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The Efficacy of Atorvastatin and Rosuvastatin on the Changes of alpha and beta Apolipoproteins; A Systematic Review and Meta-Analysis

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ABSTRACT

Background & Objective: Vascular stenosis is one of the causes of cardiovascular diseases (CVDs). Implementing appropriate therapeutic measures for CVDs requires preventing the progression of stenosis. The purpose of this study was to evaluate the efficacy of atorvastatin and rosuvastatin on the levels of alpha and beta apolipoproteins using systematic review and meta-analysis.

Materials & Methods: This review was performed based on the PRISMA protocol. The ISI, Cochrane Library, Google Scholar, PubMed, and Scopus databases were independently searched by two researchers. MeSH keywords were used to recruit related articles published between 2005 and 2018. Meta-analysis was conducted in STATA 11.1software.

Results: A total of 65 articles were found. Out of these, nine studies were ultimately included in meta-analysis. The findings showed that alpha lipoprotein level increased by 4.24 mg/dl (95% CI: -0.03; -8.45) and 8.71 mg/dl (95% CI: -1.95; -15.48) in patients treated with atorvastatin and rosuvastatin, respectively. Also, patients treated with either atorvastatin or rosuvastatin showed 40.55mg/dl (95% CI: 32.16; 45.93) and 44.78 g/dl (95% CI: 34.16; 55.39) decreases in beta-lipoprotein levels, respectively.

Conclusion: According to the results, rosuvastatin is more effective than atorvastatin in reducing alpha apolipoprotein and increasing beta apolipoprotein levels within a short period of time.

Keywords: Atorvastatin, Rosuvastatin, Alphaapolipoprotein, Beta apolipoprotein, Systematic review, Meta-analysis

Introduction

Cardiovascular diseases (CVDs) are rising in today's societies due to changes in lifestyle (1). Coronary artery stenosis is a type of vascular diseases that develops during childhood, and if it is left treated, the symptoms may progress and manifest during adult hood or elderly (2). This disease has been estimated to be the most common cause of death worldwide by 2020 (3). The most common risk factor of this condition is the dysregulation of serum lipids, particularly, low-density cholesterol as the most important contributor (4). Despite the role of lipid dysregulation in the pathogenesis of coronary artery diseases, most patients with myocardial infarction have no history of elevated blood lipids and may even present with lower-than-normal levels of blood cholesterol (5, 6).

Fat deposition in arteries is a substantial risk factor for atherosclerosis .Knowing the risk factors of atherosclerosis can help prevent and treat the disease. Dysregulated alpha and beta apolipoproteins have been mentioned as novel risk factors of atherosclerosis (7, 8). Biochemically, high-density alphalipoprotein contains anti-atherogeniccholesterol, while beta-apolipoprotein roles as a potential atherogenic factor (9, 10).

Alpha and beta apolipoproteins are the building blocks of high- and low-density cholesterols, respectively, activating enzymes participating in the metabolization of α- and β-lipoproteins (7, 8). These two apolipoproteins also provide a bridge for lipoproteins to attach to cell membrane receptors (9, 10).

The ratio of beta- to alpha-apolipoprotein is a predictor of the risk of coronary artery disease (11). The results of a study on a group of men showed that the plasma concentration of atherogenic beta-lipoprotein was a better predictor of coronary artery disease than cholesterol transported by lipoproteins (12). In a study by Sabino *et al*. on young adults, after adjusting the effects of variables such as age, sex, smoking, hypertension, and lipid disorders, apo-lipoprotein betalevelsandthe ratio of beta- to alpha-apolipoprotein were identified as independent predictors for cerebral stroke and peripheral vascular disease (13).

The study of Ray *et al*. on patients with acute coronary syndrome treated with statin revealed that the ratio of beta- to alpha-apolipoprotein provided a prognostic value equivalent to the ratio of triglyceride to high-density cholesterol (14). In a study by SwitNam *et al.*, a strong correlation was observed between beta-apolipoprotein levels and the incidence of ischemic heart disease; however, this relationship disappeared after adjustment for cofounding variables. There was also a strong association between reduced levels of alpha apolipoprotein and the incidence of ischemic heart disease; nonetheless, this relationship was also shadowed atelevated levels of high-density cholesterol (15).

