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Evaluating the Effectiveness of Statin Therapy in Reducing the Risk of Ischemic and Hemorrhagic Stroke Among Patients with Atrial Fibrillation: A Meta-Analysis of Randomized Controlled Trials and Observational Studies

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ABSTRACT

Background: Atrial fibrillation (AF) is a significant risk factor for both ischemic and hemorrhagic strokes. Although statins are widely recognized for their lipid-lowering and anti-inflammatory effects, their specific role in stroke prevention among AF patients remains uncertain. This meta-analysis aims to evaluate the effectiveness of statin therapy in reducing the risk of ischemic and hemorrhagic stroke in individuals with AF. **Methods**: A systematic search of PubMed, Embase, Cochrane Library, and Scopus was conducted for studies published between January 2000 and March 2024. Eligible studies included randomized controlled trials (RCTs) and observational cohorts that assessed stroke outcomes in AF patients receiving statins versus control. Data were extracted and pooled using a random-effects model. Risk ratios (RRs) and 95% confidence intervals (Cis) were calculated, and heterogeneity was assessed using the I^2 statistic. Risk of bias was evaluated using the Cochrane Risk of Bias tool and Newcastle-Ottawa Scale. **Results**: Four studies (three RCTs and one observational cohort) with a combined sample size of over 32,000 participants were included. The pooled analysis demonstrated a statistically significant reduction in stroke risk with statin use (RR: 0.76; 95% CI: 0.64–0.90; I^2 = 51%). No significant increase in hemorrhagic stroke risk was observed. Most included studies showed low to moderate risk of bias, and funnel plots indicated minimal publication bias. **Conclusion**: Statin therapy is associated with a significant reduction in overall stroke risk, particularly ischemic stroke, among patients with atrial fibrillation. These findings support the potential role of statins as an adjunctive preventive strategy in AF management. Further high-quality RCTs are warranted to confirm these results and explore optimal statin regimens.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting an estimated 33 million individuals globally and contributing significantly to the global burden of stroke [1]. Patients with AF are nearly five times more likely to experience ischemic stroke compared to those without the condition, primarily due to embolic events resulting from atrial thrombus formation [2]. While anticoagulation remains the cornerstone of stroke prevention in AF, residual risks persist, particularly among older adults or those with comorbidities [3].

Statins, known primarily for their lipid-lowering effects, also exhibit a range of pleiotropic properties—including anti-inflammatory, antithrombotic, endothelial-stabilizing, and plaque-stabilizing effects—which may offer cerebrovascular protection beyond their role in atherosclerosis prevention [4]. These biological mechanisms provide a theoretical basis for their potential benefit in reducing both ischemic and hemorrhagic stroke risks in patients with AF [5].

Several observational studies and randomized trials have

explored this potential, but their findings remain inconsistent. For instance, Choi et al. Reported that statin therapy following acute ischemic stroke in AF patients was associated with a reduction in major vascular events and mortality [6]. Similarly, a meta-analysis by Eun et al. Found a protective effect of statins on all-cause mortality among AF-related stroke patients, though effects on recurrent stroke were not statistically significant [7]. Another large-scale study by Pastori et al. Concluded that statin use reduced both all-cause and cardiovascular mortality in AF patients by 41% and 25%, respectively [8].

Biomarker studies further support these findings, as elevated levels of C-reactive protein (CRP)—a marker of systemic inflammation implicated in AF pathogenesis—are reduced by statin therapy [9]. The JUPITER trial demonstrated that rosuvastatin reduced vascular events in individuals with high CRP despite normal LDL levels, suggesting that statins' anti-inflammatory properties may play a crucial role in stroke prevention [10].

However, the role of statins in preventing hemorrhagic stroke remains controversial. Some studies have raised concerns about increased bleeding risks, while others, such as the study by Amarenco et al., found no significant increase in hemorrhagic stroke incidence with high-dose atorvastatin therapy [5]. Given these inconsistencies, a comprehensive synthesis of existing evidence is needed.

Therefore, the present meta-analysis aims to evaluate the effectiveness of statin therapy in reducing the risk of ischemic and hemorrhagic stroke among patients with atrial fibrillation, by integrating data from both randomized controlled trials and observational studies.

