Original Article

Efficacy and safety of statin treatment for cardiovascular disease

Zhang XiaoYan[1], Guan Qingmin[2], Liu Yantao[3], Wang Zhijuan[4], Xu Meihua[1*]

Abstract

Background: Cardiovascular disease is the primary cause of human mortality every year in several countries worldwide. It is a significant concern from a public health perspective as well. There are several therapies available in the market to treat cardiovascular diseases. Statins are considered the best therapy among the other drugs due to their multifunctional effects, such as antioxidant and anti-inflammation.

Objective: Statins are the best HMG-CoA reductase inhibitor to date, after considering the several trial reports like PROVE-IT, MEGA, LIPID CARE, ALLHAT-LLT, PROSPER to demonstrate the statin effectivity.

Methods: The different databases were studied for a comparison of statin treatment group versus control trial group. Multivariate regression analysis and other meta-analyses were performed. Statin efficacy with the other drugs and some studies were done to compare the effectiveness within different statin groups.

Results and Discussions: The findings showed a 10% mortality reduction among patients in the statin groups (Risk Ratio 0.89: 95% CI, 0.87–0.95, I^2 value 16%, P value ≤ 0.0001,). About 1.1% mortality reduction occurred with the 10% low density lipoprotein change, (P value 0.003, 95% CI,0.29–1.18), a 20% reduction in cardiovascular mortality was documented in the statin treated patients than in the control patients (RR 0.80, 95% CI value 0.73–0.88, I^2 value 27%, P value < 0.0001). Myocardial risk reduction was about 18% (RR 0.83, P-value < 0.0001, I^2 = 21%, 95% CI 0.76–0.90). Despite minimum adverse effects, there was a significantly increased rate of diabetes in the statin group (OR 1.07, P-value=0.0008, 95% CI 1.03–1.17, I^2 value 16%).

Conclusion: It has been found that statin is very safe to use in cardiovascular disease treatment, and found effective in limiting the LDL-c levels compared to the other kind of drugs such as Benazepril, Captopril, Enalapril, Iprosartan, Losartan, Olmesarta. [*Ethiop. J. Health Dev*. 2021: 35(4):297-308]

Keywords: Statin, Cardiovascular disease, HMG-CoA reductase, Low-density Lipoprotein, efficacy, cholesterol, Randomized trial, Control trail.

Introduction

Cardiovascular diseases are a group of disorders which include the heart and blood vessels, cerebrovascular disease, rheumatic heart disease, and other several conditions. According to a WHO report, this disease is the primary cause of approximately 17.9 million deaths each year. Individuals who are at risk of cardiovascular diseases may have obesity, may be overweight, or have high lipid content. Smoking, Hypertension, and Diabetes is the major risk factors for cardiovascular disease. Several medications are used in cardiovascular treatment, like angiotensin-converting enzyme (ACE) inhibitor (Benazepril, Captopril, Enalapril), Angiotensin II receptor blocker (Iprosartan, Losartan, Olmesartan), Beta-adrenergic blocking agent (acebutolol, Atenolol), and calcium channel blocker (amlodipine, Diltiazem). Statins are known as cholesterol-lowering medications that are used for the effective treatment of coronary heart disease. Besides the cholesterol-lowering effect, statin also has several other properties like anti-inflammatory, antioxidant, anti-coagulative, and graft rejection inhibition properties. This makes statin a high demand drug since 1986 in the USA, and, Statin has evolved its efficacy since its inclusion in heart treatments. Statins are HMG-CoA inhibitors, which function by reducing the low-density lipoprotein cholesterol level, thereby reducing the risk of cardiovascular diseases. The first statin which was isolated was Lovastatin from fungi *Aspergillusterreus* [1]. Some available statins in the market are Pitavastatin (Alipza, Livalo, Zypitamag), Pravastatin (Aplactin, Selectin), Rosuvastatin (Colcardiol, Colfer), etc. among them, some statins like Fluvastatin (Lesson, Lipaxan, Primesin), Pitavastatin, are synthetic drugs and some statins like Lovastatin (Altocore, Altoprev) are naturally occurring compounds found in mushrooms [2]. In this article, the effectiveness and safety of the statin treatment is explored.

Statin's chemical nature

Statins are the competitive inhibitors of the hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA catalyzes the conversion of the HMG-CoA to mevalonate. Statin inhibits the conversion pathway, thereby reducing the formation of the hepatocyte cholesterol [3]. Statin chemical structure is divided into three major parts; the equal part of the HMG CoA, the hydrophobic ring structure, and the side group attached with the hydrophobic ring. Statins bind to the enzyme active site, which creates a steric hindrance effect for the substrate. The substrate-binding site of the enzyme becomes structurally suitable for the hydrophobic ring of the Statin. Among different types of Statins, rosuvastatin has the most interaction with the HMG-CoA [4].

