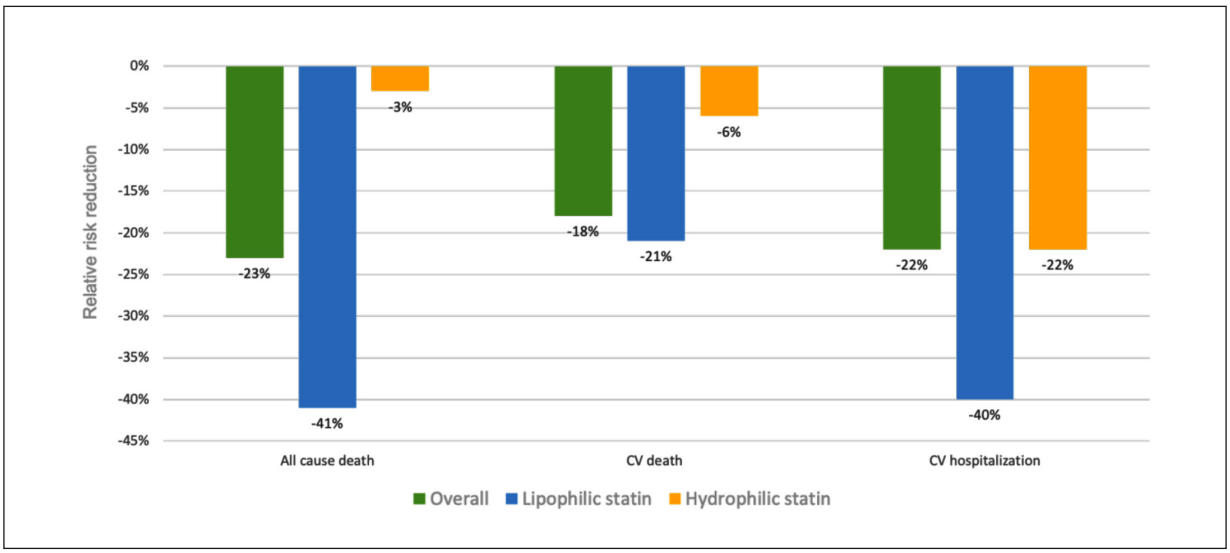

Figure 4. Major cardiovascular event reduction with statin therapy in heart failure. The data for calculating relative risk reduction data have been derived from the meta-analysis by Dabrowa et al[77]. As depicted in the Figure, lipophilic statins (blue bars) achieve significantly higher end-point reduction compared to hydrophilic statins (yellow bars).

Lipophilic Statins – the Game Changer

Statins are not a homogenous class of drugs with respect to lipid solubility. Lipophilic statins like atorvastatin and simvastatin have better uptake by liver and ultimately higher retention (80 times) in cardiac tissues compared to hydrophilic stains like rosuvastatin and Pitavastatin[79]. The elevated cardiac concentration of atorvastatin can be a potential clinical advantage over rosuvastatin in clinical parlance. This could explain in part the failure of two large RCTs – GISSI-HF and CORONA – which utilized a hydrophilic statin-rosuvastatin.

Bonsu et al[80] compared lipophilic vis-à-vis hydrophilic statin, including 13 trials with 10,996 patients. Lipophilic statins demonstrated their significant superiority with respect to all-cause mortality (HR=0.50), all-cause mortality (HR= 0.61), and worsening HF hospitalization (HR= 0.52). With follow-up of > 12 months, the results were more evident. There was no difference with respect to cardiovascular hospitalization. Liu et al[81] also evaluated the effect of lipophilic statins in meta-analysis of 13 studies with 1,352 subjects. Significant decrease in all-cause mortality (RR 0.53, $p < 0.001$), cardiovascular mortality (RR 0.66, $p = 0.04$), and hospitalization for worsening HF (RR 0.60, $p < 0.001$) were observed. These benefits were altered when stratified by age, baseline LVEF, and cause of HF. Additionally, lipophilic statins use culminated in a significant increase in LVEF (WMD 3.91%, $p < 0.001$). Another meta-analysis of 17 RCTs demonstrated that atorvastatin and not rosuvastatin use increased LVEF and reduced BNP in HF patients[82].

Post-hoc analysis of meta-analyses discussed in the previous section already had pointed at the heterogeneity of statins use for HF outcomes in favor of lipophilic statins like atorvastatin and simvastatin even when the original meta-analysis was not in favor of statins[72,73,76,77]. All four meta-analyses demonstrated a reduction of all-cause mortality and worsening HF admissions uniformly, while one of them also demonstrated improvement of EF (Figure 4).

Guidelines-ACC/AHA/EHRA/LAI

The 2016 American College of Cardiology (ACC) expert consensus document recommends that patients with HF in NYHA class II to III due to ischemic etiology may be given statins. Patients with stage B heart failure should receive statin therapy to prevent the progression of HF. The role of statins in non-ischemic or dilated cardiomyopathy is more controversial[83].

