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The Efficacy of Statin on Coronary Artery Calcification based on Agatston Score: An Updated Meta-analysis of Randomized Control Trials

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Abstract: The purpose of this study is to assess the efficacy of statin treatment on coronary artery calcifcation (CAC) in patients with asymptomatic coronary artery disease (CAD). For randomized controlled trials (RCTs) that assess the efficacy of statin treatment on CAC in patients with asymptomatic CAD, we searched in PubMed, ScienceDirect, and Cochrane. The included publications were subjected to meta-analyses using Review Manager v5.4. In comparison to control, patients with statistically significant had a lower Agatston score (MD -46.25; 95% CI -56.37 - -36.12; p < 0.00001) and had lower CAC volume (MD -24.36; 95% CI -38.21 - -10.51; p = 0.0006). Statin treatment was also linked to a decreased risk of atherosclerotic cardiovascular disease (ASCVD) events (OR 0.60, 95% CI 0.43-0.83; p = 0.002). According to our meta-analysis, the statin treatment was significant to lowering the Agatston score and CAC volume in patients with aysmptomatic CAD. Statin was also linked to a decreased risk of ASCVD events compared to control.

Keywords: Agatston Score; Coronary Artery Calcification; Statin.

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and death in worldwide (Gof, et al., 2013; Stone, et al., 2013; Mensah, et al., 2019). Globally, the leading cause of lost disability-adjusted life years is coronary artery disease (CAD) and its risk increases with age (Vedanthan, et al., 2014; Ralapanawa, et al., 2021; Bauersachs, et al., 2019; Ferreira-Gonzales, 2014). Coronary artery calcification (CAC) is a dynamic and indicator for atherosclerosis in coronary artery, intricate biological process associated with aging (Pescatore, et al.,2019; Garcia, et al., 2005; Zhu, et al., 2012). Computable tomography (CT) CAC score is recommended for risk assessments at the primary preventive level due to recent research demonstrating that CAC is a predictor of CVD and significant adverse cardiac events (Hofmann, et al., 2016; Grandhi, et al., 2020; Adelhoefer, et al., 2020).

When deciding whether to start statins for people at intermediate risk, the 2018 American Heart Association/American College of Cardiology (AHA/ACC) Dyslipidemia Management Guidelines advise using CAC scoring selectively (Grundy, et al., 2018). In addition to established atherosclerotic risk factors, CAC is now used as an independent diagnostic marker for the diagnosis of CAD. The Agatston score technique is most frequently used to quantify CAC (Arad, et al., 2005; Agatston, et al., 1990). For risk stratification in asymptomatic individuals, CAC measurement is widely utilized. In asymptomatic patients, the lack of CAC is linked to low incidence of cardiovascular events including myocardial infarction, cardiovascular mortality, or unstable angina pectoris (Kronmal, et al., 2007). Results from the assessment of

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CAC as an independent parameter for the identification of obstructive CAD have been mixed. However, based on non-calcified plaque lesions, the lack of coronary artery calcium does not consistently rule out CAD (Knuuti, et al., 2020; Vilines, et al., 2011).

The gold standard for cardiovascular risk assessment is still the Agatston scoring system of CAC, which has been endorsed by several important guidelines and is recommended for use in risk stratification for statin medication based on extensive cohort data. Consequently, because of its well-established cardiovascular preventive effects, CAC has become one of the criteria for beginning statin medication. HMG-CoA reductase inhibitors, or statins, are thought to be the most effective family of medications for lowering low-density lipoprotein cholesterol (Greenland, et al., 2018; Mortensen, et al., 2018). Nonetheless, new research on the pharmacological principles of statins has indicated that there may be a paradoxical impact as they may hasten vascular calcification (Ferencik, et al., 2015). It is unknown how stains affect the CAC score in individuals with asymptomatic CAD, even though they may promote calcification in mechanistic and imaging investigations. This study aims to evaluate the impact of statin therapy on CAC in CAD patients.

Method

The current review and analysis refer to statements in the instruction of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Figure 1). We reviewed the whole body of literature to incorporate all pertinent research up to January 2024. We looked through Cochrane, ScienceDirect, and PubMed databases. Studies that satisfied the following requirements were included: [1] The study examined the effects of statin on coronary artery calcification in patients with asymptomatic CAD; [2] it was a randomized control trial (RCT); and [3] it was published in a peer-reviewed publication.