[1*]Department of Pharmacy Traditional Chinese medical hospital of Huangdao District, QingDao. Department of Pharmacy, Huangdao District Hospital of traditional Chinese medicine, Qingdao City, 158 Hainan Island road, Qingdao City, Shandong Province

[2]Qingdao Huangdao District Hospital of traditional Chinese Medicine, Health Insurance Office

[3]Qingdao Center for Disease Control and Prevention

[4]Department of Pharmacy, Lingshan Health Center, Huangdao district

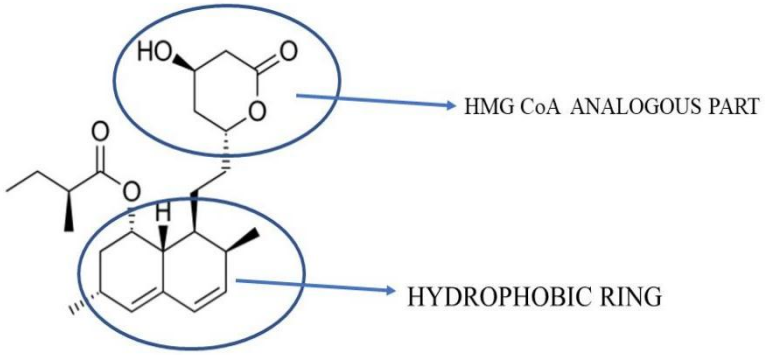

Figure 1: **Lovostatin structure**

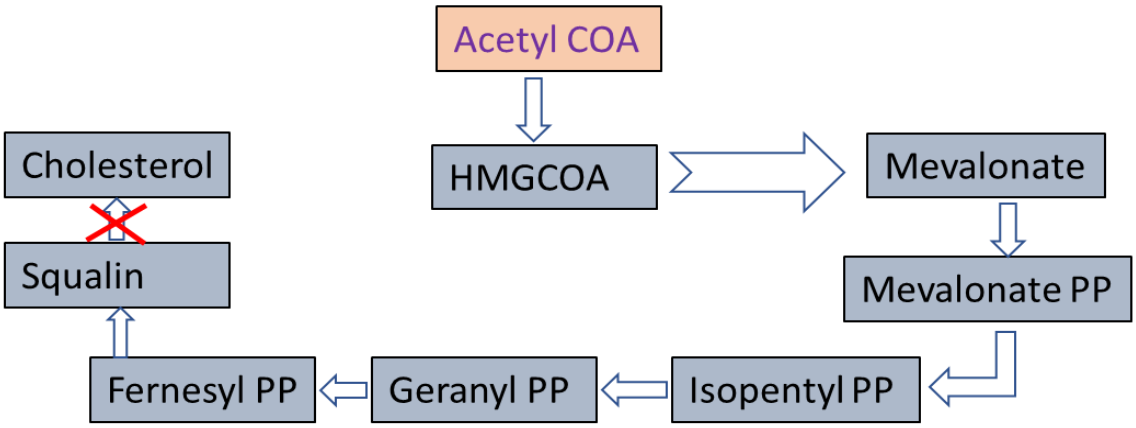

Figure 2: **Statin action in the cholesterol biosynthesis pathway (redrawn from Sadowitch et al., 2010)**

After an oral dose, Statin enters the circulatory system via intestinal cells through the active or passive transport system. In the case of the Active transport system, the ABC and SLC gene family transporter actively involves in the entry of the statin into the cell environment. The major metabolic organ is the liver, followed by the kidney. The UGT and CYP gene family catalyze the statin metabolism after the biliary excretion eliminates metabolism statin through the ABC transporter.

Material and methods

A randomized control trial has been included in this study. Fluvastatin, Pravastatin, lovastatin, atorvastatin, and simvastatin rosuvastatin used to prevent the cardiovascular disease in the patients. Cerivastatin trial was not included as this is revoked from the market because of its adverse effects. A Comparison was conducted between the placebo and statin-treated group and the no-treatment or standard treatment and cardiovascular results (mortality due to chronic vascular disease, Myocardial infarction mortality, revascularization, and stroke-like chief cardiovascular events). Report on the surrogate outcomes, reports, and follow-up studies where no randomization was done, and head-to-head statin assessments were also excluded from the study.

Search criteria

After a consult with the medical practitioners, a search criterion for our study purpose was formulated. 12 databases like Cochrane, EMBASE, Central, CINAHL, EMBO, etc. were reviewed. Additionally, different bibliographies that were published were reviewed including the Statin trial database. Therefor communication with various authors was necessary for our research.

Data collection

The information that was collected from the searched articles include, intervention type, statin data, data on the population (sex, age group, conditions of the patients), therapeutic effect on the particular outcome, change in the high-density lipoprotein, low-density lipoprotein, cholesterol, and follow-up length. Study assessment included, the generation of the sequences, intent-to-treat, analysis, al- location concealment, blinding, and follow-up percentages. Data on Cardiovascular mortality, myocardial infarction mortality, stroke, non- Cardiovascular mortality, stroke mortality, significant cardiovascular disease, revascularization, diabetes, creatinine kinase, aspartate, and alanine aminotransferase data were also extracted. Data was entered electronically, and data

was matched after each entry.

Data analysis

For the analysis of the collected data, phi statistics was used to measure the inter-observer agreement. Relative risk assessment was also performed and calculated at 95% confidence interval of the reported data for analysis. In the case of zero outcome event, the Haldane method was applied for one arm, and for the other arm of the data, 0.5 was added. For all statin combinations, the Dersimonian-Laird method of random effect was applied. Sensitivity test to determine the individual statin effect by utilizing a mixed treatment method and the Breslow–Day test to determine the baseline population risk of the statin treatment. To determine the adverse effect of the statin, Peto's odds ratio test was conducted. I^2 statistics were performed to determine the variation of the statin treatment. To assess the low-density lipoprotein impact and coronary heart disease-like covariates impact, multivariate regression analysis was conducted. Luades methods were applied for the drug effect on cardiovascular disease mortality. Markov chain Monte-Carlo method was applied for the unknown parameter's posterior densities measurement. Low-density lipoproteins change and statin dosing by Cooper's method was applied. Monte Carlo error was made for the posterior accuracy estimation. For model fitting, the deviance information criterion was performed. Also, sequential analysis was performed for the information strength determination for the meta-analysis. LD (Lan-Demets) sequential monitoring boundary estimated percentage of the control rate was 4%, and 20% was for relative risk reduction, the two-sided alpha value was 0.05. All analyses were done in the Stata (v9), R statistical software.

