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RESEARCH ARTICLE

"ROLE OF STATINS ON CARDIAC REMODELING IN HEART FAILURE: A SYSTEMATIC REVIEW"

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Abstract

Heart Failure is a chronic condition in which the heart doesn't pump blood as well as it should; it is a major cause of morbidity and mortalityglobally.Heart failure is the pathophysiologic state in which the heart, via an abnormality of cardiac function (detectable or not), fails to pump blood at a rate commensurate with the requirements of the metabolizing tissues or is able to do so only with an elevated diastolic filling pressure. As recent studies describe Statins to have a beneficial role in preventing Cardiac remodeling in Heart Failure, this systematic review aims to explore the use of Statins as a potential therapy in patients with Heart Failure. This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)2020 guidelines. The search was conducted using PubMed, PubMed Central, Google Scholar in July 2023. The inclusion criteria were set to free full-text articles published within 5 years, human studies, literature reviews, systematic reviews, meta - analyses, observational studies, RCTs, studies investigating adult samples, and the English language. Exclusion criteria included animal studies, posters, editorials. The primary search yielded18,166 studies, which were screened and subsequently assessed through quality appraisal tools respective to each study. The result of this review demonstrated that statins prevent cardiac remodeling in heart failure. In the end, both randomized and nonrandomized clinical trails are necessary for more conclusive findings.

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Introduction:-

With the aging population, heart failure (HF) is becoming more common worldwide and is believed to have affected almost 26 million people, making it an epidemic.[2] Patients with atherosclerotic cardiovascular diseases (CVDs) are currently treated mostly with statins, which significantly lower morbidity and death. It has been claimed that statin medication can reduce the risk of heart failure (HF) owing to ischemic heart disease (IHD), which is the most prevalent cause of HF, by reducing ischemic myocardial damage, given the well-established effects of statins on the decrease of myocardial infarction. Premedication before primary percutaneous coronary intervention (PPCI) often includes the use of statins. When given before PPCI in patients with STEMI, high doses of statins (atorvastatin 80 mg or rosuvastatin 40 mg) are positive predictors of prognosis, and they are linked to a lower incidence of serious adverse cardiovascular events (MACE) Maximizing myocardial microvascular perfusion to reduce infarct size[3] Additionally, recent studies point to the possible advantages of statins for non-ischemic heart failure The positive effects of statins on heart failure patients were later confirmed in a large-scale observational investigation. Moreover, the mechanism behind the advantages of statins on morbidity and mortality in heart failure has experimental support. High-density lipoproteins (HDL) are significantly elevated whereas total cholesterol and LDL are significantly decreased with statins. They also have positive effects on endothelial function, angiogenesis, neuro-hormonal activation, cardiac hypertrophy, and left ventricular (LV) remodeling[1][3]

Statins have been shown to decrease cardiac fibroblast secretion of B-type natriuretic peptide (BNP) in HF, reduce myocardial inflammatory mediators and myofibroblast accumulation and helps in delaying fibrosis and ventricular hypertrophy.[2][3][6] The majority of patients with chronic HF and reduced left ventricular ejection fraction (HFrEF) do not benefit from the start of statin therapy, according to the most recent guidelines for the diagnosis and management of HF published by the European Society of Cardiology (ESC)[4]. Nonetheless, it is important to think about continuing statin therapy in HF patients who are already receiving it due to underlying coronary artery disease (CAD) and/or hyperlipidemia**. The issue of whether to use statins in patients with HF remains controversial.**

In this systematic review, we explored statinshelps in preventing cardiac remodeling in heart failure,but randomized control trails (RCT) have to be conducted to confirm the benefits.

Methodology:-

This meta-analysis was carried out in accordance with the preferred items for systematic review and (PRISMA-2020) guidelines.

Database

The literature was searched in PubMed database and Google scholar .The regular keywords used for statins are as followsstatins, anti-hyperlipidemic ,hmg-coa reductase inhibitors, rosuvastatin ,atorvastatin and keywords for cardiac remodeling are cardiac remodeling , cardiac hypertrophy ,physiological cardiac hypertrophy ,pathological cardiac hypertrophy and keywords for heart failure include heart failure, congestive heart failure, chronic heart failure, systolic heart failure ,diastolic hear failure and the Boolean search strategy was applied using 'OR' in the regular keywords which gave 312,517 for heart failure and 51,429 for statins and 117,832 for cardiac remodeling. Regular keywords were then combined using Boolean term 'AND' for statins and heart failure which gave 2,793. We also used medical subject headings (MeSH) keywords "hydoxymethylcoa –reductase inhibitors AND congestive heart failure gave 786. The last search was done -2/7/23.