Following the elimination of duplicate entries, the initial search records were evaluated independently by SHW and KAAPP using the title and abstract as criteria. If the study do not meet the inclusion criteria of our study, the study can be excluded. A comprehensive text analysis was then carried out. The subsequent criteria for research inclusion were employed: The research was conducted as a randomized control trial (RCT), evaluated the effects of stain on coronary artery calcification in patients with asymptomatic CAD, and was published in a peer-reviewed publication. All parties involved, including the other author (YP), were satisfied with the resolution of disagreements.

The outcome is Agatston score, CAC volume, and atherosclerotic cardiovascular disease (ASCVD) events. SHW and KAAPP were responsible for retrieving the baseline parameters of all included research. SHW and KAAPP then carried out a thorough quality evaluation of the included research using the risk of bias assessment for RCT studies developed by the Cochrane Collaboration. Any differences of opinion were settled by consensus, considering the opinions of the other author (YP).

Mean Differences (MD) and Odds ratio (OR) and 95% confidence interval (CI) were calculated using the Mantel-Haenszel random-effects models. To measure statistical heterogeneity between groups, the Higgins I^2 statistic was utilized. An I^2 value of 0 suggested a lack of heterogeneity, but an I^2 value more than 50% denoted significant heterogeneity. In this work, we employed Egger's test funnel plot to estimate the likelihood of publication bias. Review Manager 5.4.1 was used for all analysis. To define statistical significance, a two-sided p value of less than 0.05 was employed**.**

Result and Discussion

The initial search strategy turned up 178 studies. Following a comprehensive text inspection of 10 potentially relevant papers, six publications were included in the systematic review and meta-analysis (Figure 1). Table 1 displays the baseline characteristics of the included studies. Each study was a randomized controlled trial that satisfied the requirements to be included in the systematic review and meta-analysis. The four studies had 2026 participants in total; 980 of them received statin treatment and 1046 with control or placebo.

Table 1. Baseline characteristics of included studies

Author	Design	Statin Type	Dossage of Statin	Sample Size		Mean Follow Up Time (months)
				Statin	Control	
Arad 2005	RCT	Atorvastatin	20 mg	417	431	24
Miyoshi 2018	RCT	Pitavastatin	4 mg	46	55	12
Schmermund 2006	RCT	Atorvastatin	80 mg	175	191	12
Terry 2007	RCT	Simvastatin	80 mg	40	40	12
Houslay 2006	RCT	Atorvastatin	80 mg	39	49	24

Mulders 2012	RCT	Atorvastatin	20 mg	263	280	48

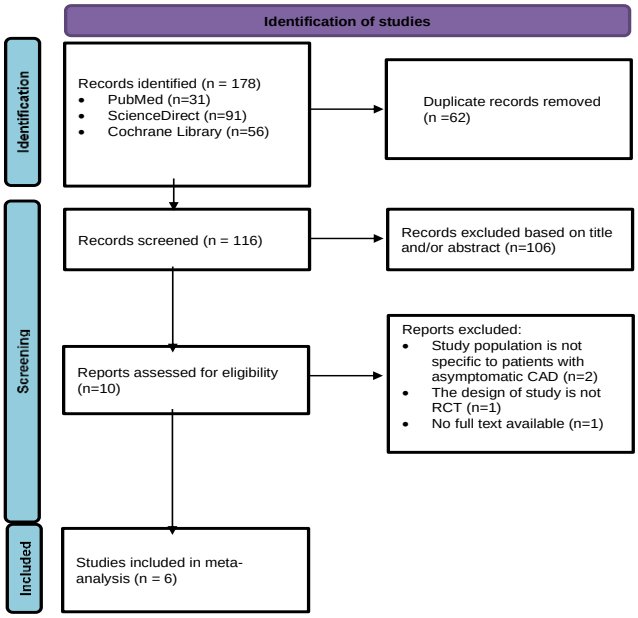

Figure 1. Figure 1. PRISMA flow chart.

The quality and bias risk were evaluated in four of the included publications using the Cochrane Collaboration's risk of bias assessment for RCT trials (Figure 2). No RCT study has a material risk of bias. It is evident from the funnel plots in Figures 3, 4, and 5 that it is impossible to overlook the publication bias of the included papers.

