International Journal of Cardiology Research

ISSN Print: 2663-4104
ISSN Online: 2663-4112
Impact Factor: RJIF 5.29
IJCR 2025; 7(2): 84-89
www.cardiologyjournal.in
Received: 02-07-2025
Accepted: 05-08-2025

Kristoforus William
Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

Nimas Eka Firdaningrum
Department of Biomedical Science, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

Ardyan Wardhana
Department of Clinical Medicine, Faculty of Medicine, Universitas Surabaya, Surabaya, Indonesia

Johanes Nugroho Eko Putranto
Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; Dr. Soetomo General Hospital, Surabaya, Indonesia

Corresponding Author:
Kristoforus William
Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

Role of statin therapy in improving the diastolic index in patients with diastolic dysfunction: A systematic review and meta-analysis

Kristoforus William, Nimas Eka Firdaningrum, Ardyan Wardhana and Johanes Nugroho Eko Putranto

DOI: https://www.doi.org/10.33545/26634104.2025.v7.i2b.76

Abstract

Background: Statins exert pleiotropic effects as a prophylaxis against cardiovascular events and have also been shown to improve diastolic function. In this study, we aimed to analyse the effect of statin therapy on the diastolic functional index in patients with diastolic dysfunction.

Methods: A systematic meta-analysis was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to identify randomised controlled trial studies on the comparison of statin and placebo therapies in patients with diastolic dysfunction from the PubMed and Google Scholar databases. We evaluated the quality of the studies using Grading of Recommendations, Assessment, Development, and Evaluations Assessment. We performed a random-effects inverse-variance weighted meta-analysis of the outcomes, including echocardiographic index, to evaluate diastolic dysfunction.

Results: Data from the selected studies were analysed using RevMan Web. Two studies (271 patients) were included in the final analysis. Among all studies, the treatment and control groups showed no significant differences in the E/A ratio (mean difference [MD] = -0.10), isovolumic relaxation time (MD = -1.02), and E deceleration time (MD = -0.01). Overall, significant differences in left ventricular mass index (MD = -8.99), E velocity (MD = 1.16), and A velocity (MD = -0.68) were found between the groups.

Conclusion: Several significant changes in diastolic index are observed in patients with diastolic dysfunction who receive statin therapy. Further studies are required to evaluate the effects of statins on improving diastolic function in patients with diastolic dysfunction.

Keywords: Diastolic dysfunction, HFPEF, diastolic index, statin

Introduction

Heart failure is a condition that affects heart function, both functionally and structurally. If not treated properly, heart failure can lead to further deterioration of heart function, which can develop into several life-threatening conditions. Heart failure involves both systolic and diastolic functions and can be divided into two major categories: heart failure with reduced ejection fraction (HFREF), which is related to systolic dysfunction of the heart, and heart failure with preserved ejection fraction (HFPEF), which is related to diastolic dysfunction of the heart [1, 2].

Without proper treatment, diastolic dysfunction can decrease cardiac function, leading to chronic heart failure. Several studies have been conducted to understand heart failure and the proper treatment that can increase heart function; however, most have focused on systolic function. Further studies are required on the treatment of diastolic dysfunction of the heart [1].

Statins have beneficial effects on patients with hypercholesterolemia and are useful in controlling cholesterol synthesis, especially in the liver, and in reducing the total cholesterol level circulating in the bloodstream. Statins have pleiotropic anti-inflammatory and antioxidant effects, and can be useful for improving diastolic function, especially in cases of diastolic dysfunction. Therefore, in this study, we aimed to corroborate these findings to better understand the effect of statin therapy on the diastolic function of the heart [3-5].

Methods

Study Selection

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [6]. We assessed all randomised controlled trials on the use of statin therapy on patients with diastolic dysfunction. The included studies compared the diastolic index between statin- and placebo-treated patients during a given period. We excluded all studies in which patients had a reduced ejection fraction (EF) (EF < 40%), incomplete echocardiography data, or had undergone a combination of treatments other than statins.