The goal of meta-analysis is to provide a comprehensive and consistent view on a specific subject (16, 17). However, no such analyses have been conducted yet on the efficacy of atorvastatin and rosuvastatin inbalancing the levels of alpha and beta apolipoproteins. Considering the publication of several papers in this field, this meta-analysis was conducted to provide precise and credible evidence for authorities and researchers regarding the lipid-lowering effects of atorvastatin and rosuvastatin.

Materials and Methods

This systematic review/meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. The five steps of the study included nurturing the concept/design, literature search, collecting and reviewing articles, qualifying articles, and, finally, meta-analysis. In order to prevent publication bias, the literature search was independently conducted by two of the authors, and the results were combined by a third researcher.

Search strategy

In order to obtain studies related to the research question, two researchers independently searched the national and international scientific databases (Magiran, Iran Medex, Scopus, PubMed, Cochrane library, and Web of Science), as well as the Google scholar search engine. Regarding the research question, the MeSH keywords of atorvastatin, rosuvastatin, alpha and beta lipoproteins, and efficiency were used to conduct the search. These keywords were initially searched individually, and then Boolean operators ("AND", "OR") were applied for creating possible keywords combinations to perform a comprehensive search. Finally, in order to find relevant articles, all references of the articles found were further explored. In the case of being relevant and non-duplicate, the full-texts of the articles were studied.

Inclusion criteria

Original articles investigating the efficacy of atorvastatin and rosuvastatin in alerting the levels of alpha and beta lipoproteins were included.

Exclusion criteria

Studies within adequate quality, irrelevant studies, and those with incomplete data were excluded. Furthermore, reviews, case reports, letters to editors, qualitative studies, abstracts of congress papers were also omitted. Finally, studies that assessed the efficacy of either drug alone were excluded.

Selection and quality assessment

The STROBE checklist (18, 19) was used to evaluate the quality of the articles. A score between 0 and 2 was independently assigned to each item of the checklist by two authors. Based on the scores obtained, the articles were divided into three quality groups: poor, moderate, and good (respective scores of 1-15, 16-30, and 31-44).Articles that acquired at least 16 scores entered meta-analysis.

Measurement tools

The studies used a numeric measure for evaluating the efficiency of atorvastatin and rosuvastatin in regulating alpha and beta apolipoproteins within a period ranging from six to 12 weeks (Table 1).

Table 1. The characteristics of the articles assessing the levels of alpha and beta lipoproteins before and after treatment with atorvastatin and rosuvastatin

Reference No.	First author	Year of publication	Location	N of total participants	Follow-up duration
19	Anton	2005	Finland	322	6 week
20	Keith	2005	Africa	774	6 week
21	Park	2010	South Korea	300	6 week
22	Hia-yan	2009	China	99	12 week
23	Abate	2008	USA	392	6 week

Reference No.	First author	Year of publication	Location	N of total participants	Follow-up duration
24	Furuyama	2018	Japan	57	12 week
25	Lablanche	2010	France	887	12 week
26	Otokozawa	2009	USA	27	6 week
27	Vavlukis	2016	Macedonia	250	12 week

Data extraction

The first author's and journal's names, the time and place of the research conduction, sample size, the effects of atorvastatin and rosuvastatin on the changes of alpha and beta apolipoproteins, and the ratio of beta to alpha lipoprotein were extracted from studies. The comparisons were made based on different geographical locations and during sixto12 weeks of follow-up. The information extracted from the final articles was entered into a researcher-prepared checklist.

Statistical analysis

As the number of the final studies was fewer than 10 (n=9), and based on the nature of the data to be pooled, there was no need to assess publication bias by drawing a funnel plot. The I square (I^2) index was used to calculate heterogeneity among the studies for individual variables (i.e., the changes of alpha and beta apolipoproteins before and after treatment with atorvastatin and rosuvastatin and the ratio of beta to alpha apolipoprotein).Considering the significant heterogeneity among the studies (P <0.001), the random effects model was used to combine the results of different studies. The data were analyzed using STATA software version 11.

