ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Review Article

Overview of Lipid-Associated Risks of Cardiovascular Diseases

Salem Mohamed Barabie[1]*, Yousef Ehab Jan[2], Anwaar Mayah Alshammary[3], Shahad Mohsen Baabdullah[4], Mohammed Khalid Kondarji[5], Maram Ali Aljohani[6], Mohammed Nasser Makeen[7], Hussain Ali Algharrash[8], Nourah Ali Aldossari[9], Abdulaziz Saud Alrahili[10], Waleed Abdulwahab Alzahrani[11] and Alaa Ghazi Alolayan[4]

[1]*Consultant Family Medicine, Family Medicine Department, King Abdulaziz University Hospital, Jeddah, Saudi Arabia*

[2]*Primary Health Care, Ministry of Health, Makkah, Saudi Arabia*

[3]*Alnesyah PHC, Hail, Saudi Arabia*

[4]*Batterjee Medical College, Jeddah, Saudi Arabia*

[5]*King Abdulaziz University, Jeddah, Saudi Arabia*

[6]*Ibn Sina National College for Medical Studies, Jeddah, Saudi Arabia*

[7]*Jazan Armed Forces Hospital, Jazan, Saudi Arabia*

[8]*Qatif Central Hospital, Qatif, Saudi Arabia*

[9]*King Faisal Hospital, Hofuf, Saudi Arabia*

[10]*Umm Al-Qura University, Makkah, Saudi Arabia*

[11]*King Fahad General Hospital, Jeddah, Saudi Arabia*

***Corresponding Author:** Salem Mohamed Barabie, Consultant Family Medicine, Family Medicine Department, King Abdulaziz University Hospital, Jeddah, Saudi Arabia.

Received: December 13, 2019; **Published:** December 18, 2019

Abstract

Introduction: It is estimated that most adults above the age of 60 years are affected by cardiovascular diseases (CVD). In addition, few years ago, about 17.3 million annual deaths all over the world have been attributed to cardiovascular diseases. Multiple factors have been shown to attribute to CVD. Management of these risk factors could substantially reduce and/or slow progression of the disease. Primary prevention aims to lower LDL-C in patients without a history of CVD. When the patient has a history of CVD, lipid-lowering approaches aim to secondary prevention of further episode and progression.

Aim of Work: In this review, we will discuss the association between lipid abnormalities and cardiovascular diseases, rational for management in primary prevention, and management consideration in these patients. Lipid-lowering as a secondary preventive in patients with established CVS will not be discussed.

Methodology: A comprehensive and systematic search was conducted regarding dyslipidemia, cardiovascular risk, primary and secondary prevention of CVD, lipid-lowering therapies. PubMed search engine and Google Scholar search were the mainly used database for search process. All relevant available and accessible articles of all types were reviewed and included.

Conclusion: Most randomized trials evidenced the impact of lipid-lowering, especially LDL-C, on reduction of cardiovascular disease events, especially myocardial infarction. The evidence is true irrespective of the pre-therapy LDL-C level. Lifestyle modification is acceptable initial recommendation for primary prevention of cardiovascular diseases. Patients with high level of low density lipoprotein-C at base line are especially privileged by lifestyle modification. The decision to initiate statin therapy is guided by low density lipoprotein-C level in addition to calculated risk for CVD. A moderate-intensity statin is the most suitable initial drug for most patients. There is no justifiable reason to increase the intensity of statin therapy in most patients who have been started on moderate-dose statin therapy. Non-statin lipid-lowering agents are not recommended for primary prevention of cardiovascular risk.

Keywords: *Cardiovascular Disease (CVD); LDL-C*

Introduction

Cardiovascular disease (CVD) is a major health concerns and cause of mortality in the general population. It is estimated that most adults above the age of 60 years are affected by CVD. Nevertheless, few years ago, about 17.3 million annual deaths all over the world have been attributed to cardiovascular diseases [1-3]. Cardiovascular diseases include 4 major categories: Coronary heart disease (CHD) such as angina pectoris and myocardial infarction; cerebrovascular disease including stroke and transient ischemic attack; peripheral artery disease; aortic atherosclerosis and aneurysm.