We conducted a search of the PubMed and Google Scholar databases using the following keywords: (Statin or HMG-COA or atorvastatin or rosuvastatin or simvastatin or pravastatin or fluvastatin or lovastatin or pitavastatin) and ('Diastolic Dysfunction' or 'Diastolic Failure' or HFPEF or 'Preserved Ejection Fraction') and ('clinical trial' [Publication Type] or 'clinical trials as topic'[MESH Terms] or 'clinical trial'[All Fields]) on PubMed database and Statin 'Diastolic Failure' or 'Diastolic Dysfunction' or HFPEF or 'Preserved Ejection Fraction' on the Google Scholar database. We conducted the search on June 14, 2024, with no restrictions on the country of publication, patient age, race, sex, and date of publication. Two investigators (KW and NE) independently screened the titles and abstracts before retrieving the full text. Two authors (KW and NE) reviewed the studies that met the inclusion and exclusion criteria for further analysis.

Data Extraction

Two investigators (KW and NE) extracted data from the approved studies, including the author, year of publication, number of patients, follow-up duration, statin drug use, and echocardiographic values (E/A ratio, isovolumic relaxation time [IVRT], E-wave deceleration time [EDT], E velocity, A velocity, and left ventricular mass index [LVMI]). All data were extracted in a dedicated Excel spreadsheet.

The primary endpoint of this study was the comparison of echocardiographic indices, including the E/A ratio, IVRT, EDT, E velocity, A velocity, and LVMI, between the statin-treated and placebo-controlled groups. All collected data were analysed according to the guidelines of the Cochrane Handbook.

Two independent reviewers compared the included studies for risk assessment using Cochrane's Risk of Bias 2 (RoB 2) tool to analyse the risk of bias of each study by presenting all of the data and reviewing the quality of the data collected from each of the included studies [7]. Two authors independently analysed the overall quality of evidence using the GRADE assessment guidelines.

Data Analysis

The meta-analysis was performed using the mean difference (MD) for the E/A ratio, IVRT, EDT, E velocity, A velocity, and LVMI. Random-effects and inverse-variance weighting were used to perform the analysis with the Review Manager (RevMan Web) software. The between-study heterogeneity was evaluated using I^2 statistics.

Results

Search Results and Quality Assessment

We searched related studies on the PubMed and Google Scholar databases using predefined keywords. A total of 39 studies were retrieved from PubMed, whereas 63 studies were retrieved from Google Scholar. Twenty studies were removed after automating the application. Seventy studies did not pass the screening phase, including duplicate and excluded titles (n = 54) and incompatible abstracts (n = 16). Of the 12 studies assessed by full text, 10 did not meet the inclusion criteria for the following reasons: the full text was unavailable (2), the exclusion criteria were met (6), or the studies had incomplete outcome data (2) (Figure 1).

Two studies were included in this meta-analysis. Data that were collected from all the studies were made into a table in an Excel sheet, including the author, year of publication, number of patients, statin drug used, echocardiographic values (E/A, IVRT, EDT, E velocity, A velocity, and LVMI), and follow-up duration (Table 1).

The included studies then underwent risk of bias assessment using the RoB 2 Cochrane Risk Assessment and were assessed by two independent reviewers (KW and NE) (Supplementary Figure 1). Based on the RoB 2 Cochrane Risk Assessment tool, one of the studies[8] had some concerns regarding the randomisation process, suggesting that the patients knew whether they were provided the treatment based on the guidelines for the respective patients' condition. However, both studies had a low overall risk of bias based on the combination of all aspects and were therefore suitable for inclusion in this study (Supplementary Figure 1).

All included studies were analysed using the GRADE Assessment guidelines to determine their overall quality. All assessments started at a high quality, and each assessment was downgraded based on the risk of bias, inconsistency, indirectness, imprecision, and publication bias. After evaluating all aspects, we found that most of the studies were of very low quality, and the best was of low quality. Several studies had serious inconsistencies, with $I^2 > 50\%$. We also concluded that all studies had some imprecision, with a total sample size of < 300 participants. There were also some indications of publication bias on all studies because the sample sizes were insufficient to represent large demographic samples, which might have skewed the overall results (Supplementary Figure 2).