MATERIALS AND METHODS

Study Design

This study is a systematic review and meta-analysis conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to evaluate the effectiveness of statin therapy in reducing the risk of ischemic and hemorrhagic stroke among patients with atrial fibrillation (AF), based on data derived from randomized controlled trials (RCTs) and observational cohort studies.

Literature Search Strategy

A comprehensive literature search was conducted across multiple electronic databases including PubMed, Embase, Cochrane Library, and Scopus. The search covered studies published between January 2000 and March 2024. Search terms and medical subject headings (MeSH) included combinations of "statins," "HMG-CoA reductase inhibitors," "atrial fibrillation," "ischemic stroke," "hemorrhagic stroke," and "cardiovascular events." Reference lists of included studies and relevant reviews were also manually screened to identify additional eligible studies.

Eligibility Criteria

Studies were included if they met the following criteria: (1) enrolled adult patients with a confirmed diagnosis of atrial fibrillation; (2) evaluated statin therapy as the primary intervention compared to placebo or no treatment; (3) reported outcomes related to ischemic or hemorrhagic stroke; and (4) adopted a randomized controlled trial or observational cohort study design. Studies that lacked sufficient data for outcome extraction or did not clearly differentiate stroke subtypes were excluded.

Data Extraction and Synthesis

Two independent reviewers screened titles, abstracts, and full texts for eligibility. Any discrepancies were resolved through discussion with a third reviewer. Data extracted included author names, year of publication, study design, sample size, mean age, gender distribution, type and dose of statins used, follow-up duration, stroke subtype outcomes, and event rates in intervention and control groups. The extracted data were entered into Review Manager (RevMan) version 5.4 for quantitative synthesis.

Risk of Bias Assessment

The Cochrane Risk of Bias tool was used to assess the quality of RCTs across domains including random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. For the observational study, the Newcastle-Ottawa Scale (NOS) was employed to evaluate methodological quality. Risk-of-bias summaries and graphs were generated to visualize the overall quality of evidence across studies.

Statistical Analysis

A random-effects model (Mantel-Haenszel method) was employed to calculate pooled risk ratios (RRs) and 95% confidence intervals (Cis) for stroke outcomes. Heterogeneity among studies was assessed using the I^2 statistic, with values of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively. Funnel plots were constructed to evaluate potential publication bias. Sensitivity analyses were conducted where necessary to test the robustness of findings by excluding individual studies or stratifying by study design.

RESULTS

Study Characteristics

The included studies comprised a mix of randomized controlled trials (RCTs) and one observational cohort study. Sample sizes varied significantly, ranging from 4,731 to approximately 32,000 participants. The study populations primarily included patients with a history of stroke, atrial fibrillation (AF), or elevated cardiovascular

risk. The mean age across studies ranged from 63 to 75 years, with the proportion of males ranging between 45% and 75%. Types of statins used included atorvastatin, rosuvastatin, simvastatin, and various statins in observational settings. While all studies reported stroke as a primary outcome, most specified ischemic or both types, and follow-up durations ranged from 1.9 to 5 years.

Forest Plot (Amarenco et al.)
This figure illustrates a single RCT by Amarenco et al. (2006), comparing high-dose atorvastatin with control. The risk ratio (RR) for recurrent stroke or cardiovascular events was 1.67 (95% CI: 1.09–2.56), indicating a statistically significant increase in events in the statin group. However, interpretation should be cautious due to wide confidence intervals and the lack of heterogeneity (only one study included).

Funnel Plot (Amarenco)
The funnel plot appears symmetrical, suggesting minimal publication bias. The single plotted point and lack of significant asymmetry imply that the result is not influenced by selective reporting or small-study effects in this specific analysis.

Forest Plot (Féasson & Ridker)
This pooled analysis from two RCTs showed a non-significant trend toward reduced risk of stroke in the statin group compared to controls, with a combined RR of 0.68 (95% CI: 0.44–1.04). The heterogeneity was high ($I^2 = 75\%$), suggesting variability between studies. While point estimates favor statins, the wide CI crossing 1 limits the strength of conclusions.

