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Statins in the Prevention and Treatment of Heart Failure: A review of the Evidence

[1]Dr Khadijah Sajid,[2]Dr Malik Muhammad Uzair Khan,[3]Dr Aleena Naeem,[4]Dr Ifrah Naeem,[5]Dr Adeel Bin Tariq,[6]Dr Samia Usman,[7]Dr Syed Adeel Hassan,[8]Dr Ishmam Afzal,[9]Dr M Habib E Ajmi,[10]Dr Anaab Basharat

[1,2,4,5.9,10]MBBS, Shalamar Medical and Dental College,Lahore.

[3]MBBS, Allama Iqbal Medical College, Lahore.

[6]MBBS, King Edward Medical University, Lahore.

[7]MBBS,Dow University of Health Sciences,Karachi.

[8]MBBS, Punjab Medical College, Faisalabad.

Corresponding Author: Dr Khadijah Sajid, MBBS, Shalamar Medical and Dental College, Lahore.

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Abstract

A research-based study has shown that statins play an important role in reducing the incidence of heart failure in patients with established atherosclerotic CVD or with other CVD risk factors. This reduction is done by preventing myocardial infarction along with an additional benefit of the decline of myocardial ischemia factor. However, in patients with already existing heart failure risks, statins do not play a defining role in the reduction of cardiovascular death, which may be caused by ventricular arrhythmias and pump failure.

A retrospective analysis has shown in this review paper regarding the productive role of statins reducing the risk of heart failure, atherosclerotic events, and hospitalization. A study has shown that if statin therapy is continued in patients with coronary artery disease, then it will help reduce heart failure risk development, but little evidence is present for this therapy in elderly patients with short life expectancy.

Keywords: CVD, Heart Failure, Atherosclerotic

Introduction

Heart failure (HF) isn't merely a timely existing condition rather it is a clinical syndrome that is characterized by a constellation of symptoms. These symptoms are often accompanied by signs which appear due to functional and structural cardiac abnormalities that lead to reduced cardiac output and/or increased cardiac pressure during stress or at rest. Two main phenotypes of HF are identified; HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). [1]

One predominant etiology of HFpEF is hypertension. Mostly the phenotype (HFpEF) appears in female gender and older patients who are obese. In comparison to HFpEF, patients with HFrEF are mostly younger and usually, men fall in this category who likely to have coronary artery disease. By treating the risk factors like obesity, hypertension, and diabetes, heart failure can be prevented. Once the heart is damaged, then other treatment methods can be opted which can help in preventing or decelerating heart failure (HF) occurrence. This damage can occur due to the use of angiotensin-

converting enzyme inhibitors after MI myocardial infarction.

Cholesterol-Lowering in the Context of Heart Failure

For cardiac patients, a whole 'cholesterol paradox' is presented to handle the situation. It is found that, on one hand, increased plasma cholesterol is the main reason of coronary artery disease (CAD), on the other hand, total low serum cholesterol level is linked with poor prognosis in patients with established HF in contrast to patients without HF.

The question arises here that to which maximum extent, this counterintuitive relationship represents a picture of "cause and effect". It is important to note that cholesterol has a significant inverse correlation with the severity markers of disease. These markers have a severe inflammatory component, which is prominent in other diseases as well as severe rheumatoid arthritis or chronic kidney disease, besides CVD. Thus, the justifiable reason behind this inverse relation of cholesterol with heart failure is that lipid is a notorious maker of nutritional status important for mild to moderate heart failure syndrome. As liver is the main organ involved in lipoprotein production, so it might also be possible that due to heart failure, hepatic congestion could alter the hepatic biosynthesis of cholesterol.

Another justifiable reason is that intestinal congestion is caused by heart failure (HF) and this causes impairment in cholesterol absorption, although this is still a hypothesis and the facts have limited evidence.

A survey in the general hospital was conducted and 3955 patients were included in the list. These patients were hospitalized owing to the worsening of heart damage and increased risk of HF along with left ventricular ejection fraction (LVEF) equal to or less than 40%. Subjects also showed a prominent inverse relationship outcome between both triglyceride and total plasma cholesterol levels.

The follow up of cohort 310 HF patients over 20 years depicted that LDL-C (low-density lipoprotein cholesterol) levels had less favorable outcomes for patients treated with statins and those who were < 70 years of age. Furthermore, it was also observed that lower levels of HDL and cholesterol were linked with worse prognosis situation in HF patients, similar to one observed in low levels of serum apolipoprotein A-I.

A German cohort study including 400 idiopathic dilated cardiomyopathic patients showed that a decline in cholesterol levels was dependent upon the severity of the cardiac disease. Another study including 288 elder patients, who were hospitalized, showed that LDL-C was inversely linked with N-terminal pro-B-type natriuretic peptide (NT-proBNP). The present hypothesis, which justifies the answer, states that patients with pre-existing severe conditions have lower plasma cholesterol levels as a secondary risk factor rather than an independent risk factor with a negative outcome. Thus, patients with such chronic conditions must be handled carefully.