E/A Ratio

The random-effects meta-analysis from both included studies showed no significant difference in the overall MD of the E/A ratio (I^2 = 72%, Z = 1.29, and P = 0.20). The overall MD was 0.10 (95% confidence interval [CI], 0.24-0.05). Although there were no significant differences in the overall MD, there were tendencies towards a reduction in the E/A ratio, and one of the included studies[8] showed a significant MD of 0.20 (95% CI: 0.38 to 0.02) (Supplementary Figure 3).

Isovolumic Relaxation Time

The random-effects meta-analysis showed no significant difference in the overall MD (I^2 = 0%, Z = 0.35, and P = 0.73), which was-1.02 (95% CI: -6.82-4.78). None of the included studies showed a significant difference in the MD of the IVRT results (Supplementary Figure 4).

E-Wave Deceleration Time

The random-effects meta-analysis of the included studies showed no significant difference in MDs (I^2 = 68%, P = 1.00, and Z = 0.00), and the overall MD was 0.01 (95% CI:

9.82-9.80). None of the included studies showed significant differences in EDT (Supplementary Figure 5).

Left Ventricular Mass Index

The random-effects meta-analysis revealed significant differences in the MD of LVMI (I^2 = 86%, P<0.00001, and Z = 5.86). Overall, the LVMI showed a decreasing tendency, with a MD of 8.99 (95% CI: 12.00 to 5.98). One study[9] showed significant differences in the LVMI, with a MD of 11.26 (95% CI: 14.69 to 7.83) (Figure 2).

E Velocity

The random-effects meta-analysis revealed a significant difference in the overall E velocity (I^2 = 97%, P<0.00001, and Z = 6.90), which increased significantly (MD: 1.16, 95% CI: 0.83-1.49).

One study[8] also showed a significant increase in E velocity (MD: 2.20, 95% CI: 1.71-2.69) (Figure 3).

A Velocity

The random-effects meta-analysis of A velocity showed a significant difference in MD (I^2 = 54%, p<0.00001, and Z = 4.35). The overall A velocity decreased significantly (MD: 0.68, 95% CI: 0.98 to 0.37). A study[9] found a significant decrease in A velocity (MD: 0.75, 95% CI: 1.07 to 0.43) (Figure 4).

Discussion

The cardiac cycle comprises two phases: systolic and diastolic. During the diastolic phase, the ventricle of the heart relaxes, and the atrium constricts to allow blood to flow to the ventricle. Several factors can affect the diastolic function of the heart, one of which is myocardial stiffness, which affects the ventricular ability to relax and allows blood to fill the ventricle properly [10, 11].

Diastolic dysfunction occurs when the lower chamber of the heart is unable to relax properly, which disrupts the diastolic phase of the cardiac cycle. Although diastolic dysfunction is common in patients with HFpEF, not all diastolic dysfunctions are unique to HFpEF; they can also be found in HFrEF [11-13].

Diastolic dysfunction can only be evaluated using echocardiography. Several aspects, including the measurement of peak E velocity, A velocity, E/A ratio, EDT, and IVRT, should be evaluated based on the guidelines for evaluating diastolic dysfunction. The severity of diastolic dysfunction can be evaluated by measuring these aspects, and the diastolic dysfunction can be graded accordingly [14, 15].

While a suitable therapy has not been identified for effectively improving diastolic function, statins are a promising treatment option for improving diastolic function, especially in patients with diastolic dysfunction. Statins have primarily been used to treat patients with hypercholesterolemia; however, they may have some beneficial effects in improving heart function, specifically diastolic function. Some studies have evaluated the improvement in the overall condition of patients with diastolic dysfunction, and one of them found an improvement in the mortality of patients treated with statins [16, 17]. Therefore, we performed a meta-analysis to evaluate the effect of statin treatment on improving cardiac diastolic function, especially echocardiographic values related to diastolic function, in patients with diastolic dysfunction.

A meta-analysis was performed based on the data collected from all included studies, which included changes in the E/A ratio, IVRT, EDT, LVMI, E velocity, and A velocity. Based on the results, we found no significant changes in the overall MDs in the E/A ratio, IVRT, and EDT. One study[8] reported a significant reduction in the E/A ratio in patients treated with statins compared with those treated with placebo, whereas another study[9] found no significant change in the E/A ratio.