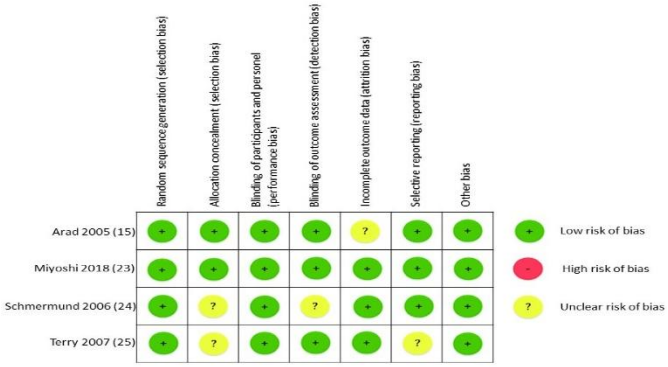

Figure 2. Risk of bias assessment for RCT studies

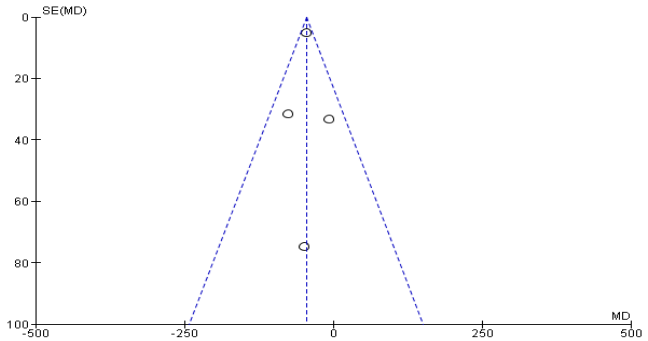

Figure 3. The funnel plot of the agatston score

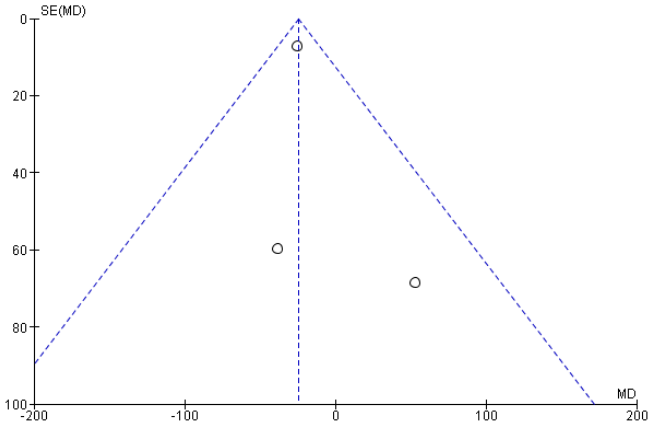

Figure 4. The funnel plot of the CAC volume

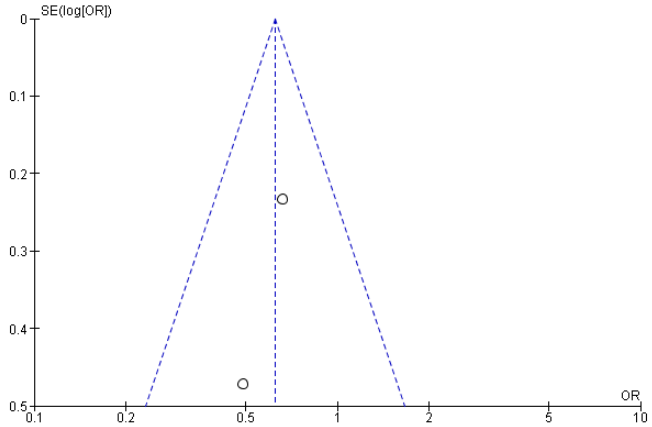

Figure 5. The funnel plot of the ASCVD events

A fixed effect model's results (Figure 6) showed that patients with statistically significant had lower Agatston score compared to control (MD -46.25; 95% CI -56.37 - -36.12; $p < 0.00001$; $I^2=0\%$). A fixed effect model's results (Figure 7) showed that patients with statin treatment was statistically significant had lower CAC volume compared to control (MD -24.36; 95% CI -38.21 - -10.51; $p = 0.0006$; $I^2=0\%$). A fixed effect model's results (Figure 8) showed that patients with statin treatment were statistically significant to a decreased risk of ASCVD events when compared to control (OR 0.60, 95% CI 0.43-0.83; $p = 0.002$; $I^2=0\%$).

Four RCT studies were included that could provide an estimate of the efficacy of statin treatment on CAC score in patients with asymptomatic CAD. In this meta-analysis, we demonstrated that statins were significant to lowering the Agatston score and CAC volume in patients with aysmptomatic CAD. Statin was also linked to a decreased risk of ASCVD events compared to control.

