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Are statins beneficial for chronic heart failure? - First update

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Abstract

This Living FRISBEE (Living FRIendly Summary of the Body of Evidence using Epistemonikos) is an update of an article published in May 2015 (doi: 10.5867/medwave.2015.04.6140), based on the detection of nine new systematic reviews.

Even though statins decrease inflammatory markers and improve some echocardiographic parameters in heart failure, it is not clear whether they have an impact on clinically important outcomes. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified 15 systematic reviews including 25 randomized trials answering the question of interest. We extracted data, combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded statins do not decrease mortality in chronic heart failure, and might lead to a small reduction in hospital admissions for heart failure, but the certainty of this evidence is low.

About the update

This Living FRISBEE (Living FRIendly Summary of the Body of Evidence using Epistemonikos) is an update of the summary published in May 2015 (doi: 10.5867/medwave.2015.04.6140), based on the detection of nine new systematic reviews.

The new evidence incorporated in this summary does not lead to changes in the certainty of the evidence, the estimates of the magnitude of effects, the key messages or the considerations for decision-making.

Problem

Apart from their main effects on serum lipid levels, statins would have pleiotropic properties, such as antihypertrophic, antifibrotic, antioxidant and inhibitor of neurohumoral activation, all of them involved in the pathophysiology of heart failure. Some studies have shown statins would improve ejection fraction and decrease inflammatory biomarkers, however it is not clear if these effects translate into a clinically important benefit.

Methods

We used Epistemonikos database, which is maintained by screening multiple databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an

evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- Statins do not decrease mortality in chronic heart failure.
- Statins might slightly reduce hospital admissions for heart failure, but the certainty of this evidence is low.
- The balance between benefits and risks for the use of statins in chronic heart failure without other indication is probably not favorable.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found fifteen systematic reviews [1],[2],[3],[4],[5],[6],[7],[8],[9], [10],[11],[12],[13],[14],[15] including 45 [16],[17],[18],[19],[20],[21], [22],[23],[24],[25],[26],[27],[28],[29],[30], [31],[32],[33],[34],[35],[36], [37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49],[50],[51], [52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64] primary studies, of which 25 correspond to randomised controlled trials, reported in 29 references [17],[18],[20],[30],[31],[33],[34],[36],[40],[41],[45],[46], [48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62], [63],[64]. This table and the summary in general are based on the latter.
What types of patients were included	The trials included patients with heart failure from any cause receiving standard treatment. Most trials only included patients with low ejection fraction, except three trials [36],[50],[57]. Four trials included patients with NYHA functional class I [40],[46],[48], [61], 23 functional class II [18],[31],[34],[36],[40],[41],[45],[46],[48], [49], [50],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64] all of the trials included functional class III and eight included functional class IV [34],[36],[49],[53],[55],[58],[59],[63],[64]. The average LDL cholesterol level ranged from 96 to 167 mg/dL in the different trials.
What types of interventions were included	Seventeen trials evaluated atorvastatin [34],[40],[41], [46],[48],[49], [50],[51],[52],[53],[55],[56],[60],[61],[62],[63],[64] five rosuvastatin [18],[31],[36],[58],[59], one cerivastatin [57], one pivastatin [54] and one simvastatin [45]. Most of the trials compared against placebo, with exception of 11 trials that compared against no-intervention [34],[48],[49],[50],[51],[52],[53],[54], [61],[62],[63].
What types of outcomes were measured	The systematic reviews reported the following outcomes: • Total mortality • Cardiovascular mortality • Hospitalization for heart failure • Myocardial infarction • Stroke • Echocardiographic parameters • Inflammatory biomarkers • B-type natriuretic peptide (BNP) levels • QT interval • NYHA functional class

Summary of findings

The information on the effects of statins is based on 25 randomized controlled trials. Seventeen trials reported
mortality [36],[40],[45],[48],[49],[50],[51],[52],[54],[55],[56],[58],[59],[60],[61],[62],[63] and 14 trials reported the risk of hospitalization for heart
failure [36],[45],[48],[49],[50],[52],[54],[55],[56],[58],[59],[60],[61],[62]. The summary of findings is the following:

- Statins do not decrease mortality in chronic heart failure. The certainty of the evidence is high.
- Statins might slightly reduce hospital admissions for heart failure, but the certainty of this evidence is low.