Results

75 trials containing the 170256 patients for the study group were included. Table 1 shows patients' characteristics. In the study group, 26.1% is female, and the average age group is 58.6. We included the age group from 39- to 76-year-old patients. As an inert control, four trials have been included. These include 52 placebo trials, 18 usual care trials, and three treatment groups, and two conventional treatments. Patients have an average follow-up rate of 2.72 years (standard deviation is 1.61), mean low density lipoprotein is 4.62 mmol/l (178.69 mg/dl), and ranged from 2.33 mmol/l (93.78 mg/dl) to 5.1 mmol/l (196 mg/dl). 25 studies show the randomization report. Nineteen articles report about the concealed group allocation. Many studies report the follow-up loss. 4 studies report the pre-protocol analysis result. 62 studies reported on the trial blinded of a specific group.

In this study, a total of 14879 patient's deaths were recorded. Cardiovascular death was 7865. Out of the 86329 patients, only 7005 patients died who received statin, and among the 80366 control group patients, there were 7716 deaths. This data presents the 10% mortality reduction in the patients (95% Confidence interval, 0.87–0.95, I^2 value 16%, P-value $\leq$ 0.0001, Risk Ratio 0.89). About 1.1% of death risk reduction happens with the 10% low-density lipoprotein change. (P-value 0.003, 95% CI, 0.29–1.18). 20% risk reduced cardiovascular death in the statin-treated patients than the control patients (I^2 value 27%, P-value < 0.0001, RR 0.80, 95% CI value 0.73–0.88). Myocardial risk reduction was about 18% in the patients (Risk Ratio value 0.83, P-value < 0.0001, I^2 = 21%, 95% CI 0.76–0.90).

All cardiovascular trial data pooled for analysis was assessed for reasonable conditions and divided into randomized control trials based on specific primary disease populations for the cardiovascular death assessment. In the data, 43 Chronic heart disease data, 6 atherosclerotic patients', 10 Primary prevention data, 5 diabetic data, 2 renal, 4 transplant, and 1 stroke patients' data was included. This study included 2 randomized control data for heart failure patients and 1 randomized control trial for hypercholesterolemic patients' p.

Out of the 146042 patient's data 6319 patients are non-fatal myocardial infarction. Overall, 26% reduced rate of the myocardial infarction death was found in the statin group compared to the control group (Risk ratio= 0.73, P-value$\leq$ 0.001, 95% CI 0.68–0.83, I^2 value = 45%). High significance data on revascularization was found in the stain treated group compared to the control group (Risk ratio= 0.77, P-value$\leq$ 0.001, 95% CI 0.69–0.82, I^2 value = 43%). High significance data was found in the ischemic stroke satin group and the control group patients (Risk ratio= 0.87, P-value= 0.004, 95% CI 0.79–0.96, I^2 value = 42%). low hemorrhagic stroke incidence was found in the statin group patients compared to the control group (Risk ratio= 0.87, P-value= 0.07, 95% CI 0.73–0.1.01, I^2 value = 0%). During a follow-up, 3.9 years 34 prospective randomized trial data was obtained (inter quartile range varied from the 2.7 to 5.0). The cancer occurrence within the satin and control group did not differ significantly (Odd ratio= 0.98, P-value=0.77, 95% CI 0.95–1.06, I^2 value = 0%). Rhabdomyolysis information did not differ significantly between the statin and control groups (Odd ratio= 1.03, P-value$\leq$ 0.001, 95% CI 0.83–1.33, I^2 value = 0%). 111002 patients have diabetes. A significantly increased rate of diabetes was found in the statin patients (Odd ratio= 1.07, P-value=0.0008, 95% CI 1.03–1.17, I^2 value = 16%).

Statin had a significantly increased aspartate aminotransferase or AST as compared to the control patients (Odd ratio= 1.13, P-value= 0.005, 95% CI 1.03–1.23, I^2 value = 0%), Satin also impacted highly on the alanine aminotransferase or ALT (Odd ratio= 1.31, P-value= 0.001, 95% CI 0.68–0.83, I^2 value = 0%) and Creatinine Kinase (Risk ratio= 1.06, P-value= 0.66, 95% CI 0.68–0.83, I^2 value = 28%).