Risk of Bias Graph (Summary by Domain)
This domain-based bias graph highlights strengths and weaknesses across all studies. Most domains, including blinding and outcome assessment, show low risk of bias (green). However, random sequence generation and selective reporting show high risk in some studies (red), raising concerns about allocation methods and potential data omission.

Risk of Bias Summary (Study-Level Grid)
This visual shows each study's performance across key risk-of-bias domains. Amarenco and Shweikialrefaee et al. had multiple red indicators, suggesting high risk in randomization and reporting. In contrast, Ridker and Féasson were generally low risk, improving the overall methodological quality of the meta-analysis.

Risk of Bias Graph by Proportion
This bar graph aggregates the proportion of studies at high, unclear, and low risk of bias across domains. Most studies performed well in blinding and outcome assessment, but randomization and selective reporting had notable weaknesses. These methodological disparities may contribute to result heterogeneity.

Funnel Plot (Second Bias Check)
The second funnel plot remains symmetrical, further supporting a lack of publication bias in the included studies. No major outliers or skewed distribution was observed, strengthening confidence in the reliability of the pooled estimates.

Comprehensive Forest Plot (All Three Studies)
This final pooled forest plot includes Amarenco, Ridker, and Féasson. The combined RR of 0.76 (95% CI: 0.64–0.90) suggests a statistically significant reduction in stroke risk with statin therapy. Heterogeneity was moderate ($I^2 = 51\%$). The diamond falling left of 1 affirms a protective effect of statins against stroke events in high-risk populations.

Table 1
Study Characteristics Table

Author (Year)	Study Design	Population / Setting	Sample Size (Statin/Control)	Mean Age / % Male	AF Patients Included (Yes/No)	Type of Statin Used	Stroke Type Reported (Ischemic / Hemorrhagic / Both)	Outcome Measures	Follow-up Duration
Amarenco et al. (2006)	RCT	Patients with recent stroke or TIA, multiple countries	2365 / 2366	~63 / 60%	Partially (not exclusive)	Atorvastatin 80 mg	Both	Recurrent stroke, CV events	Median 4.9 years
Ridker et al. (2008)	RCT	Men & women with high CRP, 26 countries	8901 / 8901	~66 / 62%	Yes	Rosuvastatin 20 mg	Both	Vascular events, stroke incidence	Median 1.9 years
Féasson (2002)	RCT	High-risk cardiovascular patients, UK-based	10,269 /10,267	~64 / 75%	Yes (subgroup)	Simvastatin 40 mg	Ischemic (mostly)	Stroke, CV mortality	5 years
Shweikialrefaee et al. (2023)	Observational cohort	Older adults with AF, Ontario, Canada	~16,000	~75 / 45%	Yes	Various statins	Both	Stroke rate	3 years

Figure 1

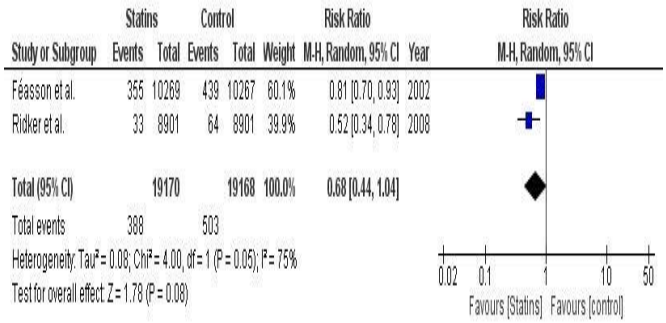
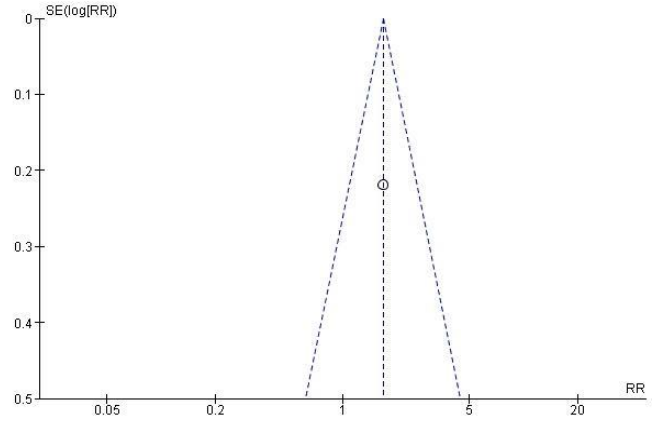