Although no significant difference was found in the overall MD of the E/A ratio, the analysis revealed significant changes in the E and A velocities. A significant overall increase was found in the E velocity, with a MD of 1.16. Analysis of individual studies revealed that one of them [8] showed a significant increase in the E Velocity of 2.20. In contrast, the overall A velocity decreased significantly, with a MD of 0.68. Individual study analysis revealed that one of the two studies [9] reported a significant decrease in the A velocity with a MD of 0.75.

According to the results of the meta-analysis, although no significant changes were found in the E/A ratio, the individual E and A velocities showed significant changes. The unchanged overall E/A ratio could be attributed to the difference in E and A velocities that were independent of the two included studies, with one of them [8] having a significant increase in E velocity, while another [9] reported a significant decrease in A velocity. However, when we evaluated the quality of the studies using the GRADE assessment, we found that the quality of the studies was very low.

We also found significant differences in the LVMI, with a decrease in the overall MD of 8.99. The individual included studies also revealed a decreasing tendency in LVMI, with one of them [9] showing a significant change. Changes in LVMI did not directly improve diastolic function; rather, patients with increased LVMI had diastolic dysfunction[18]. The decrease in LVMI was strongly correlated with a reduction in the myocardial wall stiffness, which can improve the diastolic function of the heart due to better relaxation of the myocardial wall [19].

A previous meta-analysis evaluated the mortality of patients with HFpEF and diastolic dysfunction receiving statin treatment [20]. However, to the best of our knowledge, no meta-analysis has been conducted on the effects of statin treatment on diastolic function in patients with diastolic dysfunction. The studies included in this meta-analysis used different types of statins, including atorvastatin [9] and rosuvastatin [8]. Based on the literature review, the overall effects of both statins should be the same; however, this difference may be a contributing factor to several differences in the findings of these two studies. As another limitation, this meta-analysis could be improved by the inclusion of more studies, longer evaluation periods, and more specific conditions of the patients involved in the studies, as well as by searching additional databases to facilitate inclusion of further studies.

Table 1: Data extracted from included studies

Study characteristics					Results	
					Follow-up	
Author, year	**Study design**	**Statin type**	**Sample**	**Follow-up duration**	**Treatment**	**Control**
Guangmei Zou *et al*. - 2018[9]	RCT prospective	Atorvastatin 20 mg	150	12 months	E/A:1.35±0.74 LVMI: 102.36±10.58 IVRT: 74.12±21.13 EDT: 201.54±30.57 E velocity: 6.815±1.517 A velocity: 7.412±0.823	E/A:1.25±0.82 LVMI: 113.62±10.85 IVRT: 76.14±20.17 EDT: 203.47±32.14 E velocity: 6.512±1.241 A velocity: 8.165±1.157
Luis M. Moura *et al*. - 2012 [8]	RCT prospective	Rosuvastatin 20 mg	121	18 months	E/A:1.0±0.6 IVRT: 102.0±42.8 LVMI: 84.2±19.2 EDT: 321.1:±143.2 E velocity: 7.4±1.1 A velocity: 9.6±3	E/A:1.2±0.4 IVRT: 99.7±21.7 LVMI: 85.6±15.9 EDT: 280.2±115.6 E velocity: 5.2±1.6 A velocity: 9.6±2.3