Table 1: **Patients characteristics as per obtained data**

Study Period	Trial year	Patient status/ condition	Treatment comparisons (mg/day)	Follow-up, years	Randomized Individuals	Age, mean, year	Men (%)	Prior CHD (%)	Diabetes (%)	Hypertension (%)	Current smokers (%)	baseline, mean change mg/dl	
												LDL	HDL
Yamada T	2008	Transplant patients	usual care vs.L20–80	0.5	38	64	79%	100	22%	20%	37%	180	NR
WOSCOPS	2008	Primary prevention	P-NA vs. conventional treatment	0.5	70	62	86	100	33	54	61	254	58 (2.3)
Wojnicz R	2008	Primary prevention	placebo vs.L20–80	0.5	74	38	81	100	0	0	NR	117 (–32)	57 (1.8)
Vrtovec B	2008	Primary prevention	P40 vs. usual care	0.5	77	52	83	100	14	23	12	124 (–50)	53 (1.9)
Sdringola S	2007	Primary prevention	P40 vs. placebo	0.5	79	58	89	100	10	49	0	125 (–50)	53 (0.93)
REGRESS	2006	Primary prevention	P40 vs. placebo	0.5	81	69	58	100	57	89	0	125 (–50)	52 (2.6)
PTT	2006	Primary prevention	P40 vs. placebo	0.75	97	52	53	48	0	0	0	128 (–15)	51 (1.3)
PROSPER	2005	Primary prevention	P40 vs. placebo	0.9	98	47	100	100	0	36	24	130 (–20)	50 (5.8)
PREDICT	2005	Primary prevention	P40 vs. placebo	1	106	70	45	100	9	95	NR	130 (–3.0)	50 (0.5)
PMSG	2004	Elderly patients	P40 vs. placebo	1	110	63	61	100	NR	NR	NR	130 (–30)	48 (2.6)
PLAC I, II	2004	Elderly patients	P40 vs. placebo	1	120	60	92	100	18	59	68	132 (–44)	48 (–13)
PHYLLIS	2004	Elderly patients	P40 vs. placebo	1	126	57	80	100	0	32	67	133 (–52)	47 (2.0)
PCS	2004	CHD	P40 vs. placebo	1	145	65	90	100	NR	NR	14	137 (–58)	46 (1.0)
OACIS-LIPID	2003	CHD	P40 vs. placebo	1	164	66.1	31.3	14.2	22.8	41.5	59.3	139 (–41)	46 (1.0)
Mohler	2003	CHD	P40 vs. placebo	2	226	54	100	100	14	42	11	141 (–20)	46 (1.0)
Mohler	2003	CHD	P40 vs. placebo	2	234	68	77		18		40	142 (–27)	45 (–2.0)

MEGA	2002	CHD	P20–40 vs. usual care	2	234	68	77		18		40	145 (–22)	44 (3.9)
MARS	2002	CHD	P20–40 vs. usual care	2	270	58	91	100	0	0	80	146 (–16)	44 (3.1)
Makuuchi H	2002	CHD	P20 vs. usual care	2	305	55	53	0			24	146 (–46)	44 (2.3)
LIPID	2002	CHD	P20 vs. placebo	2	331	53	81	100	14	37	27	150 (–19)	44 (–1.3)
L-CAD	2002	CHD	P10–20 vs. usual care	2.2	335	59	84	100	33	52	42	150 (–38)	43 (9)
Kobashigawa	2002	CHD	P10–20 vs. usual care	2.5	353	63	77	100	31	48	58	150 (–40)	43 (2.5)
KLIS	2000	CHD	P10–20 vs. usual care	2.5	373	59	83	100	15	42	20	151 (–24)	43 (0.4)
KAPS	2000	CHD	P10 vs. placebo	2.6	447	57.4	100	8	2	33	26	155 (–42)	42 (5.4)
HARP	2000	CHD	P10 vs. no statin	3	508	58.4	40	0	0	100	16	156 (–23)	42 (1.5)
GRACE	1999	CHD	P1 vs. usual care	3	559	58	80	100	1	41	16	156 (–41)	41 (3.2)
GISSI-P statin	1998	CHD	L73 vs. placebo	3	695	58	84	100	7	31	34	156 (–65)	41 (–14)
FATS statin	1998	CHD	L40 vs. usual care	3	884	56	100	100	0	28	28	158 (–35)	41 (1.9)
FAST	1997	CHD	L20–80 vs. placebo	3	919	61.7	52	0	2	29	12	158 (–42)	41 (1.0)
EXCEL	1996	CHD	L20–40 vs. placebo	3	1062	55	77	75	0	48	29	163 (–47)	41 (–0.8)
ESTABLISH	1996	CHD	L10–40 vs. placebo	3	1600	59	78	100	20	43	0	166 (–39)	40 (–12)
Colivicch	1995	CHD	A80 vs. usual care	3.2	2442	61	82	100	22	0	19	166 (–49)	40 (1.0)
CLAPT	1995	CHD	A80 vs. placebo	3.3	4159	59	86	100	14	42	21	172 (–47)	39 (5.0)
CCAIT	1995	CHD	A80 vs. placebo	4.3	4271	60	86	100	14	37	12	174 (–50)	39 (2.5)
CARE	1995	CHD	A40–80 vs. usual care	4.5	4349	58	100	0	23.59	43.78	39.76	179 (–74)	39 (2.2)
CAIUS	1995	CHD	A40 vs. usual care	4.8	6595	55.2	100	0	1	16	44	180 (–43)	37 (1.8)
ATHEROMA	1994	CHD	A20 vs. usual care	4.9	6605	58	85	0	6	22	12	180 (–47)	36 (3.5)
ATAHEB	1994	CHD	A20 vs. no statin	5	7832	58.3	32	0	21	42	21	181 (–36)	36 (3.5)

ASCOT-LLA	1994	Atherosclerotic–carotid stenosis	A10–80 vs. usual care	5.1	8245	56	59	33	82	40	18	182 (–36)	36 (1.8)
ALLIANCE	1993	Atherosclerotic–carotid stenosis	A10 vs. placebo	5.2	9014	62	83	100	9	42	10	185 (–62)	35 (–4)
ALLHAT-LLT	1993	Atherosclerotic–carotid stenosis	A10 vs. placebo	5.3	10 305	63.2	81	0	25	100	33	185 (–78)	32 (–2.0)
AFCAPS	1991	Atherosclerotic–carotid stenosis	A10 vs. placebo	5.4	10 355	66.4	51	14	35	100	23	192 (–46)	45
ACAPS	1990	Atherosclerotic–carotid stenosis	A10 vs. no statin	6.1	5 800	75.4	48	44	11	62	27	95 (–7)	