Inclusion Criteria-

Two investigators (pkv, vsr) screened each article's title and abstract to determine eligibility independently first. Then the studies included by both reviewers were compared and disagreements were resolved by consensus. When aconsensuscould not be reached between the two investigators, the independent investigator who did not participate in the original screening, decided the eligibility.

The following inclusion criteria was used:

1. Free full text available
2. Studies published in English language.
3. Observational studies and randomized control trail
4. Systematic and narrative review
5. Studies after 2017.

Exclusion criteria-

1. The exclusion criteria include editorial, posters, exclusively animal studies.
2. Irrelevant studies.

Only studies meeting the above criteria were evaluated for eligibility in the final review. After all the inclusions and exclusions, the number of papers was 116. Papers were screened for relevant topics, and the total number of articles retrieved are 30.

PRISMA-2020 flow diagram for new systematic reduce which included searches of databases and registers only

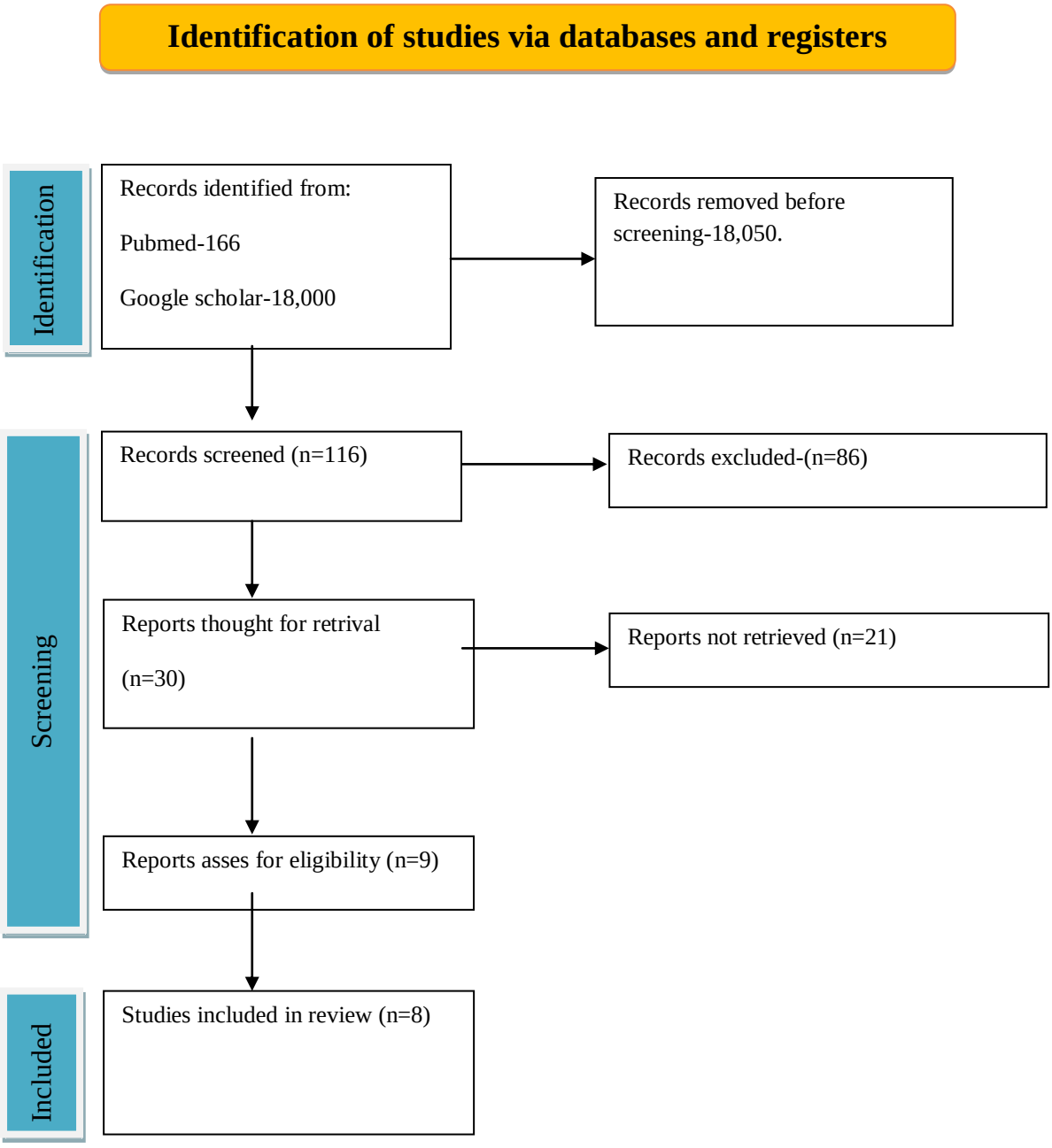


Figure 1:- Screening and study selection PRISMA Flow Diagram; The PRISMA-2020 statement.