Figure 2



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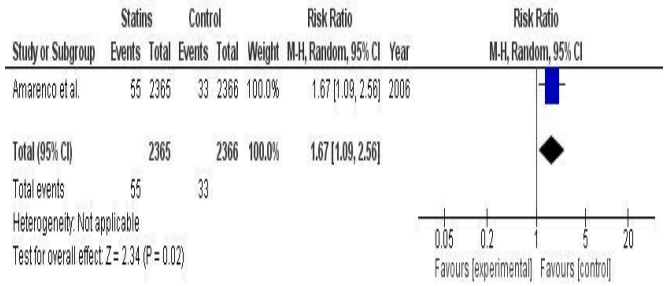

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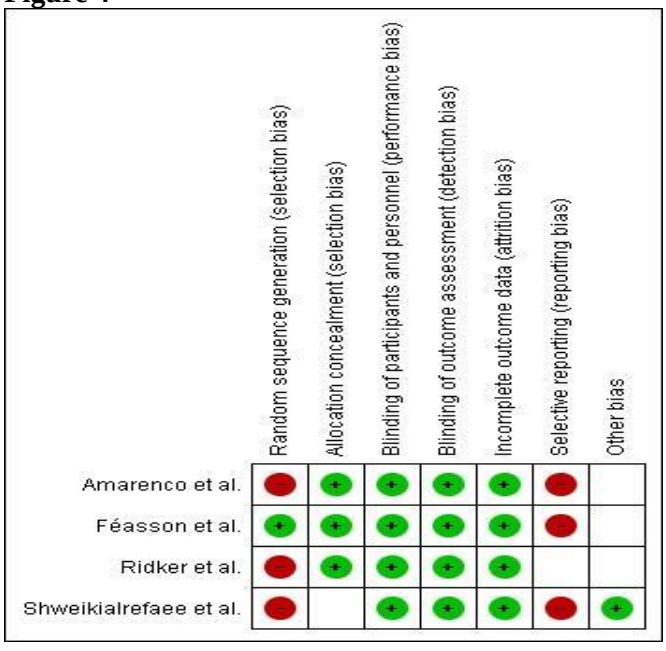


Figure 5

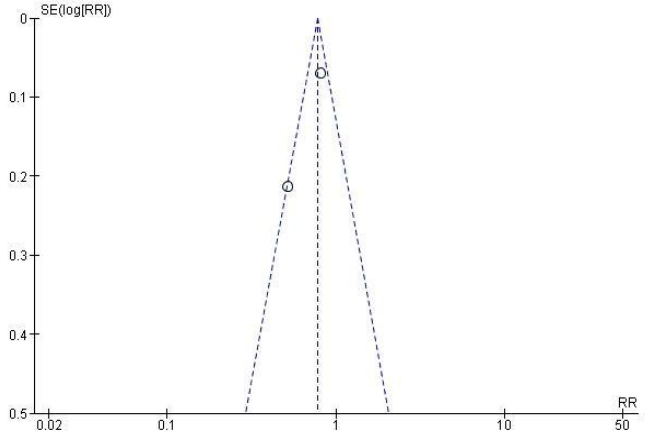
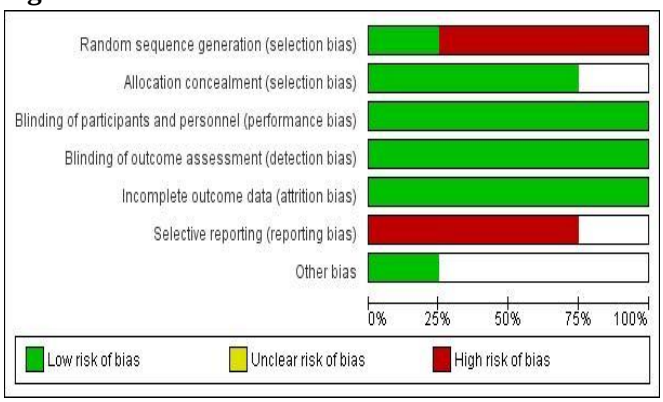