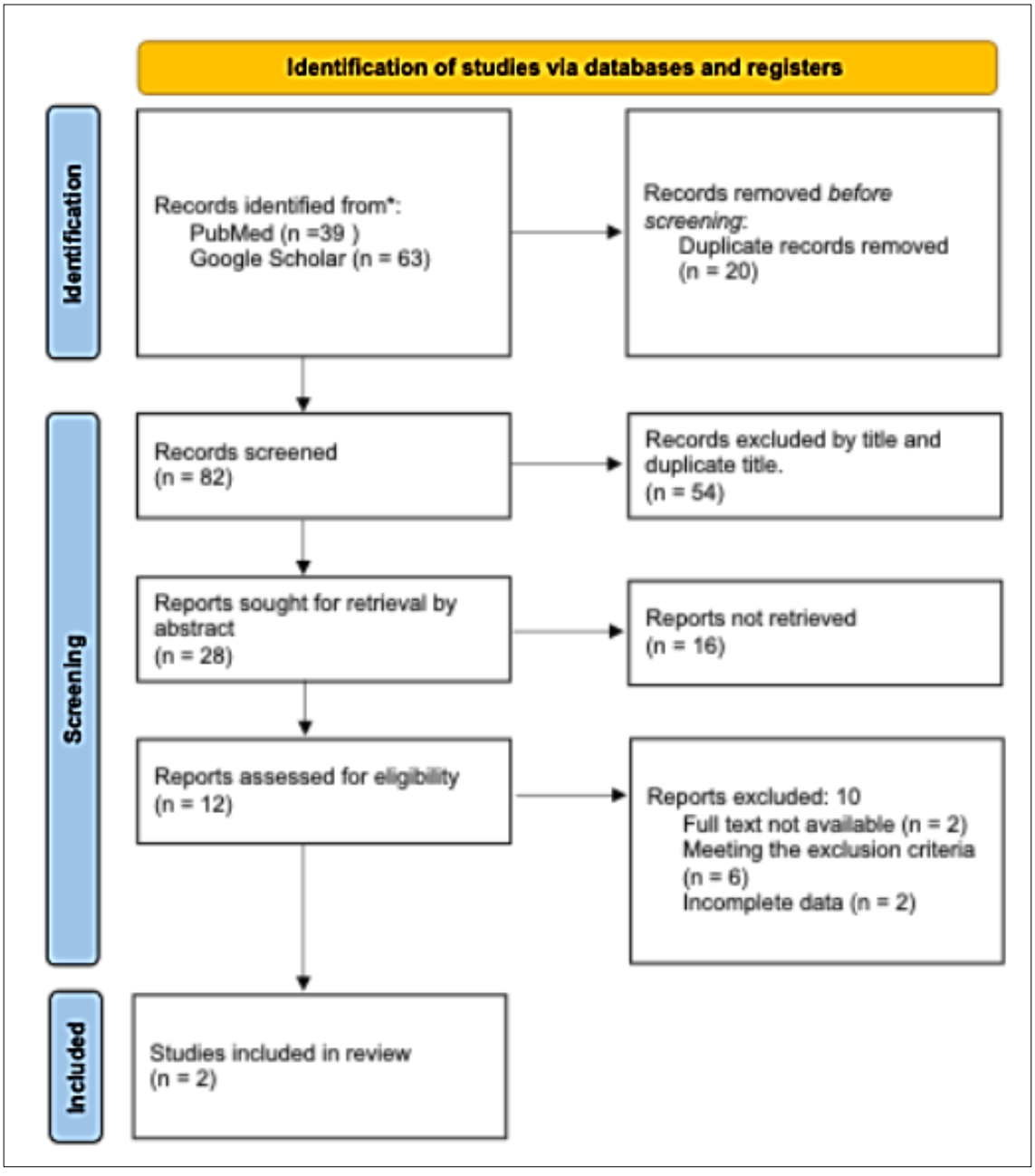

Fig 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart

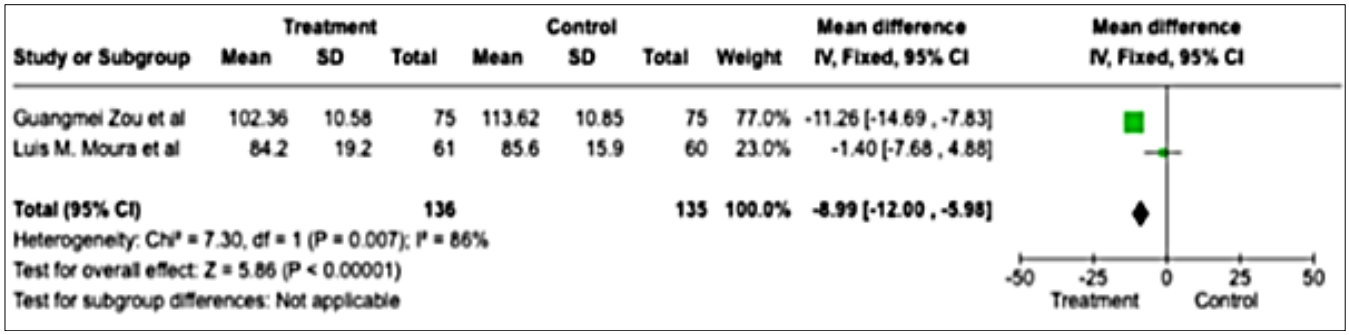

Fig 2: Forest plot of the left ventricular mass index. SD: Standard deviation, CI: Confidence interval