Quality Assessment Tools

Two investigators evaluated the risk of bias, using the Newcastle-Ottawa questionnaire for the observational studies (Table **1**) and Cochrane risk-of-bias tool (Table **2**) for clinical trials. We only included studies that had scores six and above in the Newcastle-Ottawa questionnaire for the observational studies and RCT, we only included studies that were judged as "low-risk" of bias in each of the domains. Disagreement was resolved by consensus.

Table 1:- Results of Newcastle-Ottawa questionnaire for the observational studies by review authors. Passing score: 6/9.

Author	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls based on the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Quality score
Park, Chan Soon	1	1	1	1	1	1	1	0	7
Emelyanova, Larisa	1	1	1	1	1	1	1	0	7
Zvizdić, Faris	1	1	1	1	1	1	1	0	7
Zvizdić, Faris	1	1	1	1	2	1	1	0	8
Giral, Philippe	1	1	1	1	1	1	1	0	7
Kytö, Ville	1	1	1	1	1	1	1	0	7

Table 2:- Results of Cochrane risk-of-bias tool for randomized control trails by review authors.

AUTHOR	RANDOM SEQUENCE GENERATION	ALLOCTION CONCEALEMENT	SELECTIVE REPORYING	OTHER SOURCES OF BIAS	BLINING PARTICIPANTS	BLINDING OUTCOME ASSESMENT
El Said	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK

Table 3:- Results of the SANRA 2 assessment tool for narrative reviews by review authorsPassing score -9/12.

Author	Justification of the article's importance for the readership	Statement of aims or formulation n of the question	Description of the literature search	Referencing	Scientific reasoning	Appropriate presentation of data	Sum	Pass/Fail
Climent	2	2	0	2	2	1	9	Pass

Heart Failure:

Heart failure (HF) is a clinical syndrome that is typified by typical symptoms such as fatigue, ankle swelling, and dyspnea. These symptoms may be accompanied by signs such as peripheral edema, pulmonary crackles, and elevated jugular vein pressure, which are caused by a structural and/or functional cardiac abnormality that results in reduced cardiac output and/or elevated intracardiac pressures during rest or stress[4][12][15]

Currently , pathology is caused by different etiologies involving ischemic heart disease , toxic damage ,immune-mediated and inflammatory damage, infiltration, metabolic derangements, genetic abnormalities,hypertension,valve and myocardium structural defects, pericardial and endomyocardial pathologies, high output states, volume overload, tachyarrhythmias, bradyarrhythmia's.[8][13]

The primary language used to define HF is derived from historical measurements of the LVEF. Patients with HF differ widely in terms of LVEF, from those with reduced LVEF (usually defined as <40%; HF with reduced EF (HFrEF)) to those with normal LVEF (usually defined as ≥50%; HF with preserved EF (HFpEF)). Patients in the 40–49% LVEF range are in the "grey area," which we now refer to as HFmrEF.[17]

Treatment involves oxygen therapy initially, diuretics, vasodilators, inotropic agents (dopamine, dobutamine), vasopressors(norepinephrine), thromboembolism prophylaxis (LMWH), other drugs (digoxin, opiates).[18][19].

Since lovastatin, the first 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor authorized for use in human therapy, was introduced in 1987, statins have grown to be the most popular lipid-lowering medication. Based on their effectiveness and potency in reducing low-density lipoprotein (LDL) cholesterol concentrations, statins have been divided into three groups. The first generation of statins comprises lovastatin, pravastatin, and fluvastatin; the second generation includes simvastatin and atorvastatin; the third generation includes pitavastatin and rosuvastatin.[5]. Statins can be divided into two groups based on how soluble they are: hydrophilic and lipophilic. Simvastatin, fluvastatin, lovastatin, pitavastatin, and atorvastatin are among the primarily lipophilic statins that are easily able to penetrate further into the membranes where they interact with the surrounding acyl chains. In contrast, protein transporters must enter the cell for hydrophilic drugs (pravastatin and, to a lesser extent, rosuvastatin) to bind to the polar surface of the membrane and inhibit the HMG-CoA reductase enzyme.[20]