Statins for chronic heart failure

Patients Chronic heart failure
Intervention Statins
Comparison Placebo

Outcomes	Absolute effect*		Relative effect (IC 95%)	Certainty of the evidence (GRADE)
	WITHOUT statins	**WITH statins**		
	Difference: patients per 1000			
Mortality (any cause)	272 per 1000	261 per 1000	RR 0.96 (0.90 to 1.02)	⊕⊕⊕⊕[1,2] High
	Difference: 11 patients less per 1000 (Margin of error: 27 less to 5 more)			
Hospital admission for heart failure	261 per 1000	241 per 1000	RR 0.92 (0.87 to 0.98)	⊕⊕◯◯[1,2] Low
	Difference: 20 patients less per 1000 (Margin of error: 5 to 34 less)			

RR: Risk ratio.
Margin of error = 95%. Confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risks **WITHOUT statins** are based on the risk in the control group of the trials. The risk **WITH statins** (and its margin of error) is calculated from the relative effect (and its margin of error)

[1] Most trials have important limitations, however, there are two trials (CORONA and GISSI – HF) weighing more than 90% in the meta-analysis, which have low risk of bias, so we did not downgrade the certainty of the evidence for mortality. We did downgrade the certainty for hospital admission since the trials with high risk of bias where those that suggested a beneficial effect.
[2] Even though the publication bias analysis (funnel plot) suggests there might be undetected small trials, these would probably reinforce the conclusion of no effect in mortality, so we did not downgrade for this reason. We did downgrade for publication bias in hospital admission since undetected trials would probably show no effect.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- This evidence applies to chronic heart failure of any etiology and functional class not requiring statins for other reasons.
- It does not apply to patients with previous coronary or atherosclerotic events, which is a clear indication of statins as secondary prevention.
- It is difficult to be certain whether some patients included in these trials should have received statins based on their cholesterol level. It is reasonable to evaluate this in a case-by-case basis, incorporating individualized cardiovascular risk.

About the outcomes included in this summary

- The outcomes presented in this summary are those considered critical for decision-making in the main guidelines, the systematic reviews identified, and according to the opinion of the authors of this summary.

Balance between benefits and risks, and certainty of the evidence

- Statins constitute a low-risk intervention, with mild adverse effects. However, it is difficult to balance benefits and harms because the certainty of the evidence is low for the potential benefit.
- If the benefit were certain, it would be reasonable to favor this intervention in patients with a higher hospitalization risk that have not presented important adverse effects.

Resource considerations

- Statins have low cost. However, it is difficult to balance cost and benefit because the certainty of the evidence is low. However, it is unlikely that this factor would determine the decision.