Multiple factors have been shown to attribute to CVD. Management of these risk factors could substantially reduce and/or slow progression of the disease. Elevated low density lipoprotein cholesterol (LDL-C) is considered among strongly established risk factor. Primary prevention aims to lower LDL-C in patients without a history of CVD. When the patient has a history of CVD, lipid-lowering approaches aim to secondary prevention of further episode and progression. The rationale of LDL-C reduction is based upon data from epidemiologic studies shown a continuous, positive, graded relationship between LDL-C concentration and CVD events and mortality. Lowering LDL-C reduces the risk in patients with and without CVD (primary and secondary prevention) [4-7]. Only management of an elevated LDL-C has been shown to be of clinical importance in primary prevention. Management of elevated triglycerides or low high density lipoprotein cholesterol does not carry clinical benefits in patients without established CVD.

In this review, we will discuss the association between lipid abnormalities and cardiovascular diseases, rational for management in primary prevention, and management consideration in these patients. Lipid-lowering as a secondary preventive in patients with established CVS will not be discussed.

Methodology

A comprehensive and systematic search was conducted regarding dyslipidemia, cardiovascular risk, primary and secondary prevention of CVD, lipid-lowering therapies. PubMed search engine and Google Scholar search were the mainly used database for search process. All relevant available and accessible articles of all types were reviewed and included. The keywords used in search are: dyslipidemia, cardiovascular risk, primary and secondary prevention of CVD, lipid-lowering therapies.

Association between lipids and cardiovascular risks

Lipids are water insoluble compounds. Normally, these components require protein-containing complexes called lipoproteins to be transported in blood. The level of cholesterol that should be considered as dyslipidemia is a subject of debate, guidelines and societies have attempted to delineate the hazardous levels that raise the need for intervention [8].

Studies have shown that the prevalence of dyslipidemia is double in patients with premature CHD compared with age-matched controls without CHD [9,10]. About 50 percent of first myocardial infarction (IM) episode has been attributed to dyslipidemia [11]. Nevertheless, even in the normal range, LDL level has been correlated with subclinical atherosclerosis, suggesting a continuous relationship with no clear threshold [12]. Abnormalities in lipoprotein metabolism are often familial. In one study, about 70 percent of patients with a lipid abnormality had a familial lipid disorder [10].

Randomized control have repeatedly shown that lowering total and LDL cholesterol levels reduce coronary events and mortality when given for primary and secondary prevention [13-15]. Other lipid factors that were associated with increased risk of CVD include elevated total cholesterol, decreased HDL cholesterol, hypertriglyceridemia and increased lipoprotein.

Mechanisms of reducing CVD risks by lipid-lowering therapy

The serum concentration of low density lipoprotein (LDL) partially explains the mechanisms by which lipid-lowering drugs as statins are beneficial in reducing the risk of CVD [16-19].

It is suggested that statins may lead to regression of atherosclerosis, such benefits could be observed as early six months [20,21]. Although the regression is small and occurs too fast, the magnitude of the observed clinical benefits is quite large. The regression in atherosclerosis occur without associated change in vessel wall thickness or vessel wall area [22]. After the onset of statins, coronary angiography has shown increased lumen diameter at 2 and 4 years; lesser degree of progression of stenosis also has been shown at three years [23,24].

Plaque rupture of coronary artery is a major cause of an acute coronary syndrome. Nevertheless, increasing data suggest multiple unstable plaques in different coronary arteries among these patients. Thus, intervention aimed only at the culprit lesion is not likely to be optimal and the ability of statins to induce plaque stabilization may be an important mechanism of benefit. Plaque stabilization by statins was observed in both human and animal studies [25-28]. In one study of 131 patients aimed to evaluate the effect of 12 months of atorvastatin therapy versus placebo; atorvastatin reduced the progression of plaque thickness and led to change in plaque composition from lipid-rich to fibrotic and calcified plaque which denotes plaque stability and a reduced tendency for rupture. The mechanism by which lipid-lowering statin causes plaque stabilization is through maintenance of the fibrous cap of the plaque, thereby protecting against plaque rupture. This effect appears to be mediated by inhibition of macrophage proliferation, reduced expression of matrix metalloproteinases (MMPs) and tissue factor by macrophages, and an increase in tissue inhibitor of metalloproteinase-1 [28-30].

Another effect of statins as a lipid-lowering agent is by altering endothelial dysfunction. Endothelial dysfunction is a commonly seen with atherosclerotic coronary arteries; examples include exaggerated vasoconstriction by acetylcholine and vasodilatation by nitric oxide-mediated vasodilation [31-33]. Normal arterial smooth muscle tone results from a balance of vasodilator and vasoconstrictor mediators, with the former predominating in the resting state. Most studies [31-34] have been able to demonstrate beneficial effects of statins on vasoconstriction associated with endothelial dysfunction; an effect that can improve overall vasodilator capacity and myocardial blood flow reserve within six weeks [35-39]. However, some studies failed to show such effects [40].