Role of Statin in Heart Failure

Statins have demonstrated benefits beyond decreasing cholesterol, including enhanced endothelial function, decreased inflammation, and stabilization of coronary artery thrombus plaque.A portion of statins' effects that are not dependent on cholesterol are mediated via inhibition of isoprenoids, which are lipid attachments for tiny Rho guanosine triphosphate binding proteins and other intracellular signaling molecules, explaining their antioxidative properties.Neurohormonal stimulation, reversal of cardiac remodeling, vasodilation, and reduced platelet aggregation are further pleiotropic effects.[8][9]

The favorable effects of statins in delaying myocardial remodeling and hypertrophy are well-supported by data. Angiotensin II, endothelin 1, and norepinephrine are examples of hypertrophic stimulants that are counteracted by statins, according to in vitro research.[21]

Myocardial strain causes cardiac myocytes to release BNP and NT-pro BNP. A useful cardiac marker in the diagnosis, prognosis, and treatment of HF is NT-pro BNP.The idea of biomarker-guided HF care has gained traction since drugs that enhance outcomes in the condition also lower natriuretic peptide levels. Multiple studies' findings suggest that statin use is linked to a decrease in NT-pro BNP levels in patients with heart failure.[22][23]

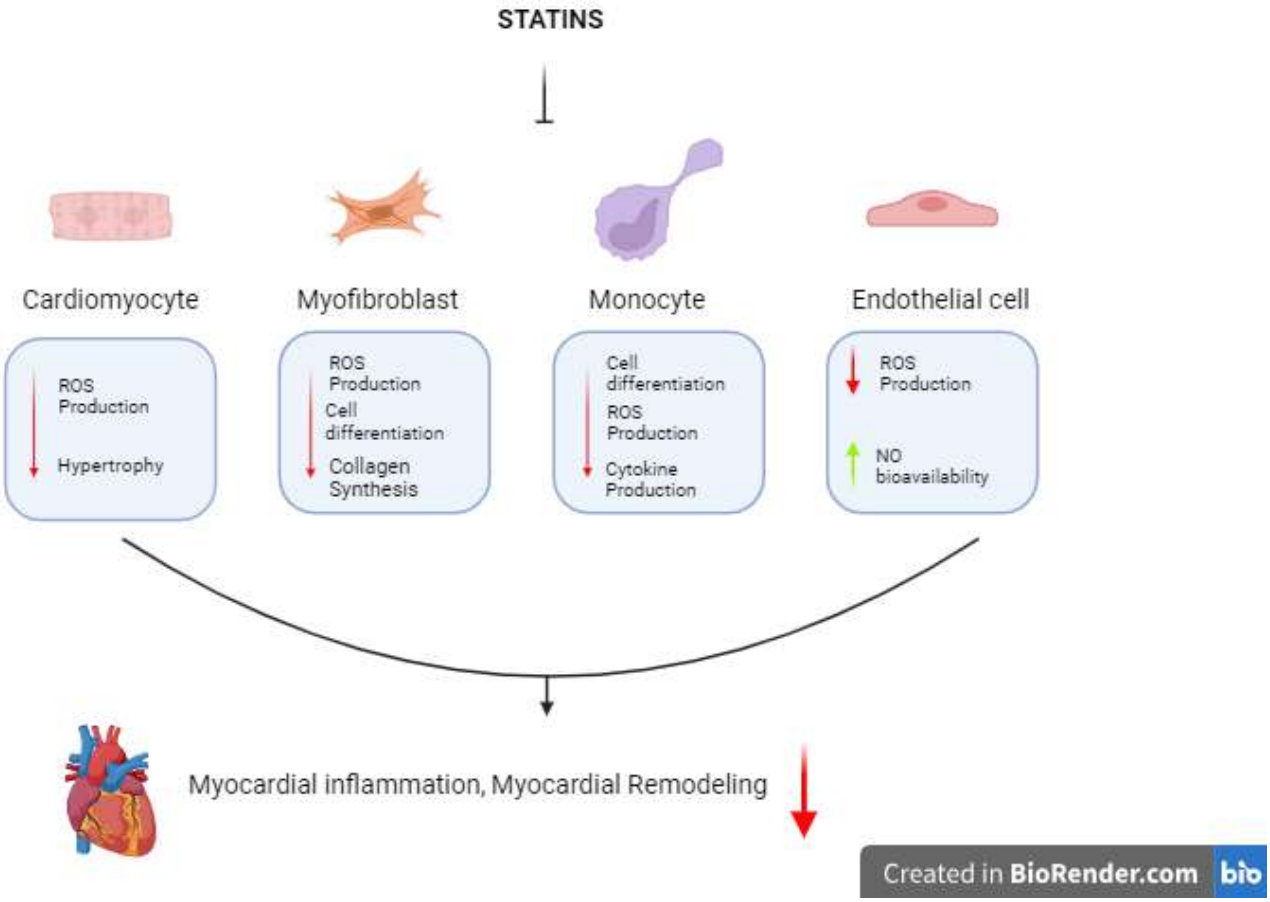
Interleukin-1, interleukin-6, tumor necrosis factor-α, and high sensitivity C-reactive protein are examples of inflammatory indicators that cause endothelial dysfunction and left ventricular remodeling in chronic heart failure [24]. Moreover, elevated proinflammatory cytokine levels are linked to a higher death rate in HF patients. By reducing circulating proinflammatory cytokines, statin treatment may disrupt the pathophysiological pathways associated with heart failure. Numerous writers have documented the advantageous impacts of statin usage on the reduction of inflammatory indicators.[25]