Differences between this summary and other sources

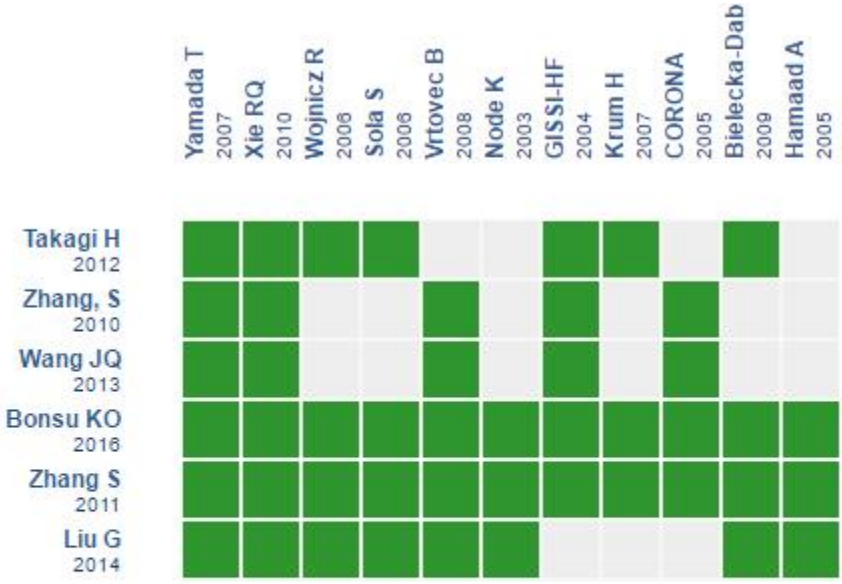
- The systematic reviews identified differ in their conclusions, and some even state there is a clear mortality benefit [11]. However, this summary is in agreement with the main guidelines addressing this question [65],[66], which conclude there is no benefit in heart failure patients.

Could this evidence change in the future?

- The probability that the information on the effect of statins on mortality change in the future is very low.
- We did not identify any ongoing trial answering this question in the International Clinical Trials Registry Platform of the World Health Organization

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Are statins beneficial in chronic heart failure?

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

References

1. Zhang S, Zhang L, Sun A, Jiang H, Qian J, Zhou JM, et al. Effects of statin treatment on long-term clinical outcomes in chronic heart failure: a meta-analysis of 15 prospective clinical trials. Eur Heart J [Internet]. 2010;31:848 | Link |
2. Holland DJ, Kumbhani DJ, Ahmed SH, Marwick TH. Effects of treatment on exercise tolerance, cardiac function, and mortality in heart failure with preserved ejection fraction. A meta-analysis. J Am Coll Cardiol. 2011 Apr 19;57(16):1676-86 | CrossRef | PubMed |
3. van der Harst P, Voors AA, van Gilst WH, Böhm M, van Veldhuisen DJ. Statins in the treatment of chronic heart