Thrombus formation, at the site of plaque rupture, plays critical role in acute coronary events. Statin therapy, and other lipid-lowering agents, has a variety of mechanisms by which thrombus formation is reduced [41]. Examples include: improved fibrinolytic profile [42]; decreased platelet activation [43,44]; decreased prothrombin activation and thrombin generation [45,46].

Clinical significance of lipid-lowering therapy

Most Randomized trials evidenced the impact of lipid-lowering, especially LDL-C, on reduction of cardiovascular disease events. The evidence is true irrespective of the pre-therapy LDL-C level. Some old trials have suggested no benefits of non-statin lipid-lowering drugs with increase non-cardiovascular disease mortality [15,47-49]. However, recent large trials with stronger evidence support the clinical benefits with reductions in myocardial infarction and cardiovascular mortality; no evidence of an increase in non-cardiovascular mortality has been seen. In one trial 40 mg of pravastatin for five years was associated with reduction in nonfatal myocardial infarctions and coronary heart disease (CHD) mortality [15]. Pravastatin resulted in LDL-C lowering by 26 percent. All-cause mortality was also decreased however, this result was not of robust significance. Other trials have examined the outcomes for longer (10, 15, and 20 years) duration have found continued reductions in mortality in patients who had initially been assigned to receive pravastatin [50-53].

In AFCAPS/TexCAPS Trials, 20 - 40 mg of lovastatin reduced the incidence of a first major coronary event in low-risk men and women without clinical evidence of cardiovascular disease (primary prevention); lowered the LDL-C by 25 percent [14]. Per 1000 individuals treated with lovastatin for five years, 19 major coronary events, 12 myocardial infarctions, and 17 coronary revascularizations could be prevented. However, no benefit on all-cause mortality was observed. More than meta-analysis on clinical trials on lipid-lowering drugs in patients with and without manifest CVD have been published [54-56]. The combined data strongly suggest reductions in CVD events and CVD mortality [57]. Most meta-analyses of primary prevention trials found a reduction in all-cause mortality benefit [54,55]. In 2016, a meta-analysis was conducted on 49 clinical trials with more than 300,000 individuals with variable evaluated outcomes of lipid-lowering therapy [58]. The relative risk for major cardiovascular events associated with LDL-C lowering was 0.77 for statins and 0.75 for non-statin

therapies. Among these trials, 8 trials have focused on primary prevention; the level of LDL-C after treatment was positively correlated with CVD events; meaning that lower LDLs were associated with lower cardiovascular events and higher levels were correlated with higher events.

Generally, strong evidence based on reliable data demonstrates that lowering LDL-C with statin therapy for primary prevention is effective at reducing CVD events particularly MI. This results is true for a wide range of LDL-C levels and lipid profiles at baseline. Similar benefits of statin therapy were evidenced for secondary prevention in patients with known CVD.

Management approach

Lifestyle modification is acceptable initial recommendation for primary prevention of cardiovascular diseases. Patients with high level of low density lipoprotein-C at base line are especially privileged by lifestyle modification. Lifestyle modifications include weight reduction in overweight patients, aerobic exercise, and healthy eating diets with low saturated fats. One study from the UK, with more than 2500 individuals included, found that diet alone has led to 1.8 percent weight reduction in 60 percent of participants; this was associated with 5 - 7 percent reductions in serum total and LDL-C [59]. In patients with unhealthy diets at baseline, marked dietary change can lower LDL-C by 30 percent [60]. In a randomized trials of 180 postmenopausal women and 197 men with low levels of high-density lipoprotein cholesterol (HDL-C) and moderately-elevated levels of LDL-C, participant were allocated to aerobic exercise, diet, diet plus exercise, or no treatment groups [61]. Although there were no significant changes in HDL-C in any group, there were significant reductions in LDL-C in both men and women in the diet plus exercise group compared with control or diet alone and, in men, in the diet plus exercise group compared with exercise alone.

Despite these benefits on LDL-C lowering as a primary prevention, the evidence is limited regarding the effect of lifestyle modifications on cardiovascular outcomes. In the MRFIT trials, dietary advice to reduce cholesterol levels did not significantly reduce coronary heart disease mortality or all-cause mortality [62]. However, the differences in achieved total cholesterol levels between the groups were probably too small to expect significant effects on mortality.