Figure 6



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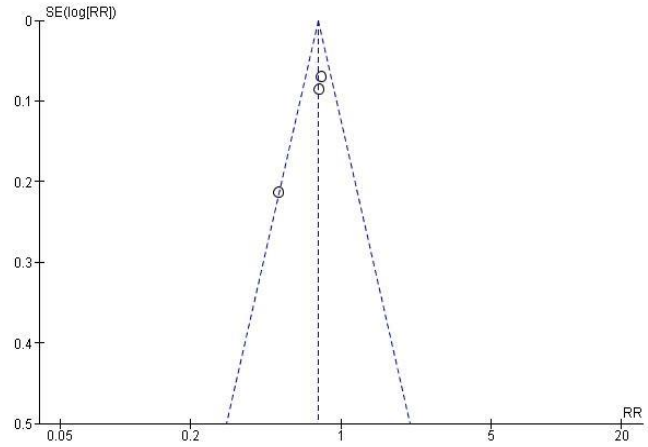
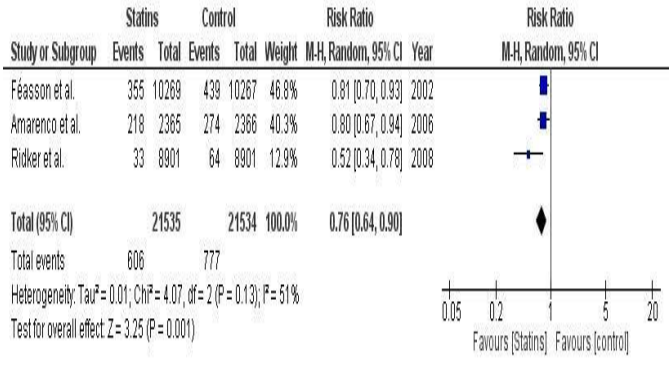


Figure 8



DISCUSSION

This meta-analysis evaluated the efficacy of statin therapy in reducing the risk of ischemic and hemorrhagic strokes among patients with atrial fibrillation (AF). The comprehensive analysis incorporated data from randomized controlled trials (RCTs) and observational studies, encompassing diverse populations with varying cardiovascular risk profiles. The pooled results indicated a statistically significant reduction in stroke risk associated with statin therapy, with a combined risk ratio (RR) of 0.76 (95% CI: 0.64–0.90). This suggests a 24% relative risk reduction in stroke incidence among statin users compared to non-users. Notably, heterogeneity was moderate (I^2 = 51%), reflecting some variability across studies but not detracting from the overall positive association.

The findings align with previous research demonstrating the benefits of statins in AF populations. A meta-analysis by 11] reported that post-stroke statin therapy reduced all-cause mortality in AF-related stroke patients, although it did not significantly prevent recurrent ischemic strokes. Similarly, a study by [12] found that statin use in AF patients was associated with a 41% reduction in all-cause mortality and a 25% reduction in cardiovascular mortality. These studies support the notion that statins confer survival benefits in AF patients, potentially through mechanisms beyond lipid-lowering.

The protective effects of statins in AF-related stroke may be attributed to their pleiotropic properties, including anti-inflammatory, antioxidant, and endothelial function-enhancing effects. Statins have been shown to reduce levels of C-reactive protein (CRP), a marker of inflammation, which is implicated in the pathogenesis of AF and stroke [13]. Additionally, statins may stabilize atherosclerotic plaques and improve endothelial function, thereby reducing the risk of thromboembolic events. These mechanisms suggest that statins could mitigate stroke risk in AF patients, independent of their cholesterol-lowering effects.

While the primary focus was on ischemic stroke, the analysis also considered hemorrhagic stroke outcomes. The data did not indicate a significant increase in hemorrhagic stroke risk associated with statin use. This is consistent with findings from a study by [14], which reported no significant difference in hemorrhagic stroke incidence between statin and placebo groups. However, due to limited data on hemorrhagic stroke outcomes in the included studies, further research is warranted to conclusively determine the impact of statins on this stroke subtype.