failure: a systematic review. PLoS Med. 2006Aug;3(8):e333 | PubMed |
4. Deo SV, Rababa'h A, Altarabsheh SE, Lim JY, Cho YH, Park SJ. Statin therapy improves long-term survival in non-ischaemic cardiomyopathy: a pooled analysis of4500 patients. Heart Lung Circ. 2014 Oct;23(10):985-7 | CrossRef |
5. Takagi H, Umemoto T. Atorvastatin, not rosuvastatin, improves cardiac function in heart failure: a meta-analysis of randomized trials. Int J Cardiol. 2012 Mar 8;155(2):296-9 | CrossRef | PubMed |
6. Bonsu KO, Reidpath DD, Kadirvelu A. Lipophilic Statin Versus Rosuvastatin (Hydrophilic) Treatment for Heart Failure: a Meta-Analysis and Adjusted Indirect Comparison of Randomised Trials. Cardiovasc Drugs Ther. 2016 Apr;30(2):177-88 | CrossRef | PubMed |
7. Liu G, Zheng XX, Xu YL, Ru J, Hui RT, Huang XH. Meta-analysis of the effect of statins on mortality in patients with preserved ejection fraction. Am J Cardiol. 2014 Apr 1;113(7):1198-204 | CrossRef | PubMed |
8. Xu M, Yuan G, Wei F. Effect of atorvastatin in patients with chronic heart failure - insights from randomized clinical trials. Arch Med Sci. 2010 Dec;6(6):866-73 | CrossRef | PubMed |
9. Zhang L, Zhang S, Jiang H, Sun A, Wang Y, Zou Y, et al. Effects of statin therapy on inflammatory markers in chronic heart failure: a meta-analysis of randomized controlled trials. Arch Med Res. 2010 Aug;41(6):464-71 | CrossRef | PubMed |
10. Lipinski MJ, Cauthen CA, Biondi-Zoccai GG, Abbate A, Vrtovec B, Khan BV, et al. Meta-analysis of randomized controlled trials of statins versus placebo in patients with heart failure. Am J Cardiol. 2009 Dec 15;104(12):1708-16 | CrossRef | PubMed |
11. Wang JQ, Wu GR, Wang Z, Dai XP, Li XR. Long-term clinical outcomes of statin use for chronic heart failure: a meta-analysis of 15 prospective studies. Heart Lung Circ. 2014 Feb;23(2):105-13 | CrossRef | PubMed |
12. Zhang L, Zhang S, Jiang H, Sun A, Zou Y, Ge J. Effects of statin treatment on cardiac function in patients with chronic heart failure: a meta-analysis of randomized controlled trials. Clin Cardiol. 2011 Feb;34(2):117-23 | CrossRef | PubMed |
13. Zhang S, Zhang L, Sun A, Jiang H, Qian J, Ge J. Efficacy of statin therapy in chronic systolic cardiac insufficiency: a meta-analysis. Eur J Intern Med. 2011 Oct;22(5):478-84 | CrossRef | PubMed |
14. Liu G, Zheng XX, Xu YL, Lu J, Hui RT, Huang XH. Effects of lipophilic statins for heart failure: a meta-analysis of 13 randomised controlled trials. Heart Lung Circ. 2014 Oct;23(10):970-7 | CrossRef | PubMed |
15. Al-Gobari M, Le H-H, Fall M, Gueyffier F, Burnand B. No benefits of statins for sudden cardiac death prevention in patients with heart failure and reduced ejection fraction: A meta-analysis of randomized controlled trials. Abete P, editor. PLoS One [Internet]. Public Library of Science; 2017 Feb 6 [cited 2017 Feb 24];12(2):e0171168 | Link |
16. Tehrani F, Morrissey R, Phan A, Chien C, Schwarz ER. Statin therapy in patients with diastolic heart failure. Clin Cardiol. 2010 Apr;33(4):E1-5 | CrossRef | PubMed |