The decision to initiate statin therapy is guided by low density lipoprotein-c level in addition to calculated risk for CVD. If statin therapy was tolerable and affordable with no financial burden, it could be recommended to all at-risk individuals, similar to a healthy diet and exercise. In addition, the high burden and lifetime risk of cardiovascular disease in industrialized societies must be kept in mind. Unfortunately, most drugs come with financial and adherence challenges as well as side effects, hence, these need to be a reasonably balanced with benefits. Since cardiovascular risk is on a continuum, the threshold of baseline risk which statin therapy is reasonable is arbitrary with variable recommendation by experts, societies, and guidelines. Thus, for most patients in the middle range of baseline risk, it is of great importance to discuss the benefits and costs of statin therapy with the individual patient to reach shared-decision making.

The 2018 guideline on management of blood cholesterol by the American Heart Association/American College of Cardiology states the initiation of a moderate-intensity statin in adults 40 - 75 years of age with LDL-C levels ≥ 70 mg/dL without diabetes mellitus and 10-year atherosclerotic cardiovascular disease risk of ≥ 7.5 percent if the patient prefers statin therapy [63]. Other experts argue for other justifiable east-to-use cut-off. Example include statin therapy for patients with LDL-C > 100 mg/dL and a 10-year CVD risk ≥ 10 percent. This cut-off may differ in specific populations as the very young, the very old, and those with diabetes. For patients with a 10-year risk between 5 and 10 percent, shared decision making with balanced benefits and cost should be done. Patients with 10-years risk below 5 percent, statin therapy will not be needed, periodic evaluation is recommended for these patients. In case of high level of LDL-C (> 160 mg/dL), statin therapy is advised regardless of calculated risk of CVD. The presence of other factors such as family history of premature CVD, chronic kidney disease, or chronic inflammatory disorder increase the risk of CVD, hence, initiation of statin therapy should be considered [63].

Individuals should undergo CVD risk evaluations and discussions at 20 years of age or at first healthcare visit beyond that. In order to decide reducing the level of LDL-C, the risk of CVD events needs to be assessed using validated risk evaluation tools. Patients and their providers can then decide whether a 20 to 30 percent relative risk reduction, which is a reasonable expectation for statin therapy, translates into an absolute risk reduction large enough to be worth the cost, burdens, and potential side effects of daily therapy. For example, a 45-year-old non-smoking normotensive woman with an LDL-C of 180 mg/dL and a high-density lipoprotein cholesterol (HDL-C) of 40 mg/dL has a 10-year risk of a myocardial infarction of approximately 1 percent. This could likely be reduced by 0.2 to 0.3 percentage points if she were treated with a statin daily for 10 years. Hence, the decision to start statin therapy is questionable and patient preferences should be respected. On the other hand, a non-smoking normotensive 60-year-old male patient with the exact same laboratorial values has a 10-year risk of a myocardial infarction of approximately 12 percent. Use of a statin would reduce this risk to 8 to 9 percent, a 3 to 4 percentage point reduction. Statin therapy in this patient should be advised.

Most clinical trials that evaluated the effects of lipid-lowering pharmacologic therapy on cardiovascular disease (CVD) events have compared a fixed dose of a single pharmacologic agent with placebo, with ordinary lifestyle in both groups without lifestyle counseling. Until present, no trials have directly tested combination of medication with statins or treatment to specific LDL-C goals.

Ezetimibe has not been well studied in patients without cardiovascular disease. There is no robust data about the efficacy of PCSK9 inhibitors in primary prevention in patients without familial hypercholesterolemia. Their effects in secondary prevention suggest that they could be expected to reduce cardiovascular outcomes to a similar degree, as is seen with statin therapy. However, their cost, the requirement for injections, and the lack of long-term safety data render them as an option for only highest-risk primary prevention patients who are unable to tolerate statin therapy. A moderate-intensity statin is the most suitable initial drug for most patients; these include: Lovastatin 40 mg; Pravastatin 40 mg; Simvastatin 40 mg; Atorvastatin 10 - 20 mg; Rosuvastatin 5 - 10 mg. Non-statin lipid-lowering agents are not recommended for primary prevention of cardiovascular risk. The exception for this is patients who do not tolerate statins presenting with a very high level of low density lipoprotein-C (more than 190 mg/dL).