Discussion

Efficacy of statin for Cardiovascular treatment: Jones et al., 1998 in the early '90s, introduced statin drugs needed to reduce cholesterol levels. They have a low potential to reduce levels (5). Among the different Statin drugs, pravastatin was the most tested drug. Pravastatin has undergone three trials with 40 mg daily dose versus no statin therapy condition, namely ALLHAT-LLT, PROSPER, and WOSCOPS, to evaluate the low-density lipoprotein-C level reduction. The West Scotland Coronary prevention study on men demonstrated an approximate 26% reduction in the LDL C level and 28% cardiac mortality and 22% less in coronary mortality after Pravastatin administration; which become more evident after a Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) after the Pravastatin administration result (34%LDL C level reduction, 24%cardiac mortality reduction, and 19% coronary mortality reductions respectively) [6] and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) study result (28% reduction in the cholesterol level) (7). Pravastatin is also very effective in coronary artery disease, proven in the cholesterol and Recurrent events trials. The CARE trial and Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study has found a 24% reduction in the coronary problem than placebo therapy patients, when patients are treated daily with about 40 mg Pravastatin [8,9]. Fluvastatin reduces coronary mortality in the case of renal transplanted and percutaneous coronary intervention patients [10,11]. Whereas the Lovastatin treated Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed a 25% cholesterol level reduction and 37% coronary mortality reduction (12). Additionally, Pravastatin and Fluvastatin are non-metabolized by cytochrome P450 complex, so there is less potential for a drug-drug interaction. This phenomenon makes Pravastatin and Fluvastatin the preferable drug than other statins like simvastatin or atorvastatin despite their low potentiality.

Atorvastatin and Simvastatin have a significant effect in the LDL cholesterol level reduction [5]. Atorvastatin efficacy trials by the Anglo-Scandinavian. Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) resulted in LDL-C level reduction in 29% of Collaborative Atorvastatin Diabetes patients; the Study shows 40% LDL-C level reduction after 10mg daily atorvastatin treatment.

According to Sever et al., the ASCOTT trial with the atorvastatin treatment among 20000 hypertension patients demonstrated 29% coronary mortality reduction, whereas according to CARDS trials with the diabetes mellitus patients demonstrated 36 % reduced coronary death with the Atorvastatin (13).

Whereas Scandinavian Simvastatin Study in 1994 shows Simvastatin treatment reduced 35% LDL C level, 42% in cardiac mortality, and 34% in coronary mortality. The heart Protection Study supported this study with the trial among the 20,000 patients, which shows that after 40 mg daily Simvastatin treatment, coronary mortality reduced by 26% and cardiac mortality reduced by 18%. Atorvastatin study for prevention of coronary heart disease demonstrated 29% LDL cholesterol reduction (14). From the above discussion, it has been observed that Atorvastatin and simvastatin have the same benefit for LDL-c reduction. In the case of coronary artery disease, patients treated with 80mg of the atorvastatin had a reduction of 20% in coronary events (15). Another atorvastatin trial with the atorvastatin Myocardial ischaemic patient when compared with Simvastatin trial had no significant reduction of coronary problems (16).

According to Schwartz et al., 2001 atorvastatin treatment for 16% coronary problem reduction was found. Patients who have not received any statin therapy also have reduced cholesterol level after pravastatin and atorvastatin treatment by 22% and 51% respectively. (17)

Atorvastatin permitted cholesterol-lowering drugs for the reduction in heart failure in 2007. The decision was based on the result of the statistical analysis of the TNT study. TNT study demonstrated significantly reduced heart failure cases in patients treated daily atorvastatin 80 mg than previous patients who have not undergone such treatments. All the above findings show the benefits of statin treatment at cardiac myocytes level, which reduced heart failure risk by 0.6% (18).

Nowadays, there is a single high potential statin that is commercially available known as Rosuvastatin. Rosuvastatin has some exceptional features like special functional groups in the structure, enhanced binding enthalpy, and hydrophilic nature (19), which increase potentiality against HMG CoA reductase. Rosuvastatin provides multiple active sites against HMG CoA reductase enzymes due to fluorine-containing phenyl groups and sulphonamide groups in the chemical structure (20). According to Carbonell and Freire, Rosuvastatin is a better enzyme inhibitor due to shorter bond length and sulfonyl groups. The efficiency of Rosuvastatin has been demonstrated by trial with 20,000 patients with a different disease like cardiovascular disease (36%), renal dysfunction (53%), and diabetes mellitus (17%) (21).

A study among 1542 people by Bener et al., 2014 has revealed that among the various strains of statin drugs, the most effective drug in LDL reduction was Rosuvastatin, followed by simvastatin (16.7%), atorvastatin (15.9%), pravastatin (11.59%) (22).

In a trial, it was found that treatment with 10 mg rosuvastatin reduced cholesterol by 35%, triglyceride by 19%, and raised High-density cholesterol level by 8% (23). Another Rosuvastatin trial found that Low-density lipoprotein cholesterol level reduced by 57% whereas atorvastatin treatment reduced by 50% (24). AstraZeneca started their GALAXY program to study the rosuvastatin effect on cardiovascular reduction (25), whereas the STELLAR study was designed to demonstrate the rosuvastatin efficiency with the comparison to other statin drugs (26). A trial with 2400

patients who had hypercholesterolemia with statins 10 to 80 mg, Atorvastatin and Simvastatin, 10 to 40 mg Rosuvastatin and Pravastatin applied for six weeks shows that Low-density lipoprotein was reduced by 55% compared to atorvastatin (51% reduction), simvastatin (46% reduction) and pravastatin (30% reduction). Rosuvastatin reduced low-density lipoprotein by 12% more than simvastatin and 8% more than atorvastatin. Rosuvastatin raises high-density lipoprotein levels by 7.7% than other groups of statins.