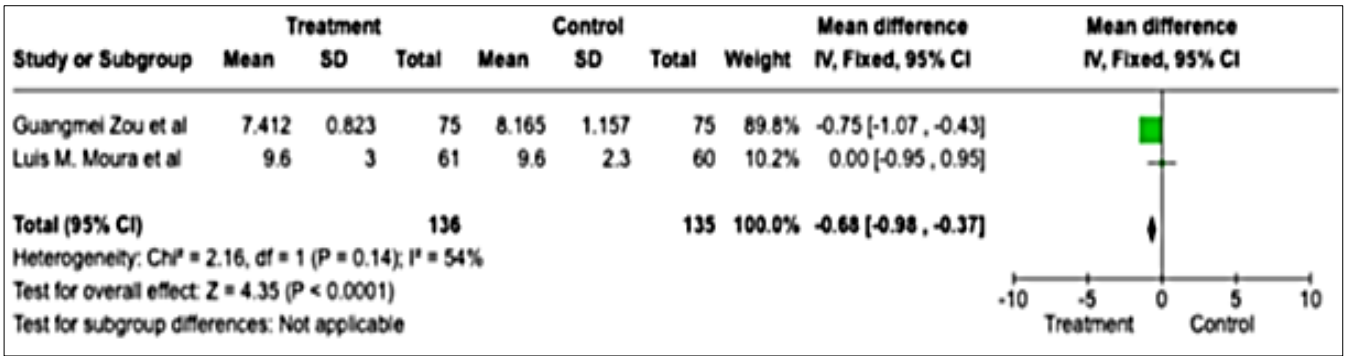

Fig 3: Forest plot of E velocity. SD: Standard deviation, CI: Confidence interval

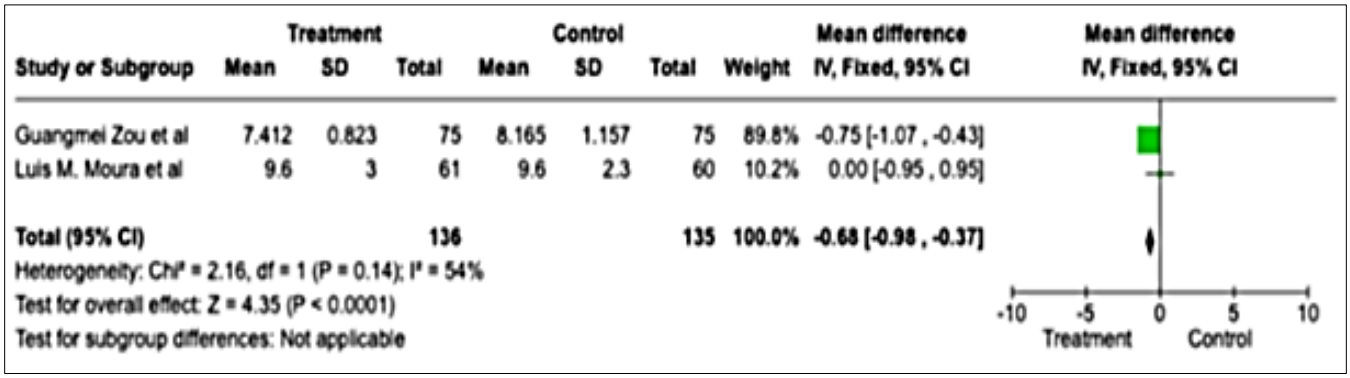

Fig 4: Forest plot of A velocity. SD: Standard deviation, CI: Confidence interval