17. Strey CH, Young JM, Molyneux SL, George PM, Florkowski CM, Scott RS, et al. Endothelium-ameliorating effects of statin therapy and coenzyme Q10 reductions in chronic heart failure. Atherosclerosis. 2005 Mar;179(1):201-6 | PubMed |
18. Andreou I, Tousoulis D, Miliou A, Tentolouris C, Zisimos K, Gounari P, et al. Effects of rosuvastatin on myeloperoxidase levels in patients with chronic heart failure: a randomized placebo-controlled study. Atherosclerosis. 2010 May;210(1):194-8 | CrossRef | PubMed |
19. Joynt KE, Gattis WA, Hasselblad V, Fuzaylov SY, Serebruany VL, Gurbel PA, et al. Effect of angiotensin-converting enzyme inhibitors, beta blockers, statins, and aspirin on C-reactive protein levels in outpatients with heart failure. Am J Cardiol. 2004 Mar 15;93(6):783-5 | PubMed |
20. Kjekshus J, Dunselman P, Blideskog M, Eskilson C, Hjalmarson A, McMurray JV, et al; CORONA Study Group. A statin in the treatment of heart failure? Controlled rosuvastatin multinational study in heart failure (CORONA): study design and baseline characteristics. Eur J Heart Fail. 2005 Oct;7(6):1059-69 | PubMed |
21. Shah R, Wang Y, Foody JM. Effect of statins, angiotensin-converting enzyme inhibitors, and beta blockers on survival in patients >or=65 years of age with heart failure and preserved left ventricular systolic function. Am J Cardiol. 2008 Jan 15;101(2):217-22 | CrossRef | PubMed |
22. Mozaffarian D, Nye R, Levy WC. Statin therapy is associated with lower mortality among patients with severe heart failure. Am J Cardiol. 2004 May 1;93(9):1124-9 | PubMed |
23. Tousoulis D, Antoniades C, Bosinakou E, Kotsopoulou M, Tsioufis C, Tentolouris C, et al. Effects of atorvastatin on reactive hyperaemia and the thrombosis-fibrinolysis system in patients with heart failure. Heart. 2005 Jan;91(1):27-31 | PubMed |
24. Ray JG, Gong Y, Sykora K, Tu JV. Statin use and survival outcomes in elderly patients with heart failure. Arch Intern Med. 2005 Jan 10;165(1):62-7 | PubMed |
25. Ouzounian M, Tu JV, Austin PC, Chong A, Liu PP, Lee DS. Statin therapy and clinical outcomes in heart failure: a propensity-matched analysis. J Card Fail. 2009 Apr;15(3):241-8.8 | CrossRef | PubMed |
26. Cosentino ER, Rinaldi ER, Santi F, Immordino V, Esposti DD, Bacchelli S, et al. Role of statins on mortality in patients with heart failure. High Blood Press Cardiovasc Prev [Internet]. 2012;19(3):143–95 | Link |
27. Horwich TB, MacLellan WR, Fonarow GC. Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. J Am Coll Cardiol. 2004 Feb 18;43(4):642-8 | PubMed|
28. Segal R, Pitt B, Wilson PP, Sharma D, Bradstreet DC, Ikeda LS. Effects of HMG-COA reductase inhibitors (statins) in patients with heart failure. Eur J Heart Fail [Internet]. 2000;2(S1):96 | Link |
29. Lahoti A, Saeed W, Badri M, Gnall E, Sardar R, Zolty R. Impact of Statins on Long Term Mortality in Heart Failure With Preserved Ejection Fraction (Hfpef). J Am Coll Cardiol [Internet]. 59(13):E1010–E1010 | Link |