It is believed that one of the main risk factors for both mechanical and electrical dysfunctions in heart failure is excessive cardiac fibrosis. To cause fibrosis, fibroblast trans-differentiation into myofibroblasts must be activated. This is shown by increased expression of α-smooth muscle actin (α-SMA) and excessive secretion and deposition of extracellular matrix.[6].Characteristic of many fibrotic illnesses, such as progressive heart failure and cardiac hypertrophy, is the accumulation of myofibroblasts within pathologic lesions.[26] Myofibroblasts isolated from human failing hearts can undergo de-differentiation when taking statins. Statin therapy reduces the number of left ventricular myofibroblasts by GGPP-sensitive signaling, decreased bioenergetics, and KATP channels leading to

statin-induced de-differentiation.[6] Since the persistence of myofibroblasts causes chronic or severe fibrosis, which leads to heart failure.

Research indicates that if those using statins for primary prevention continue to take them after the age of 75, there may be a possible reduction in cardiovascular risk.[7]

There is no doubt that following statin therapy will reduce your chance of dying and having negative cardiovascular effects. Even in secondary prevention, nonadherence to statin treatment is very common and poses a significant obstacle to lowering death and morbidity [8].



AUTHOR OF STUDY	YEAR OF PUBLICATION	NO: OF SUBJECTS INVOLVED	FOCUSED SUBTOPIC	STUDY RESULTS
Zvizdic [9]	2018	155	To compare the efficacy of lipophilic and hydrophilic statins and to investigate which statin subtype provides better survival and other outcome benefits	lipophilic statin therapy is associated with better long-term survival in patients with HF
Zvizdic[3]	2021	80	Benefit of high-dose lipophilic statin therapy on cardiac remodelling, function and progression of heart failure (HF)	Reduction in the right and left ventricle diameters after a sixmonth atorvastatin

				therapy
Park, Chan Soon[1]	2021	1680	survival benefit associated with statins in HF patients	survival benefit of statins is confined to patients with HFpEF and those with ischaemic HF
Kytö, Ville[8]	2022	10,051	Statin therapy assecondary prevention after myocardial infarction (MI)	Lack of statin therapy early after MI is associated with adverse outcomes across the spectrum of MI patients
Giral, Philippe[7]	2019	120,173	statin therapy in primary prevention of cardiovascular disease in persons older than 75 year	Statin discontinuation was associated with a 33% increased risk of admission for cardiovascular event in 75-year-old
Emelyanova, Larisa[6]	2019	Not known	Statins can de-differentiate myofibroblasts	study demonstrates the de-differentiating effect of statins
Climent[5]	2021	Not known	evidence on possible differences in cardiovascular outcomes among statins when their solubility profile is considered,	Conflicting results have been observed on the superiority of hydrophilic or lipophilic statins regarding cardiovascular outcomes
Agata Bielecka-Dabrowa[4]	2019	Not known	Association of statin use with clinical outcomes in patients with HF	statins may have a beneficial effect on CV outcomes irrespective of HF etiology
El Said[2]	2020	85	compare the effects of lipophilic (atorvastatin) vs hydrophilic (rosuvastatin) on left ventricular function, inflammatory and fibrosis biomarkers in patients	The study results suggest that lipophilic atorvastatin is superior to hydrophilic rosuvastatin in increasing left ventricular ejection fraction and reducing fibrosis marker sST2 in HF patients.

Conclusion:-

In conclusion, our review underlines the importance of statinsin controlling the cardiac remodeling in Heart failure patients. It has a number of pleotropic effects that may be useful in both prevention and treatment of heart failure, including anti-inflammatory and immunomodulatory properties, which can significantly lower the inflammation in heart.

Clinical trials are required to discover the best therapy regimen, including optimal dosage and treatment methods.

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