Since its publication by Agatston et al. in the 1990s, the Agatston score has grown to be the most widely

accepted technique for estimating CAC as determined by different CT scanners (Mahabadi, et al., 2015; Ahmed, et al., 2015). It meets the demands of clinical practice since it considers both calcium volume and density and just needs a basic calculation. The interscan repeatability of the Agatston score has been questioned despite its widespread use. Higher heart rates, motion artifacts, equipment from various suppliers, and software platforms might all affect the score (Malguria, et al., 2018).

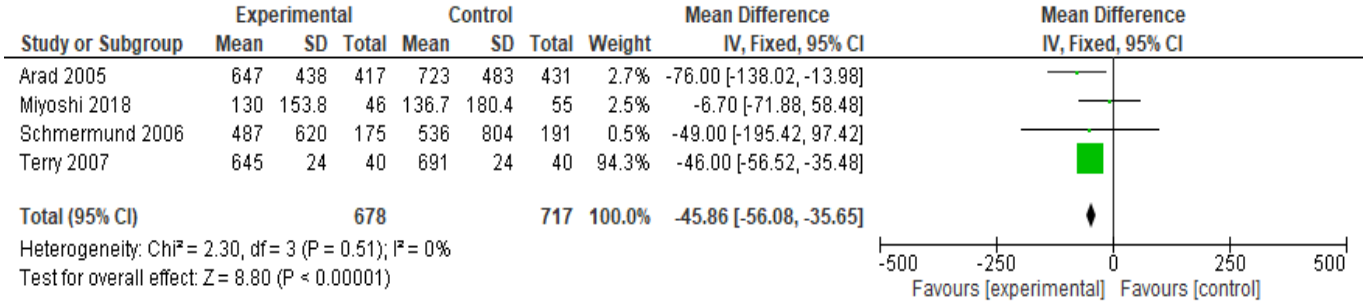

Figure 6. The forest plot of the agatston score

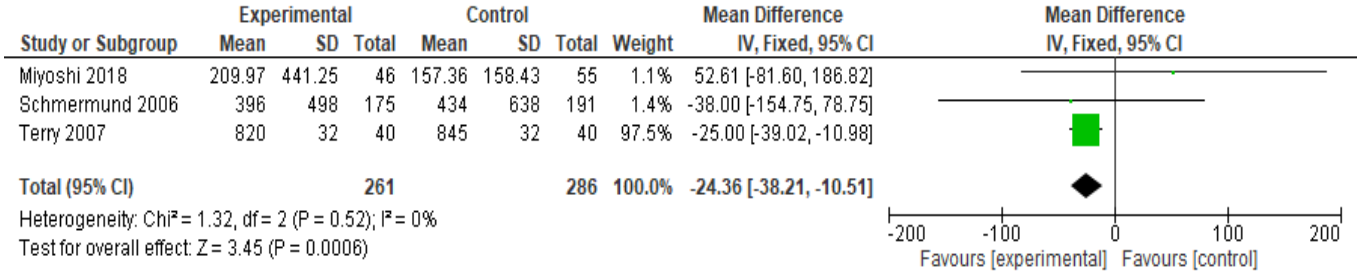

Figure 7. The forest plot of the CAC volume

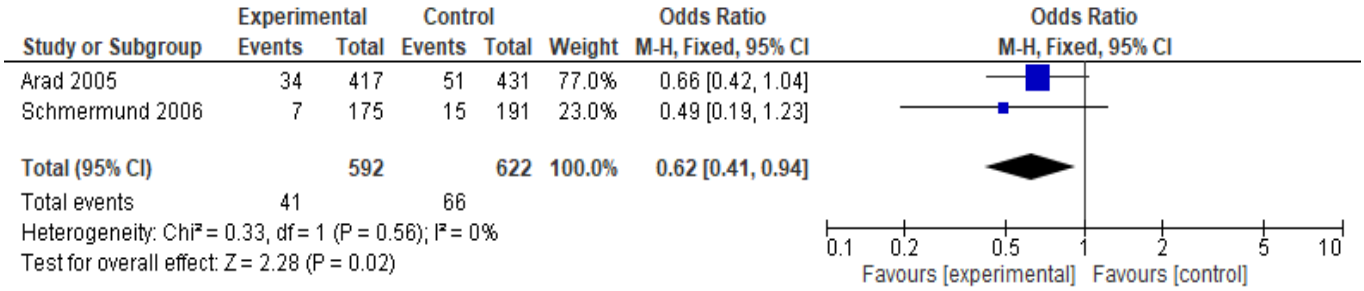

Figure 8. The forest plot of the ASCVD events

The development and healing stages of inflammation are tightly linked to calcium during atherosclerosis (Shioi, et al., 2018), and previous studies have shown that the effect of statins on reducing inflammation was more pronounced within advanced coronary lesions as measured using computed tomographic imaging. One possible explanation for the decreased Agatston score and CAC volume observed with statin medication may be the brief follow-up durations of the included trials. It may take longer for calcium to advance in asymptomatic people with lesser atherosclerosis than in those with established CAD (Singh, et al., 2016).