30. Ghio S, Scelsi L, Latini R, Masson S, Eleuteri E, Palvarini M, et al; GISSI-HF investigators. Effects of n-3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: a substudy of GISSI-HF trial. Eur J Heart Fail. 2010 Dec;12(12):1345-53 | CrossRef | PubMed |
31. Erbs S, Beck EB, Linke A, Adams V, Gielen S, Kränkel N, et al. High-dose rosuvastatin in chronic heart failure promotes vasculogenesis, corrects endothelial function, and improves cardiac remodeling--results from a randomized, double-blind, and placebo-controlled study. Int J Cardiol. 2011 Jan 7;146(1):56-63 | CrossRef | PubMed |
32. Tehrani F, Phan A, Chien CV, Morrissey RP, Rafique AM, Schwarz ER. Value of medical therapy in patients >80 years of age with heart failure and preserved ejection fraction. Am J Cardiol. 2009 Mar 15;103(6):829-33 | CrossRef | PubMed |
33. Tavazzi L, Tognoni G, Franzosi MG, Latini R, Maggioni AP, Marchioli R, et al; GISSI-HF Investigators. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. Eur J Heart Fail. 2004 Aug;6(5):635-41 | PubMed |
34. Tousoulis D, Antoniades C, Bosinakou E, Kotsopoulou M, Pitsavos C, Vlachopoulos C, et al. Effects of atorvastatin on reactive hyperemia and inflammatory process in patients with congestive heart failure.Atherosclerosis. 2005 Feb;178(2):359-63 | PubMed |
35. Go AS, Lee WY, Yang J, Lo JC, Gurwitz JH. Statin therapy and risks for death and hospitalization in chronic heart failure. JAMA. 2006 Nov 1;296(17):2105-11 | PubMed |
36. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al; Gissi-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Oct 4;372(9645):1231-9 | CrossRef | PubMed |
37. Huan Loh P, Windram JD, Tin L, Reddy P, Velavan P, Rigby AS, et al. The effects of initiation or continuation of statin therapy on cholesterol level and all-cause mortality after the diagnosis of left ventricular systolic dysfunction. Am Heart J. 2007 Apr;153(4):537-44 | PubMed |
38. Roik M, Starczewska MH, Huczek Z, Kochanowski J, Opolski G. Statin therapy and mortality among patients hospitalized with heart failure and preserved left ventricular function--a preliminary report. Acta Cardiol. 2008 Dec;63(6):683-92 | PubMed |
39. Fukuta H, Sane DC, Brucks S, Little WC. Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report. Circulation. 2005 Jul 19;112(3):357-63 | PubMed |
40. Horwich TB, Middlekauff HR, Maclellan WR, Fonarow GC. Statins do not significantly affect muscle sympathetic nerve activity in humans with nonischemic heart failure: a double-blind placebo-controlled trial. J Card Fail. 2011 Nov;17(11):879-86 | CrossRef | PubMed |
41. Strey CH, Young JM, Lainchbury JH, Frampton CM, Nicholls MG, Richards AM, et al. Short-term statin treatment improves endothelial function and neurohormonal imbalance in normocholesterolaemic patients with non-ischaemic heart failure. Heart. 2006 Nov;92(11):1603-9 | PubMed |
42. Gomez-Soto FM, Romero SP, Bernal JA, Escobar MA, Puerto JL, Andrey JL, et al. Mortality and morbidity of newly diagnosed heart failure treated with statins: a propensity-adjusted cohort study. Int J Cardiol. 2010 Apr 15;140(2):210-8 | CrossRef | PubMed |
43. Jordán AJ, Anguita MP; BADAPIC study researchers. Effect of statin treatment on mortality in a large cohort of heart failure patients. Rev Esp Cardiol. 2009 Mar;62(3):323-7 | PubMed |
44. Sola S, Mir MQ, Rajagopalan S, Helmy T, Tandon N, Khan BV. Statin therapy is associated with improved cardiovascular outcomes and levels of inflammatory markers in patients with heart failure. J Card Fail. 2005 Oct;11(8):607-12 | PubMed |
45. Node K, Fujita M, Kitakaze M, Hori M, Liao JK. Short-term statin therapy improves cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy. Circulation. 2003 Aug 19;108(7):839-43 | PubMed |
46. Bleske BE, Nicklas JM, Bard RL, Brook RD, Gurbel PA, Bliden KP, et al. Neutral effect on markers of heart failure, inflammation, endothelial activation and function, and vagal tone after high-dose HMG-CoA reductase inhibition in non-diabetic patients with non-ischemic cardiomyopathy and average low-density lipoprotein level. J Am Coll Cardiol. 2006 Jan 17;47(2):338-41 | PubMed |
47. Anker SD, Clark AL, Winkler R, Zugck C, Cicoira M, Ponikowski P, et al. Statin use and survival in patients with chronic heart failure--results from two observational studies with 5200 patients. Int J Cardiol. 2006 Sep 20;112(2):234-42 | PubMed |
48. Yamada T, Node K, Mine T, Morita T, Kioka H, Tsukamoto Y, et al. Long-term effect of atorvastatin on neurohumoral activation and cardiac function in patients with chronic heart failure: a prospective randomized controlled study. Am Heart J. 2007 Jun;153(6):1055.e1-8 | PubMed |
49. Xie RQ, Cui W, Liu F, Yang C, Pei WN, Lu JC. Statin therapy shortens QTc, QTcd, and improves cardiac function in patients with chronic heart failure. Int J Cardiol. 2010 Apr 15;140(2):255-7 | CrossRef | PubMed |
50. Wojnicz R, Wilczek K, Nowalany-Kozielska E, Szyguła-Jurkiewicz B, Nowak J, Poloński L, et al. Usefulness of atorvastatin in patients with heart failure due to inflammatory dilated cardiomyopathy and elevated cholesterol levels. Am J Cardiol. 2006 Mar 15;97(6):899-904 | PubMed |
51. Vrtovec B, Okrajsek R, Golicnik A, Ferjan M, Starc V, Radovancevic B. Atorvastatin therapy increases heart rate variability, decreases QT variability, and shortens QTc interval duration in patients with advanced chronic heart failure. J Card Fail. 2005 Dec;11(9):684-90 | PubMed |