A study with 412 patients with cholesterol ranges between 160-250 mg/dL treated with the 10mg atorvastatin daily and 5 mg rosuvastatin daily for 12 weeks, resulted in a significant reduction of LDL-C compared to atorvastatin. After treatment with the Rosuvastatin with 10mg daily, it has been found that approximately 98% patients reached the National Cholesterol Education Panel/Adult Treatment Panel -II limitations than atorvastatin treatment [22]. A trial with 477 patients with hypercholesterolemia treated with 20 mg simvastatin and 5mg to 10 mg rosuvastatin up to 12 weeks after that dose, titration up to 40 mg simvastatin and 40 mg pravastatin. In comparison, Rosuvastatin dose titration was about 80 mg. Result obtained after 12 weeks was a significant reduction in LDL-C with rosuvastatin (39% and 47% reduction) than simvastatin (34.6% reduction) and pravastatin (26.5% reduction), respectively. After a total of 52 weeks of treatment, rosuvastatin treated patients reached Adult Treatment Panel -II level (88% and 87%) than the other two statins [27]. Controlled Rosuvastatin Multinational Trial in Heart Failure study among 5011 patients shows that after daily treatment with 10mg rosuvastatin, the risk of fatal myocardial ischemia or stroke was reduced by 10.6%.

Statin is associated most with muscle symptoms observed among the 10-29% of patients who take statin daily [28,29]. Compared with the control trial between the statin treatment group and placebo group a significant difference in muscle symptoms in these two groups were observed [30]. These symptoms were due to the discontinuation of the statin treatment. These include, muscle cramps, weakness, and myalgias, all of which can be considered as Statin-associated muscle symptoms. These symptoms can arise after the initiation of statin treatment or after the increase of regular statin dosages. Immediate discontinuation of the treatment will resolve all these symptoms. [31]

Though statin treatment is one of the best ways to combat cardiovascular problems, it has been found that statins are intolerable to many patients [32-34]. So, statin intolerance is a significant challenge for cardiovascular patient management. Statin intolerance is defined as the inability to tolerate at least two different statin drugs. National Lipid association characterized statin intolerance as a clinical syndrome by intolerance of at least two statin drugs, where one statin at the lowest dose and another one at any dose, that shows any symptoms or any anomalous laboratory results which are immediately removed by stopping statin treatment and it will return after reinforcing the statin doses [35]. According to the trial data, statin intolerance will increase nonfatal cardiovascular symptoms and health care costs. The most common symptoms due to statin intolerance are muscular symptoms. During statin treatment, muscle problems are widespread. Some patients may suffer due to the nocebo effect. According to the American college of cardiology guideline 2016 (36), if a patient has a statin intolerance problem during the statin treatment, non-statin therapy can be considered in place of statin therapy. In that case, ezetimibe could be a substitute (37). IMPROVE-IT trial data (38) shows that ezetimibe and simvastatin combined will not promote myopathy, myalgia, and rhabdomyolysis symptoms. ODYSSEY LTERNATIVE trial shows that statin intolerance patients can be treated safely with PCSK9 inhibitors evolocumab and alirocumab (39,40,41). Daily 20 mg Rosuvastatin can increase the diabetes risk compared to the placebo treatment documented by the JUPITER trial in 2008 (42). After statin therapy, a 9% increase in diabetes risk has been documented by a pooled analysis. SPARCL trial (43) has demonstrated that daily 80 mg Atorvastatin can cause a 44% increase in the diabetes risk compared to the placebo treatment. Many trials like SEARCH (44) PROVE-IT TIMI (45) have been known to find the risk of diabetes in the statin treatment. Though the relation between the Statin treatment and diabetes is not clear, an experiment related to HMGCR gene polymorphism shows that statin inhibits 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) (46). HMG COA reduction is associated with low-density cholesterol, and a decrease and increases in the plasma glucose concentration. Statin is also related to Hepatitis c virus treatment. Statins like rosuvastatin should be avoided during the ledipasvir and sofosbuvir treatment during Hepatitis c due to the drug-to-drug interaction (47). According to some study reports, Statin can occur because of cognitive impairment. Though the exact reason is still unclear, some animal model studies demonstrated that cholesterol synthesis reduction below a critical level can cause myelin inhibition in the Central nervous system, which results in cognitive problems (48). Two studies with 209 patients with a lovastatin effect and 308 patients with a simvastatin effect showed the harmful effect of statin on cognition (49). There are several trials like PROSPER (50) studies among the 5804 patients with the daily 40mg Pravastatin treatment which shows no effect on the cognitive function, a similar result has been found when simvastatin treatment was done on the 20,536 patients in HPS studies; there was no effect found on the 75-85 years group people (51). Several Randomized trials did not indicate the proper relationship between the Statin treatment and cognitive effect. Before starting statin treatment, there is no need to do any cognitive. In 2010, the 26 randomized trials of the statin drugs demonstrated that the risk of stroke was reduced by about 16% and ischaemic stroke by 21%, by reducing cholesterol levels per 1mmol/l (52).

SPARCL trial demonstrated that high-intensity statin treatment reduced fatal stroke by 16% compared with the placebo group (43), which was tested among 4,731 patients with cholesterol levels of about 100–190

mg/dl. Although the statin therapy group reduced the risk of fatal stroke and there is a chance to haemorrhagic stroke (53). A metanalysis among the 248,391 patients (14,784 intracerebral haemorrhages) demonstrated no relationship between statin therapy and intracerebral stroke (54).