A large-scale cohort investigation conducted by Mitchell et al. previously demonstrated the existence of a threshold of the CAC score, which they assessed to be 100, over which asymptomatic individuals would benefit more from statin medication (Mitchell, et al., 2018). Based on baseline characteristics of four included RCT trials, we determined that the cutoff value in our instance was more than 100. There may be a murky and contradictory link between the advancement of CAC when on statin medication and the consequence for the cardiovascular system. According to some, the progression of calcification is a sign that micro-fractured calcium is becoming macro-sheet calcium, which stabilizes plaques (Mori, et al., 2018). Other studies showed that patients receiving statins and other lipid-lowering agents showed greater CAC progression in those who experienced subsequent cardiovascular events (Raggi, et al., 2003). There are two types of statin therapy: low and moderate intensity statin therapy

(LIST) and high intensity or high-intensity statin therapy (HIST). According to research by Puri et al., individuals with HIST also showed considerable plaque regression and the largest rise in calcium. The study looked at the relationship between statin treatment and serial CAC readings. In contrast, despite considerable atheroma growth, individuals who had never used statins (statin-naive) demonstrated the least amount of plaque calcification over time. The patients with LIST had a twofold rise in calcium compared to the participants without stains, even though both groups of patients exhibited equal plaque development. These results are consistent with statins having a potential procalcification impact in addition to their potential effect on atheroma volume stabilization of plaque.

The difference in the rate of calcification of HIST compared with LIST, was studied by Vogel and colleagues, and published in 2023. There was no significant difference found between patients with HIST and those with LIST in the rate of Agatston scores in a year, both experienced an increase in the rate of Agatston scores in a year which was not significantly different, namely 53.4 + 163.8 in the LIST group and 58.2 + 180.2 with p 0.68. The study also demonstrated the effect of reducing LDL levels which was also not significant on increasing the Agatston score within a year (p 0.063). Additionally, compared to controls, our meta-analysis indicated that statin use was associated with a lower risk of ASCVD events. While CAC volume was positively and independently related to cardiovascular risks, prior study from the Multi-Ethnic Study of Atherosclerosis shown that CAC density was significantly negatively associated with cardiovascular risks (Criqui, et al., 2014). A more recent investigation discovered that, even when time-varying statin usage was taken into consideration, CAC > 0 compared with CAC = 0 was linked to a considerably increased risk of atherosclerotic cardiovascular disease events. This association held true independent of baseline or incident statin use (Rifai, et al., 2020). Given different backgrounds, CAC development at an early stage of atherosclerosis may indicate both the need for more intense primary preventive therapy and the potential of plaques to become more calcific and stable over time despite statin therapy. There has to be more research done on the processes and risk factors behind the various cardiovascular outcomes that calcification progressors experience (Houslay, et al., 2006; and Mulders, et al., 2012).

The first limitation of our analysis is the small number of included studies due to the RCT study design, which may have reduced the generalizability of our conclusions to a wider population. As a result, caution should be exercised when interpreting our results. Second, it hopes that future RCT research or meta-analyses will employ more diverse CAC score cut-offs. Currently, it only employs four RCT studies with a baseline CAC score of greater than 100. Third, the type and intensity of statin used in each included study, which may influence the study results.

Conclusion

Our findings showed that the statin treatment significantly to lower the Agatston score and CAC volume in patients with aysmptomatic CAD. Statin was also linked to a decreased risk of ASCVD events compared to control. Our results highlight the need for more research, especially RCT studies or RCT-based systematic reviews and meta-analyses.

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Author Contributions
Conceptualization, S.H.W and Y.P; methodology, S.H.W and Y.P.; software, K.A.A.P.P.; validation, S.H.W and Y.P.; formal analysis, S.H.W , Y.P, and K.A.A.P.P; investigation, S.H.W and Y.P.; resources, S.H.W and Y.P.; data curation, S.H.W and Y.P.; writing—original draft preparation, S.H.W and Y.P.; writing—review and editing, S.H.W and Y.P.; visualization, S.H.W and Y.P; supervision, S.H.W and Y.P.All authors have read and agreed to the published version of the manuscript."

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Conflicts of Interest
The authors declare no conflict of interest

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