52. Vrtovec B, Okrajsek R, Golicnik A, Ferjan M, Starc V, Schlegel TT, et al. Atorvastatin therapy may reduce the incidence of sudden cardiac death in patients with advanced chronic heart failure. J Card Fail. 2008 Mar;14(2):140-4 | CrossRef | PubMed |
53. Tousoulis D, Antoniades C, Vassiliadou C, Toutouza M, Pitsavos C, Tentolouris C, et al. Effects of combined administration of low dose atorvastatin and vitamin E on inflammatory markers and endothelial function in patients with heart failure. Eur J Heart Fail. 2005 Dec;7(7):1126-32 | PubMed |
54. Takano H, Mizuma H, Kuwabara Y, Sato Y, Shindo S, Kotooka N, et al; PEARL Study Investigators. Effects of pitavastatin in Japanese patients with chronic heart failure: the Pitavastatin Heart Failure Study (PEARL Study). Circ J. 2013;77(4):917-25 | PubMed |
55. Sola S, Mir MQ, Lerakis S, Tandon N, Khan BV. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. J Am Coll Cardiol. 2006 Jan 17;47(2):332-7 | PubMed |
56. Mozaffarian D, Minami E, Letterer RA, Lawler RL, McDonald GB, Levy WC. The effects of atorvastatin (10 mg) on systemic inflammation in heart failure. Am J Cardiol. 2005 Dec 15;96(12):1699-704 | PubMed |
57. Laufs U, Wassmann S, Schackmann S, Heeschen C, Böhm M, Nickenig G. Beneficial effects of statins in patients with non-ischemic heart failure. Z Kardiol. 2004 Feb;93(2):103-8 | PubMed|
58. Krum H, Ashton E, Reid C, Kalff V, Rogers J, Amarena J, et al. Double-blind, randomized, placebo-controlled study of high-dose HMG CoA reductase inhibitor therapy on ventricular remodeling, pro-inflammatory cytokines and neurohormonal parameters in patients with chronic systolic heart failure. J Card Fail. 2007 Feb;13(1):1-7 | PubMed |
59. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, et al; CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med. 2007 Nov 29;357(22):2248-61 | PubMed |
60. Hamaad A, Sosin M, Lip GY, MacFadyen RJ. Short-term adjuvant atorvastatin improves frequency domain indices of heart rate variability in stable systolic heart failure. Cardiovasc Drugs Ther. 2005 May;19(3):183-7 | PubMed |
61. Bielecka-Dabrowa A, Goch JH, Mikhailidis DP, Rysz J, Maciejewski M, Banach M. The influence of atorvastatin on parameters of inflammation and function of the left ventricle in patients with dilated cardiomyopathy. Med Sci Monit. 2009 Dec;15(12):MS12-23 | PubMed |
62. Abulhul E, McDonald K, Martos R, Phelan D, Spiers JP, Hennessy M, et al. Long-term statin therapy in patients with systolic heart failure and normal cholesterol: effects on elevated serum markers of collagen turnover, inflammation, and B-type natriuretic peptide. Clin Ther. 2012 Jan;34(1):91-100 | CrossRef | PubMed |
63. Hong YJ, Jeong MH, Hyun DW, Hur SH, Kim KB, Kim W, et al. Prognostic significance of simvastatin therapy in patients with ischemic heart failure who underwent percutaneous coronary intervention for acute myocardial infarction. Am J Cardiol. 2005 Mar 1;95(5):619-22 | PubMed |
64. Liu M, Wang F, Wang Y, Jin R. Atorvastatin improves endothelial function and cardiac performance in patients with dilated cardiomyopathy: the role of inflammation. Cardiovasc Drugs Ther. 2009 Oct;23(5):369-76 | CrossRef | PubMed |
65. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K,et al; ESC Committee for Practice Guidelines.. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012 Jul;33(14):1787-847 | CrossRef | PubMed |
66. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. Circulation. 2013;128(16):240–327

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