IMPROVE-IT trial (55) Data from the ezetimibe and simvastatin treatment shows a less significant increase in the haemorrhagic stroke treatment, and the FOURIER trial (56) shows a less significant increase in the haemorrhagic stroke when compared with the statin treatment group and the placebo group. In conclusion, only a parcel trial demonstrated the increasing relationship between atorvastatin and haemorrhagic stroke (43). After JUPITER study analysis (57), patients were treated with the 20 mg rosuvastatin and reached the cholesterol level below 50mg, were compared with the patient having cholesterol level more than 50 mg for diabetes, neuropsychiatric condition cancer, etc., there was no significant difference found between the two groups of patients. A similar analysis was done after the IMPROVE-IT trial (55) within the groups of cholesterol level below 30mg, and more than 30 mg in simvastatin and simvastatin plus ezetimibe treated patients, results indicated no difference between the plasma aminotransferase levels, haemorrhagic, Stroke, or severe muscle problems.

Conclusion

American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines of (2013) proves the importance of statin therapy in atherosclerotic cardiovascular disease. Even if the benefit of statin medication has been demonstrated, there is a comparable antagonistic impact that forces the patient to continue with statin therapy. The most common problem of statin therapy reported were Muscular symptoms. Similarly, Hepatic problems were also considered as a significant effect of statin therapy. There is a significant amount of evidence that demonstrates statin's harmful effect and proves that statins are safe for liver disease like hepatitis c. Statin is also safe for diabetes. The trial data has demonstrated that after regular statin treatment, the risk of being diabetic is minimal. Also, the relation between diabetes and statin treatment is very unclear to date. Statins can also reduce the risk of ischaemic stroke, but according to the SPARCL trial, statin can increase the haemorrhagic stroke risk. The absolute low-density lipoprotein cholesterol level reduction is directly proportional to the reduced risk of cardiovascular problems. So, the primary goal of the treatment is to reach the target of lowering LDL-c without any side effects. High statin treatment along with the ezetimibe and PCSK9 inhibitor reduces the cardiovascular risk by reducing Low-density lipoprotein level up to 30 mg/dl (0.8 mmol/l) deprived of any side effect. Statin treatment is a very safe and effective treatment for cholesterol reduction despite some adverse effects.

Reference

1. Hajjaj H, Niederberger P, Duboc P. Lovastatin biosynthesis by *Aspergillus terreus* in a chemically defined medium. Applied and Environmental Microbiology. 2001;67(6):2596-602.
2. McKenney JM, Ganz P, Wiggins BS, Saseen JS. Statins. Clinical Lipidology: Elsevier; 2009. p. 253-80.
3. Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Human mutation. 1992;1(6):445-66.
4. Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. Science. 2001;292(5519):1160-4.
5. Jones P, Kafonek S, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). The American journal of cardiology. 1998;81(5):582-7.
6. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. The Lancet. 2002;360(9346):1623-30.
7. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002 Dec 288(23):2998-3007.
8. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. New England Journal of Medicine. 1996;335(14):1001-9.
9. Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. New England Journal of Medicine. 1998;339(19):1349-57.
10. Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. Jama. 2002;287(24):3215-22.
11. Holdaas H, Fellström B, Jardine AG, Holme I, Nyberg G, Fauchald P, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. The Lancet. 2003;361(9374):2024-31.
12. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average

cholesterol levels: results of AFCAPS/TexCAPS. Jama. 1998;279(20):1615-22.
13. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. The Lancet. 2004;364(9435):685-96.
14. Arca M. Atorvastatin efficacy in the prevention of cardiovascular events in patients with diabetes mellitus and/or metabolic syndrome. Drugs. 2007;67(1):43-54.
15. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart J-C, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. New England Journal of Medicine. 2005;352(14):1425-35.
16. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. Jama. 2005;294(19):2437-45.
17. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. Jama. 2001 Apr 4;285(13):1711-8.
18. Khush KK, Waters DD, Bittner V, Deedwania PC, Kastelein JJ, Lewis SJ, et al. Effect of high-dose atorvastatin on hospitalizations for heart failure. Circulation. 2007;115(5):576-83.
19. Holdgate GA, Ward WH, McTaggart F. Molecular mechanism for inhibition of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase by rosuvastatin.
20. Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. Science. 2001;292(5519):1160-4.
21. Brewer Jr HB. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. The American journal of cardiology. 2003 Aug 21;92(4):23-9.
22. Bener A, Dogan M, Barakat L, Al-Hamaq AO. Comparison of efficacy, safety, and cost-effectiveness of various statins in dyslipidemic diabetic patients. Indian journal of pharmacology. 2014;46(1):88.
23. Olsson AG, Istad H, Luurila O, Ose L, Stender S, Tuomilehto J, et al. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. American Heart Journal. 2002;144(6):1044-51.
24. Schneck DW, Knopp RH, Ballantyne CM, McPherson R, Chitra RR, Simonson SG. Comparative effects of rosuvastatin and atorvastatin across their dose ranges in patients with hypercholesterolemia and without active arterial disease. The American journal of cardiology. 2003;91(1):33-41.
25. Schuster H. The GALAXY Program: an update on studies investigating efficacy and tolerability of rosuvastatin for reducing cardiovascular risk. Expert Review of Cardiovascular Therapy. 2007;5(2):177-93.
26. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). The American journal of cardiology. 2003;92(2):152-60.
27. Brown WV, Bays HE, Hassman DR, McKenney J, Chitra R, Hutchinson H, et al. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial. American heart journal. 2002;144(6):1036-43.
28. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. Cardiovascular drugs and therapy. 2005;19(6):403-14.
29. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. Journal of clinical lipidology. 2012;6(3):208-15.
30. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. The Lancet. 2016;388(10059):2532-61.
31. Colantonio LD, Huang L, Monda KL, Bittner V, Serban M-C, Taylor B, et al. Adherence to high-intensity statins following a myocardial infarction hospitalization among Medicare beneficiaries. JAMA cardiology. 2017;2(8):890-5.
32. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the statin muscle safety task force: 2014 update. Journal of clinical lipidology. 2014;8(3): S58-S71.
33. Mancini GJ, Baker S, Bergeron J, Fitchett D, Frohlich J, Genest J, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Consensus Working Group Update (2016). Canadian Journal of Cardiology. 2016;32(7): S35-S65.
34. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society consensus panel statement on assessment, aetiology and management. European heart journal. 2015;36(17):1012-22.