Results

In this systematic review, 65 articles were initially identified. After reviewing the articles' titles, the abstracts of 30 articles were read, whose specifications were recorded into a checklist. After final evaluation, nine papers were selected, and their full-text swerere viewed by the researchers (Figure 1b, c).

The final studies had been conducted between 2005 and 2018. The total sample size was 3351, giving an average of 372 subjects per study. Regarding the geographical distribution of the studies, three (33.33%) were from Asia (South Korea, Japan, and China); three (33.33%) were from Europe (the Netherlands, France, and Macedonia), and three (33.33%) were from the United States. The characteristics of the articles included in meta-analysis have been summarized in Table 1. The heterogeneity among the studies was 95.2%, indicating a high heterogeneity (I^2 = 95.2, p <0.001). This high I^2indexindicates that the results of these studies significantly differed from each other (18).

All studies reported the changes of alpha and beta apolipoproteins as mg/dl. Considering the high heterogeneity among the studies (I^2 index= 95.2%), the total confidence interval and the confidence interval of individual studies were calculated based on the random effects model (Figure 1a). Also, the changes of alpha apolipoprotein before and after treatment with atorvastatin and rosuvastatin have been shown in Figure 1b. Figures 2a and 2bshow the efficacy of atorvastatin and rosuvastatin in regulating the level of beta apolipoprotein.

Table 2 shows the fluctuations of alpha and beta apolipoproteins after treatment with atorvastatin and rosuvastatin in terms of SMD and WMD, as well as the ratio of beta to alpha apolipoprotein before and after sixand 12 weeks of treatment with these drugs.

The meta-regression analysis of alpha and beta apolipoproteins levels before and after treatment with atorvastatin and rosuvastatin based on the year of study conduction and sample size have been shown in Figure 3.

Table 2. The effects of atorvastatin and rosuvastatin on the changes of alpha and beta apolipoproteins in terms of SMD and WMD and the ratio of beta to alpha apolipoprotein

SMD	Article(n)	Mg/dl	CI/95	I^2	P Value
Mean changein Apo lipoprotein Alpha (Atorvastatin)	7	-0.16	-0.31-0.00	88	0.000
Mean changein Apo lipoprotein Alpha (Rosuvastatin)	6	-0.34	-0.61,-0.09	94.9	0.000
Mean changein Apo lipoprotein Beta (Atorvastatin)	9	2.23	1.73-2.74	98.5	0.000
Mean changein Apo lipoprotein Beta (Rosuvastatin)	9	2.35	1.83-2.86	98.5	0.000
WMD	Article(n)	Mg/dl	CI/95	I^2	P Value

SMD	Article(n)	Mg/dl	CI/95	I^2	P Value
Mean changein Apo lipoprotein Alpha (Atorvastatin)	7	-4.24	-8.45, -0.03	90.6	0.000
Mean changein Apo lipoprotein Alpha (Rosuvastatin)	6	-8.71	-15.48, -1.95	96.2	0.000
Mean changein Apo lipoprotein Beta (Atorvastatin)	9	40.55	32.16-48.93	98.3	0.000
Mean changein Apo lipoprotein Beta (Rosuvastatin)	9	44.78	34.16-55.39	98.9	0.000
The ratio of beta to alpha lipoprotein	Study	ratio	95% CI	I^2	P value
Before atorvastatin treatment	3	1.07	0.78-1.36	0	0.948
After atorvastatin treatment	3	40.83	17.94-63.72	0	0.584
Before rosuvastatin treatment	3	1.08	0.79-1.38	0	0.946
After rosuvastatin treatment	3	43.90	19.86-67.95	0	0.742