There is no justifiable reason to increase the intensity of statin therapy in most patients who have been started on moderate-dose statin therapy. There is little evidence to suggest that intensification provides a level of benefit that requires more aggressive LDL-C lowering. However, it is worth to mention that some patients are at very high risk of CVD, intensification of statin therapy may be reasonable in patients with a 10-years risk of 20 and LDL-C greater than 100 mg/dL.

Conclusion

It is estimated that most adults above the age of 60 years are affected by cardiovascular diseases (CVD). Multiple factors have been shown to attribute to CVD. Management of these risk factors could substantially reduce and/or slow progression of the disease. Studies have shown that the prevalence of dyslipidemia is double in patients with premature CHD compared with age-matched controls without CHD. Abnormalities in lipoprotein metabolism are often familial. Randomized control have repeatedly shown that lowering total and LDL cholesterol levels reduce coronary events and mortality when given for primary and secondary prevention.

The mechanism by which statin reduce the risk of CVD include regression of atherosclerosis, plaque stabilization, altering endothelial dysfunction, and affecting thrombus formation.

Most Randomized trials evidenced the impact of lipid-lowering, especially LDL-C, on reduction of cardiovascular disease events, especially myocardial infarction. The evidence is true irrespective of the pre-therapy LDL-C level. Lifestyle modification is acceptable initial recommendation for primary prevention of cardiovascular diseases. Patients with high level of low density lipoprotein-C at base line are especially privileged by lifestyle modification. The decision to initiate statin therapy is guided by low density lipoprotein-C level in addition to calculated risk for CVD. A moderate-intensity statin is the most suitable initial drug for most patients. There is no justifiable

reason to increase the intensity of statin therapy in most patients who have been started on moderate-dose statin therapy. Non-statin lipid-lowering agents are not recommended for primary prevention of cardiovascular risk.

Bibliography

1. Laslett LJ., *et al*. "The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology". *Journal of the American College of Cardiology* 60 (2012): S1.

2. GBD 2013 Mortality and Causes of Death Collaborators. "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013". *Lancet* (2015).

3. Roth GA., *et al*. "Global and regional patterns in cardiovascular mortality from 1990 to 2013". *Circulation* 132 (2015): 1667.

4. The Expert Panel. "Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults". NIH Publication No. 93-3095, US Government Printing Office Washington, DC (1993).

5. Stamler J., *et al*. "Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screeners of the Multiple Risk Factor Intervention Trial (MRFIT)". *Journal of the American Medical Association* 256.20 (1986): 2823-2828.

6. Ballantyne CM., *et al*. "Hyperlipidemia: diagnostic and therapeutic perspectives". *The Journal of Clinical Endocrinology and Metabolism* 85 (2000): 2089.

7. Wallis EJ., *et al*. "Coronary and cardiovascular risk estimation for primary prevention: validation of a new Sheffield table in the 1995 Scottish health survey population". *British Medical Journal* 320 (2000): 671.

8. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report".

9. Roncaglioni MC., *et al*. "Role of family history in patients with myocardial infarction. An Italian case-control study. GISSI-EFRIM Investigators". *Circulation* 85 (1992): 2065.

10. Genest JJ Jr., *et al*. "Familial lipoprotein disorders in patients with premature coronary artery disease". *Circulation* 85 (1992): 2025.

11. Yusuf S., *et al*. "Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study". *Lancet* 364 (2004): 937.

12. Fernández-Friera L., *et al*. "Normal LDL-Cholesterol Levels Are Associated with Subclinical Atherosclerosis in the Absence of Risk Factors". *Journal of the American College of Cardiology* 70 (2017): 2979.

13. Sacks FM., *et al*. "The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators". *The New England Journal of Medicine* 335 (1996): 1001.

14. Downs JR., *et al*. "Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study". *Journal of the American Medical Association* 279 (1998): 1615.

15. Shepherd J., *et al*. "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group". *The New England Journal of Medicine* 333 (1995): 1301.

16. Thompson GR., *et al*. "Percentage change rather than plasma level of LDL-cholesterol determines therapeutic response in coronary heart disease". *Current Opinion in Lipidology* 6 (1995): 386.

17. Sacks FM., *et al*. "The influence of pretreatment low density lipoprotein cholesterol concentrations on the effect of hypocholesterolemic therapy on coronary atherosclerosis in angiographic trials". Harvard Atherosclerosis Reversibility Project Research Group".

18. "Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S)". *Lancet* 345 (1995): 1274.

19. "Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS)". *Circulation* 97 (1998): 1440.

20. "Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. The Pravastatin Multinational Study Group for Cardiac Risk Patients". *The American Journal of Cardiology* (1993).