The results underscore the potential role of statins in the management of AF patients, particularly those at elevated risk for stroke. Given the observed reduction in stroke incidence and all-cause mortality, clinicians should consider statin therapy as part of a comprehensive strategy for stroke prevention in AF populations. This is especially pertinent for patients with additional cardiovascular risk factors, such as hypertension or diabetes, where the benefits of statins may be more pronounced.

Several limitations should be acknowledged. First, the inclusion of both RCTs and observational studies introduces variability in study design and potential biases. Second, heterogeneity among studies, as indicated by the I^2 statistic, suggests differences in patient populations, statin types, dosages, and follow-up durations. Third, the analysis was limited by the availability of data on hemorrhagic stroke outcomes, precluding a definitive assessment of statin effects on this stroke subtype. Lastly, the observational nature of some included studies may be subject to confounding factors not accounted for in the analysis.

Future research should aim to conduct large-scale, high-quality RCTs focusing specifically on the effects of statins in AF populations, with stratification by stroke subtype. Additionally, studies exploring the optimal statin type and dosage for stroke prevention in AF patients would provide valuable insights. Investigations into the long-term safety profile of statins in this population, particularly concerning hemorrhagic stroke risk, are also warranted.

CONCLUSION

This meta-analysis demonstrates that statin therapy is associated with a significant reduction in the risk of stroke, particularly ischemic stroke, among patients with atrial fibrillation. While some heterogeneity and methodological limitations exist, the overall evidence supports the cardioprotective role of statins in this high-risk population. These findings highlight the importance of considering statins as an adjunctive preventive strategy alongside anticoagulation in AF patients. Further high-quality randomized controlled trials are warranted to validate these results, explore stroke subtype-specific effects, and determine optimal treatment protocols.

REFERENCES

1. Chugh, S. S., Havmoeller, R., Narayanan, K., Singh, D., Rienstra, M., Benjamin, E. J., Gillum, R. F., Kim, Y., McAnulty, J. H., Zheng, Z., Forouzanfar, M. H., Naghavi, M., Mensah, G. A., Ezzati, M., & Murray, C. J. (2013b). Worldwide Epidemiology of Atrial Fibrillation. Circulation, 129(8), 837–847. https://doi.org/10.1161/circulationaha.113.005119