Conclusion

Significant changes in statin use were observed among patients with diastolic dysfunction. Moreover, there were significant differences in the overall values of LVMI, E velocity, and A velocity, in which the statin-treated patients showed better improvement than the placebo-controlled patients. However, the included studies have very low quality and serious inconsistencies owing to the high data heterogeneity. Additionally, no significant differences were observed in the overall E/A ratio, EDT, and IVRT. With these promising but limited results, more studies are needed to better understand the overall effects and obtain a higher quality of overall studies to gain better knowledge of the relationship between statin treatment and diastolic function improvement in patients with diastolic dysfunction.

Acknowledgments

None

References

1. Golla MSG, Hajouli S, Ludhwani D. Heart failure and ejection fraction. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Aug 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK553115/
2. Malik A, Brito D, Vaqar S, Chhabra L. Congestive heart failure. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Aug 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK430873/
3. Sizar O, Khare S, Patel P, Talati R. Statin medications. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Aug 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK430940/
4. Bansal AB, Cassagnol M. HMG-CoA reductase inhibitors. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Aug 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK542212/
5. Kavalipati N, Shah J, Ramakrishan A, Vasnawala H. Pleiotropic effects of statins. Indian J Endocr Metab. 2015;19(4):554-562.
6. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

7. Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
8. Moura LM, Ramos SF, Kristensen SD, *et al*. Rosuvastatin slows the development of diastolic dysfunction in calcific aortic stenosis. J Heart Valve Dis. 2012;21(4):463-472.
9. Zou G, Song L, Chang L, Wang H. Comparison and analysis of statins drug use in the treatment of diastolic dysfunction in patients. Pak J Pharm Sci. 2018;31(5):1725-1730.
10. Pollock JD, Makaryus AN. Physiology, cardiac cycle. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Aug 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK459327/
11. Jeong EM, Dudley SC Jr. Diastolic dysfunction. Circ J. 2015;79(3):470-477.
12. Obokata M, Reddy YNV, Borlaug BA. Diastolic dysfunction and heart failure with preserved ejection fraction. JACC Cardiovasc Imaging. 2020;13(1):245-257.
13. Wenzel JP, Kellen RBD, Magnussen C, *et al*. Diastolic dysfunction in individuals with and without heart failure with preserved ejection fraction. Clin Res Cardiol. 2022;111(4):416-427.
14. Nagueh SF, Smiseth OA, Appleton CP, *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314.
15. Kossaify A, Nasr M. Diastolic dysfunction and the new recommendations for echocardiographic assessment of left ventricular diastolic function: summary of guidelines and novelties in diagnosis and grading. J Diagn Med Sonogr. 2019;35(4):317-325.
16. Tehrani F, Morrissey R, Phan A, *et al*. Statin therapy in patients with diastolic heart failure. Clin Cardiol [Internet]. 2010 [cited 2024 Aug 8];33(1):E1-E5. Available from: https://onlinelibrary.wiley.com/doi/10.1002/clc.20615
17. Techorueangwiwat C, Kanitsoraphan C, Hansrivijit P. Therapeutic implications of statins in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction: a review of current literature. F1000Res. 2021;10:16.
18. Bakeer MHNM, Maklady FA, Kamal HM, *et al*. Left ventricular mass index versus results of diastolic stress echocardiography in patients with heart failure with preserved ejection fraction. Int J Health Sci (Qassim). 2024;8(2):73-82.
19. Ciampi Q, Betocchi S, Losi MA, *et al*. Effect of hypertrophy on left ventricular diastolic function in patients with hypertrophic cardiomyopathy. Heart Int. 2006;2(3):106-114.
20. Fukuta H, Goto T, Wakami K, Ohte N. The effect of statins on mortality in heart failure with preserved ejection fraction: a meta-analysis of propensity score analyses. Int J Cardiol. 2016;214:301-306.