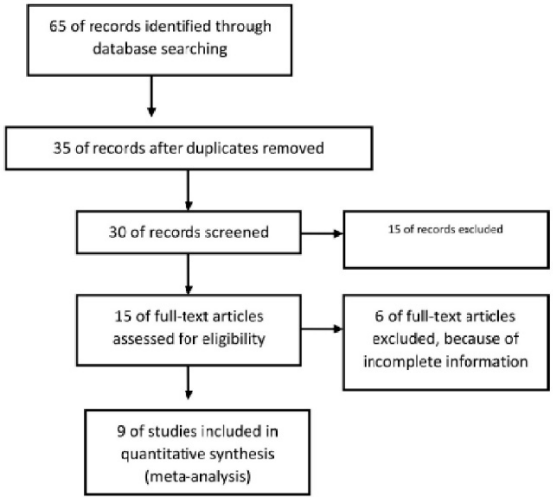

Figure 1a. Flowchart of the present systematic review and meta-analysis

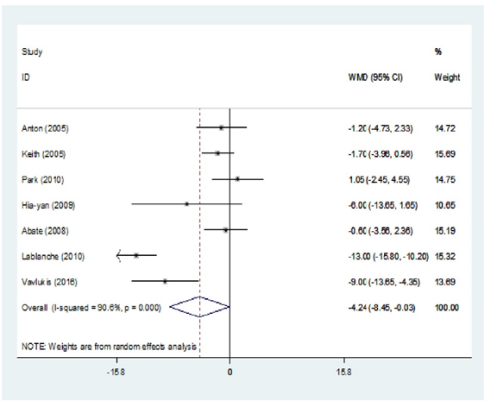

Figure 1b. The forest plot of the effects of atorvastatinon alpha apolipoprotein changes with 95% confidence interval

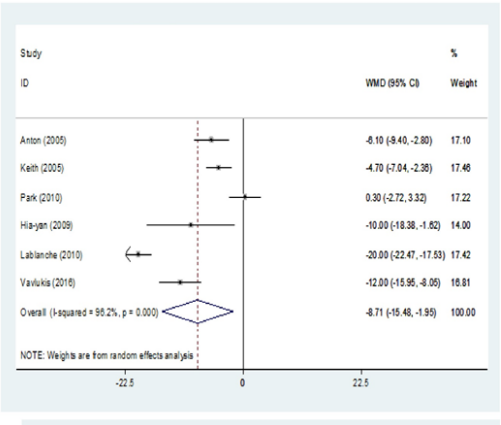

Figure 1c. The forest plot of the effects of rosuvastatin on alpha apolipoprotein changes with 95% confidence interval

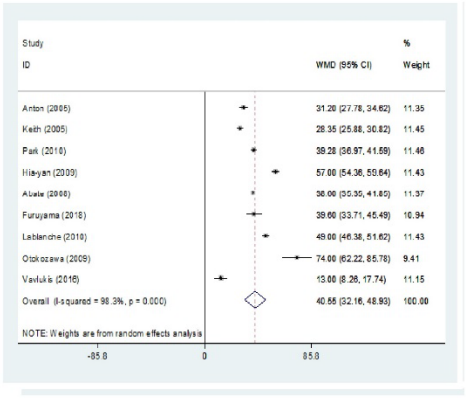

Figure 2a. The forest plot of the effects of atorvastatin on the changes of beta apolipoprotein with 95% confidence interval

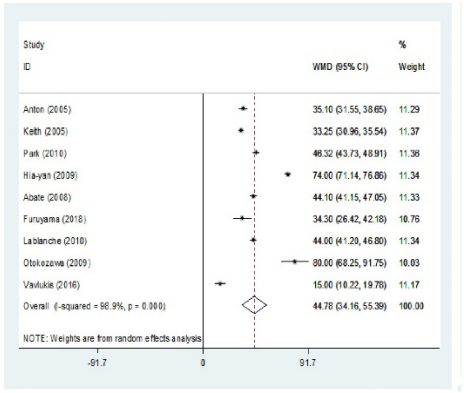

Figure 2b. The forest plot of the effects of rosuvastatin on the changes of beta apolipoprotein with 95% confidence interval

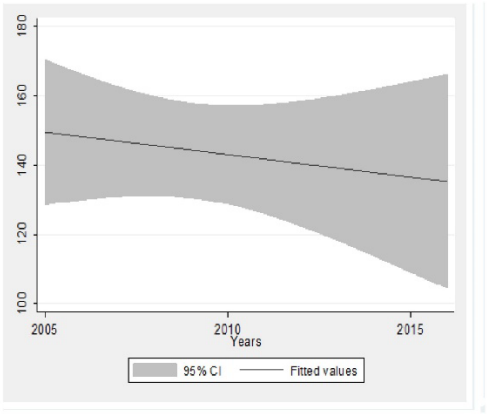

Figure 3a. Meta-regression of studiesbased on the year of publication. With an increase in the year of publication, atorvastatin and rosuvastatin decreased the levels of alpha and beta apolipoproteins.