The European Society of Cardiology (ESC) guidelines for the management of HF recommend that patients who are receiving statins for CAD should continue them. It also recommends

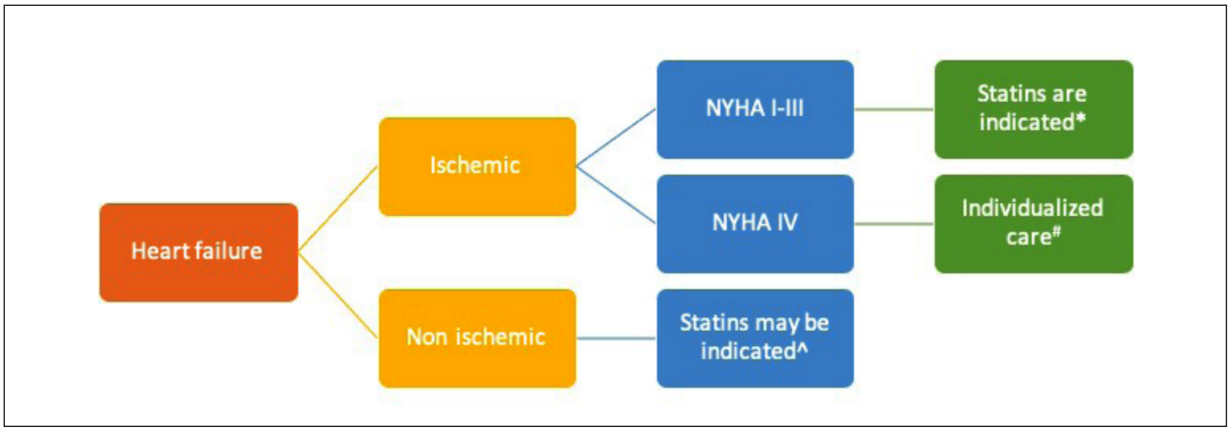

Figure 5. A proposed algorithm for statin use in established heart failure based on the expert consensus statement by Lipid Association of India (LAI) for Dyslipidemia in Indians. [* Lipophilic statins like atorvastatin, simvastatin should be preferred. # The dose of statin should be 10 mg of Rosuvastatin or equivalent, which was used in GISSI-HF & CORONA. If a patient with CAD on statin develops advanced HF, the statin may be continued. ^ Based on positive data for non-ischemic from 2 small RCT, one Post Hoc analysis, one meta-analysis; with at least one of the following features-Low NT-pro BNP, Low Galectin-3, Age < 65 and LVEF >30%].

use of statins in patients at risk of HF to prevent or delay onset of heart failure. The use of statins is contraindicated in non-CAD patients who are in NYHA class III-IV[84].

The Lipid association of India (LAI) in their expert consensus statement on management of dyslipidemia advocate that statins may be given to patients with ischemic HF with NYHA Class II-III symptoms (Figure 5)[85]. However, patients with advanced stages of symptomatic HF require an individualized decision for statin therapy. For example, in a patient of CAD who was on statin therapy prior and subsequently developed symptomatic HF, statins may be continued. High-dose statin therapy with a goal to achieve a 50% reduction in LDL-C levels should be utilized. These guidelines also recommended statins for ischemic HF patients awaiting heart transplantation. However, there is no recommendation for use in advanced HF patients with short life expectancy and in non-ischemic HF[86,87]. However, few studies have demonstrated benefits of statin therapy irrespective of etiology, i.e., ischemic or non-ischemic[57,70-72]. In the absence of a randomized study, we suggest statin use even in the non-ischemic subset when the patient is not in advanced HF (NYHA I-III) and exhibits at least one of these features shown to predict good outcome with statin therapy-Low galectin-3, Low NT-proBNP, Age < 65 and EF >30%[59,63-64,74].

Summary

The benefits of statin therapy for hypercholesterolemia and primary and secondary prevention of CAD have been established. However, their effects on HF survival remain unclear. Evidence shows that statins modulate the pathophysiology of HF to an extent that may overlap the recommended HF therapies. Also, statins act on various pathways to reduce or reverse progression of many HF comorbidities beyond the mechanism of actions of some of the guideline recommended therapies of HF. Therefore, statins may be considered as second-line or adjuvant therapy. Positive evidence from prospective but non-randomized studies and small RCTs of statins in HF could not be replicated in two large RCTs – GISSI-HF and CORONA. On the contrary, multiple meta-analyses and post-hoc studies suggest a beneficial effect on clinical outcomes and surrogate marker. Few subsets of the population have been observed to attain unequivocal advantage from statin therapy – Age < 65, Low baseline galectin-3, Low NT-proBNP, and EF >30%, all of which point towards a less advanced stage of HF. Among statin candidates, there is a clear signal that lipophilic statins give better clinical outcomes than hydrophilic statins. Thus, the need of the hour is to conduct a well-designed RCTs which is sufficiently powered to answer whether the benefit of statin in HF are modulated by type of statin (Lipophilic or hydrophilic), type of etiology (ischemic or non-ischemic) and stage of initiation (early versus late; stratified either by biomarkers, NYHA class, age or EF).

Conclusions

In conclusion, there is a discrepancy between observational studies and RCTs regarding the benefits of statins on the outcomes of HF. In general, both observational studies and meta-analyses of RCTs have demonstrated statins to improve surrogate markers and endpoints, reducing the frequency of hospitalization and mortality in HF. Early initiation of statin in the course of HF (with low level of biomarkers, higher EF and early age) is unequivocally superior for clinical benefit. Whenever indicated, a lipophilic statin may be preferred.

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Conflict of Interest
None of the authors have any conflicts to declare.

Informed Consent
Not applicable.

Data Availability
Not applicable.

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