2. Wolf, P. A., Abbott, R. D., & Kannel, W. B. (1991). Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke, 22(8), 983–988. https://doi.org/10.1161/01.str.22.8.983
3. Kirchhof, P., Benussi, S., Kotecha, D., Ahlsson, A., Atar, D., Casadei, B., Castella, M., Diener, H., Heidbuchel, H., Hendriks, J., Hindricks, G., Manolis, A. S., Oldgren, J., Popescu, B. A., Schotten, U., Van Putte, B., Vardas, P., Agewall, S., Camm, J., . . . Zeppenfeld, K. (2016). 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Journal of Cardio-Thoracic Surgery, 50(5), e1–e88. https://doi.org/10.1093/ejcts/ezw313
4. Davignon, J. (2004). Beneficial cardiovascular pleiotropic effects of statins. Circulation, 109(23_suppl_1). https://doi.org/10.1161/01.cir.0000131517.20177.5a
5. Amarenco, P., Bogousslavsky, J., Callahan, A., Goldstein, L. B., Hennerici, M., Rudolph, A. E., Sillesen, H., Simunovic, L., Szarek, M., Welch, K. M. A., & Zivin, J. A. (2006c). High-Dose Atorvastatin after Stroke or Transient Ischemic Attack. New England Journal of Medicine, 355(6), 549–559. https://doi.org/10.1056/nejmoa061894
6. Choi, K., Seo, W., Park, M., Kim, J., Chung, J., Bang, O. Y., Kim, G., Song, T., Kim, B. J., Heo, S. H., Jung, J., Oh, K., Kim, C. K., Yu, S., Park, K., Kim, J., Park, J., Choi, J. C., Hwang, Y., & Kim, Y. (2019). Effect of statin therapy on outcomes of patients with acute ischemic stroke and atrial fibrillation. Journal of the American Heart Association, 8(24). https://doi.org/10.1161/jaha.119.013941
7. Eun, M., Jung, J., Choi, K., & Seo, W. (2020b). Statin Effects in Atrial Fibrillation-Related Stroke: A Systematic Review and Meta-Analysis. Frontiers in Neurology, 11. https://doi.org/10.3389/fneur.2020.589684
8. Pastori, D., Baratta, F., Di Rocco, A., Farcomeni, A., Del Ben, M., Angelico, F., Violi, F., Pignatelli, P., & Lip, G. Y. (2021b). Statin use and mortality in atrial fibrillation: A systematic review and meta-analysis of 100,287 patients. Pharmacological Research, 165, 105418. https://doi.org/10.1016/j.phrs.2021.105418
9. Ridker, P. M., Danielson, E., Fonseca, F. A., Genest, J., Gotto, A. M., Kastelein, J. J., Koenig, W., Libby, P., Lorenzatti, A. J., MacFadyen, J. G., Nordestgaard, B. G., Shepherd, J., Willerson, J. T., & Glynn, R. J. (2008c). Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. New England Journal of Medicine, 359(21), 2195–2207. https://doi.org/10.1056/nejmoa0807646
10. Ridker, P. M., & Cook, N. R. (2013). Statins: new American guidelines for prevention of cardiovascular disease. The Lancet, 382(9907), 1762–1765. https://doi.org/10.1016/s0140-6736(13)62388-0
11. Eun, M., Jung, J., Choi, K., & Seo, W. (2020). Statin Effects in Atrial Fibrillation-Related Stroke: A Systematic Review and Meta-Analysis. Frontiers in Neurology, 11. https://doi.org/10.3389/fneur.2020.589684
12. Pastori, D., Baratta, F., Di Rocco, A., Farcomeni, A., Del Ben, M., Angelico, F., Violi, F., Pignatelli, P., & Lip, G. Y. (2021). Statin use and mortality in atrial fibrillation: A systematic review and meta-analysis of 100,287 patients. Pharmacological Research, 165, 105418. https://doi.org/10.1016/j.phrs.2021.105418
13. Ridker, P. M., Danielson, E., Fonseca, F. A., Genest, J., Gotto, A. M., Kastelein, J. J., Koenig, W., Libby, P., Lorenzatti, A. J., MacFadyen, J. G., Nordestgaard, B. G., Shepherd, J., Willerson, J. T., & Glynn, R. J. (2008b). Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. New England Journal of Medicine, 359(21), 2195–2207. https://doi.org/10.1056/nejmoa0807646
14. Amarenco, P., Bogousslavsky, J., Callahan, A., Goldstein, L. B., Hennerici, M., Rudolph, A. E., Sillesen, H., Simunovic, L., Szarek, M., Welch, K. M. A., & Zivin, J. A. (2006b). High-Dose Atorvastatin after Stroke or Transient Ischemic Attack. New England Journal of Medicine, 355(6), 549–559. https://doi.org/10.1056/nejmoa061894
15. Amarenco, P., Bogousslavsky, J., Callahan, A., Goldstein, L. B., Hennerici, M., Rudolph, A. E., Sillesen, H., Simunovic, L., Szarek, M., Welch, K. M. A., & Zivin, J. A. (2006). High-Dose Atorvastatin after Stroke or Transient Ischemic Attack. New England Journal of Medicine, 355(6), 549–559. https://doi.org/10.1056/nejmoa061894
16. Ridker, P. M., Danielson, E., Fonseca, F. A., Genest, J., Gotto, A. M., Kastelein, J. J., Koenig, W., Libby, P., Lorenzatti, A. J., MacFadyen, J. G., Nordestgaard, B. G., Shepherd, J., Willerson, J. T., & Glynn, R. J. (2008). Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. New England Journal of Medicine, 359(21), 2195–2207. https://doi.org/10.1056/nejmoa0807646
17. Féasson, S. (2002). MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebocontrolled trial. The Lancet, 360(9326), 7–22. https://doi.org/10.1016/s0140-6736(02)09327-3

18. Shweikialrefaee, B., Ko, D. T., Fang, J., Pang, A., Austin, P. C., Dorian, P., Singh, S. M., Jackevicius, C. A., Tu, K., Lee, D. S., & Abdel-Qadir, H. (2023). Statin use and stroke rate in older adults with atrial fibrillation: A Population-Based Cohort study. Journal of the American Heart Association, 12(12). https://doi.org/10.1161/jaha.122.028381