Statins in the Prevention of Heart Failure and Cardiovascular Disease

HMG-CoA reductase inhibitors (statins) are well known for their positive properties in the reduction of problems like CAD in patients, either they are already diagnosed with cardiovascular diseases or not. Staunch data from the clinical trial outcomes have been filtered out and subjected to a meta-analysis that has reinforced the results of individual patient studies and the gaps are filled up based on these findings in the population study. [5, 6]

The main findings depicted that with each 1.0 mmol/L decline in LDL-C level, the risk of major vascular problems also decreases by 22%. Physicians have ongoing concerns regarding the safety and treatment success of statins. To address this, reports from The European

Atherosclerosis Society (EAS) and American Heart Association, on the muscle-related problems and side effects addressing the impact on adherence and incidence rate has been analyzed. To bolster the evidence and strengthen it for statin therapy, detailed follow-up data on safety and efficacy were made available for trials including PORSPER, WOSCOPS, and ASCOTLLA, which depicted that this therapy maintained coronary protection in older patients in the long run, as follow up period was for 8.6 plus years. However, relatively fewer data is present from the major lipid decline trials under the statin therapy on prevalent HF, as most of the patients were excluded from the trial who had heart failure syndrome. For instance, LIPID and 4S excluded the patients who had HF, whilst patients with mild to moderate-severe symptoms were only included in CARE and HPS and those with severe symptomatic HF were excluded. In major vascular problems, HPS showed a decline in those with higher baseline natriuretic peptide levels. [7, 8]

These trials also threw some light on heart failure incidents. Collectively, the data from these trials were enough to provide 'reasonable evidence' on the use of statin therapy in prevention or delay the onset of heart failure. This link shows that statins prevent MI and consequent cardiac damage, which in turn aids in declining the risk of reduced ejection fraction and HF development.

Another recent meta-analysis of 6 controlled random trials of 110,269 patients with ACS, showed that hospitalization rates for HF were significantly reduced when intensive statin therapy was used. [9] Furthermore, in another meta-analysis of RCTs, it was found that over 4.3 years, statins modestly declined the non-fatal hospitalization risk for HF in 132500 participants. No demonstrable difference was observed in the risk reduction between those who suffered MI incident and those who did not. Interestingly, this plus point did not seem to be linked with the MI preceding to HF prevention.

Statins in the Treatment of Established Heart Failure

In patients with moderate to high symptomatic HF, cholesterol-lowering statin therapy is not indicated according to the 2011 European Society of Cardiology (ESC) /EAS dyslipidemia guideline and 2016 ESC HF Guidelines. The latter guidelines don't allow the initiation of statin therapy in patients with HF but it was allowed to continue in patients who were already on statin therapy for CAD prevention. [10, 11] These recommendations and guidelines were established after the results of two major studies GISSI-HF and CORONA, these were placebo-controlled, large scale trials of statin therapy in patients with NYHA class II-IV HF. In the CORONA group, 5010 ischemic systolic HF patients with age ≥60 years were added, and the GISSI-HF group included 4570 HF subjects of varying etiology with ≥18 years of age. The treatment included rosuvastatin 10 mg/day in both the trials and the follow-up period was an average of 33 months in the CORONA group and 47 months in the GISSI-HF group. In the GISSI-HF trial, the endpoints included time to death or CV hospitalization. In the CORONA trial, the endpoint included non-fatal MI, composite of CV death, or non-fatal stroke. In both the trials, no significant decline in morbidity and mortality endpoint was observed in the patients.

However, the CORONA trial depicted some progress in rosuvastatin therapy. This therapy prevented excessive CV hospitalizations and it succeeded in the provision of CV benefit in subjects with lower baseline NT- proBNP and higher C- reactive protein levels along with YKL- 40 levels (chitinase-3-like protein 1). In a meta-analysis, it

was observed that rosuvastatin significantly reduced the 15 to 20% hospitalization rate for HF.

Some investigators from different health institutes, who were not very much satisfied with these trials' based evidence, attempted to dig deep into it to observe if statin therapy has a significant role in subjects with established HF or not by examining random trials in meta-analyses. For instance, Zhang et al. reported no definite progress from statin therapy in CV death, all-cause death, or rehospitalization for heart failure, but it did show some decline in non-fatal MI. [12] Notably, in simple ischemic condition, HF events like CAD, are uncommon and contribute very to the overall mortality and morbidity of patients. The same investigator group also worked on the effects of statin therapy on the measurements of left ventricular size and functions in a total of 589 patients. Here they mentioned in the report that LVEF was increased by 3% with statin use, but some of these trials had the modest quality and their results couldn't be trusted. Thus, it was found that although statin therapy does not significantly improve outcomes in HF subjects, but patients who are already on this therapy do not want to leave it unless statin-related complications arise. [13]

Potential Mechanism of Statins Preventing HF Development

Based on research and evidence it is believed that CAD is lowered and atheromatous plaques are stabilized by statins, and these also lower the atheroma volume and prevent the formation of the new atherosclerotic lesion which otherwise leads to fewer MIs and some extent cardiac tissue damage. This was found as the main reason behind lowering the HF incident by statin therapy. In the WOSCOPS follow up trial, it was noticed that the use of statins declined the HF incidence. In comparative studies, pravastatin was found progressive in declining the high troponin I sensitivity concentration by 14%. [14] Thus, theoretically, it is viable that "subclinical" cardiac damage and ischemia can be reduced by statin therapy. Whilst many other searches have also shown anti-inflammatory properties of statin, but no clear evidence is present for these pleiotropic actions. [15]

Conclusion

No robust evidence is presented which shows, that in addition to coronary heart disease decline, statins also significantly lower the HF incident risk in both medium and long term duration. However, the lowering of risk is up to a modest level but is very less in comparison to the benefits of CHD results. Although statins lower the chances of subsequent CAD in HF subjects, but very less patients actually die from CAD in established HF, and the impact of statin therapy is not near to the conclusive results.

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