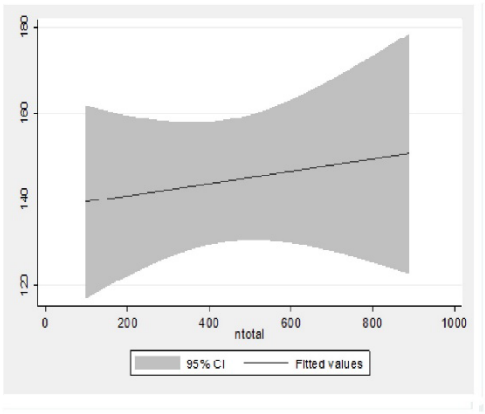

Figure3b. Meta-regression of studies based on the sample size. With an increase in the sample size, atorvastatin and rosuvastatin boosted the levels of alpha and beta apolipoproteins.

Discussion

Drugs from the statin family are among the most common medications used to reduce blood lipids **(28, 29)**. The doses of these drugs are determined according to patients'clinical conditions. This was the first systematic review and meta-analysis comparing the efficacy of atorvastatin and rosuvastatin in regulating alpha and beta apolipoproteins levels.

The results of this study showed that the level of alpha lipoprotein increased by 4.24and 7.71 mg/dlin the patients who received at or vastatin and rosuvastatin, respectively. Other studies have reported that rosuvastatin increased alphalipoprotein to a greater extent than atorvastatin. This effect canreduce the risk of coronary artery disease, preventing stenosis and alleviating the clinical symptoms of the disease **(30, 31)**.

In patients treated with either atorvastatin or rosuvastatin, the levels of beta apolipoproteins decreased by 40.55 and 44.78 mg/dl, respectively. This was consistent with the results of Tsimikas *et al*. **(32)**. This is an important finding as reduced levels of beta apolipoproteins lower the risk of coronary artery stenosis.

Based on our review, the ratio of beta to alpha apolipoproteins elevated from 1.07 to 40.83 in the patients treated with atorvastatin and from 1.08 to 43.90 in the individuals administrated with rosuvastatin, indicating the better effectiveness of rosuvastatin. Similar findings have also been observed in other studies **(19, 20, 25)**. It is notable that higher ratios of beta to alpha lipoproteins have been associated with a lower risk of vascular stenosis.

At 6-and 12-weekfollow-up periods, the level of alpha apolipoprotein increased by3.42 and 12.2 mg/dl in patients treated with atorvastatin and by6.25 and 14.3 mg/dl in patients treated with rosuvastatin, and the level of beta lipoprotein decreased by36.27 and 43.21 mg/dl in those receiving rosuvastatinandby42.44 and

56.79 mg/dl in individuals treated with rosuvastatin, respectively. Regarding these findings and the results of other studies **(33, 34)**, a longer course of treatment with these drugs seems to be accompanied by greater improvements in the levels of alpha and beta apolipoproteins. Furthermore, rosuvastatin was more effective than atorvastatin in regulating the changes of apolipoproteins during a shorter period of time.

Conclusion

According to our results, rosuvastatin acted better and faster than atorvastatinin regulating the levels of apolipoproteins.

Limitations

Most of the participants had been selected non-randomly, leading to the exclusion of people with elevated blood lipids. Assessing a small numberofvariables during different treatment periods (i.e., days, weeks, and months) and using variable drug dosages were among other limitations of the studies included. Also, some studies did not compare variables between males and females or between different age groups, and some others reported only the overall changes of apolipoproteins with no sub-group analysis based on different age groups and risk factors.

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Conflict of Interest

Authors declare no conflict of interest.

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