35. Guyton JR, Bays HE, Grundy SM, Jacobson TA. An assessment by the Statin Intolerance Panel: 2014 update. Journal of clinical lipidology. 2014;8(3):S72-S81.
36. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD, DePalma SM, Minissian MB, Orringer CE, Smith SC, Writing Committee. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. Journal of the American College of Cardiology. 2016 Jul 5;68(1):92-125.
37. Athyros VG, Tziomalos K, Kakafika AI, Koumaras H, Karagiannis A, Mikhailidis DP. Effectiveness of ezetimibe alone or in combination with twice a week Atorvastatin (10 mg) for statin intolerant high-risk patients. The American journal of cardiology. 2008 Feb 15;101(4):483-5.
38. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. ezetimibe added to statin therapy after acute coronary syndromes. New England Journal of Medicine. 2015;372(25):2387-97.
39. Moriarty PM, Jacobson TA, Bruckert E, Thompson PD, Guyton JR, Baccara-Dinet MT, et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. Journal of clinical lipidology. 2014;8(6):554-61.
40. Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, Sattar N, Preiss D, Bruckert E, Češka R, Lepor N, Ballantyne CM. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. Jama. 2016 Apr 19;315(15):1580-90.
41. Orringer CE, Jacobson TA, Saseen JJ, Brown AS, Gotto AM, Ross JL, et al. Update on the use of PCSK9inhibitors in adults: recommendations from an Expert Panel of the National Lipid Association. Journal of clinical lipidology. 2017;11(4):880-90.
42. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto Jr AM, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England journal of medicine. 2008 Nov 20;359(21):2195-207.
43. Amarenco P. For the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators: high-dose atorvastatin after stroke or transient ischemic attack. N engl j med. 2006;355:549-59.
44. Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Peto R, Collins R. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. Lancet (London, England). 2010 Nov 8;376(9753).
45. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. New England journal of medicine. 2004 Apr 8;350(15):1495-504.
46. Swerdlow DI, Preiss D, Kuchenbaecker KB, Holmes MV, Engmann JE, Shah T, Sofat R, Stender S, Johnson PC, Scott RA, Leusink M. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. The Lancet. 2015 Jan 24;385(9965):351-61.
47. Henderson LM, Patel S, Giordano TP, Green L, El-Serag HB. Statin therapy and serum transaminases among a cohort of HCV-infected veterans. Digestive diseases and sciences. 2010 Jan 1;55(1):190.
48. Rojas-Fernandez CH, Goldstein LB, Levey AI, Taylor BA, Bittner V. An assessment by the statin cognitive safety task force: 2014 update. Journal of Clinical Lipidology. 2014 May 1;8(3): S5-16.
49. Ott BR, Daiello LA, Dahabreh IJ, Springate BA, Bixby K, Murali M, Trikalinos TA. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. Journal of general internal medicine. 2015 Mar 1;30(3):348-58.
50. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. The Lancet. 2002 Nov 23;360(9346):1623-30.
51. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20 536 high-risk individuals: a randomised placebo-controlled trial. The Lancet. 2002 Jul 6;360(9326):23-33.
52. Trialists CT. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet. 2010 Nov 13;376(9753):1670-81.
53. Goldstein LB, Amarenco P, Szarek M, Callahan A3, Hennerici M, Sillesen H, Zivin JA, Welch KM. Hemorrhagic stroke in the stroke prevention by aggressive reduction in cholesterol levels study. Neurology. 2008 Jun 10;70(24 Part 2):2364-70.
54. Hackam DG, Woodward M, Newby LK, Bhatt DL, Shao M, Smith EE, Donner A, Mamdani M, Douketis JD, Arima H, Chalmers J. Statins and intracerebral hemorrhage: collaborative systematic review

and meta-analysis. Circulation. 2011 Nov 15;124(20):2233-42.

55. Giugliano RP, Wiviott SD, Blazing MA, De Ferrari GM, Park JG, Murphy SA, White JA, Tershakovec AM, Cannon CP, Braunwald E. Long-term safety, and efficacy of achieving very low levels of low-density lipoprotein cholesterol: a prespecified analysis of the IMPROVE-IT trial. JAMA cardiology. 2017 May 1;2(5):547-55.
56. Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, Toth K, Gouni-Berthold I, Lopez-Miranda J, Schiele F, Mach F. Clinical efficacy, and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. The Lancet. 2017 Oct 28;390(10106):1962-71.
57. Hsia J, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol< 50 mg/dl with rosuvastatin: the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). Journal of the American College of Cardiology. 2011 Apr 19;57(16):1666-75.
58. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. The Lancet. 2010 Feb 27;375(9716):735-42.
59. Sadowitz B, Maier KG, Gahtan V. Basic science review: Statin Therapy-Part I: The pleiotropic effects of statins in cardiovascular disease. Vascular and endovascular surgery. 2010 May;44(4):241-51.