21. Furberg CD., *et al*. "Pravastatin, lipids, and major coronary events". *The American Journal of Cardiology* 73 (1994): 1133.

22. Corti R., *et al*. "Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging". *Circulation* 104 (2001): 249.

23. "Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS)". *Lancet* 344 (1994): 633.

24. Brown BG., *et al*. "Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease". *The New England Journal of Medicine* 345 (2011): 1583.

25. Schartl M., *et al*. "Use of intravascular ultrasound to compare effects of different strategies of lipid-lowering therapy on plaque volume and composition in patients with coronary artery disease". *Circulation* 104 (2001): 387.

26. Williams JK., *et al*. "Pravastatin has cholesterol-lowering independent effects on the artery wall of atherosclerotic monkeys". *Journal of the American College of Cardiology* 31 (1998): 684.

27. Ambrose JA and Martinez EE. "A new paradigm for plaque stabilization". *Circulation* 105 (2002): 2000.

28. Crisby M., *et al*. "Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization". *Circulation* 103.7 (2001): 926-933.

29. Aikawa M., *et al*. "An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing matrix metalloproteinases and tissue factor in vivo and in vitro". *Circulation* 103 (2001): 276.

30. Bellosta S., *et al*. "HMG-CoA reductase inhibitors reduce MMP-9 secretion by macrophages". *Arteriosclerosis, Thrombosis, and Vascular Biology* 18 (1998): 1671.

31. Egashira K., *et al*. "Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia". *Circulation* 89 (1994): 2519.

32. Anderson TJ., *et al*. "The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion". *The New England Journal of Medicine* 332 (1995): 488.

33. Treasure CB., *et al*. "Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease". *The New England Journal of Medicine* 332 (1995): 481.

34. Tsunekawa T., *et al*. "Cerivastatin, a hydroxymethylglutaryl coenzyme a reductase inhibitor, improves endothelial function in elderly diabetic patients within 3 days". *Circulation* 104 (2001): 376.

35. Yokoyama I., *et al*. "Improvement of impaired myocardial vasodilatation due to diffuse coronary atherosclerosis in hypercholesterolemics after lipid-lowering therapy". *Circulation* 100 (1999): 117.

36. Lefer AM., *et al*. "Simvastatin preserves the ischemic-reperfused myocardium in normocholesterolemic rat hearts". *Circulation* 100 (1999): 178.

37. Dupuis J., *et al*. "Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes. The RECIFE (reduction of cholesterol in ischemia and function of the endothelium) trial". *Circulation* 99 (1999): 3227.

38. Landmesser U., *et al*. "Simvastatin versus ezetimibe: pleiotropic and lipid-lowering effects on endothelial function in humans". *Circulation* 111 (2005): 2356.

39. Liu PY., *et al*. "Evidence for statin pleiotropy in humans: differential effects of statins and ezetimibe on rho-associated coiled-coil containing protein kinase activity, endothelial function, and inflammation". *Circulation* 119 (2009): 131.

Bibliography

40. Vita JA., *et al*. "Effect of cholesterol-lowering therapy on coronary endothelial vasomotor function in patients with coronary artery disease". *Circulation* 102 (2000): 846.

41. Rosenson RS and Tangney CC. "Antiatherothrombotic properties of statins: implications for cardiovascular event reduction". *Journal of the American Medical Association* 279 (1998): 1643.

42. Dangas G., *et al*. "Pravastatin therapy in hyperlipidemia: effects on thrombus formation and the systemic hemostatic profile". *Journal of the American College of Cardiology* 33 (1999): 1294.

43. Lacoste L., *et al*. "Hyperlipidemia and coronary disease. Correction of the increased thrombogenic potential with cholesterol reduction". *Circulation* 92 (1995): 3172.

44. Pignatelli P., *et al*. "Immediate antioxidant and antiplatelet effect of atorvastatin via inhibition of Nox2". *Circulation* 126 (2012): 92.

45. Undas A., *et al*. "Simvastatin depresses blood clotting by inhibiting activation of prothrombin, factor V, and factor XIII and by enhancing factor Va inactivation". *Circulation* 103 (2001): 2248.

46. Szczeklik A., *et al*. "Inhibition of thrombin generation by simvastatin and lack of additive effects of aspirin in patients with marked hypercholesterolemia". *Journal of the American College of Cardiology* 33 (1999): 1286.

47. WHO. "Cooperative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. Report of the Committee of Principal Investigators". *Lancet* 2 (1980): 379.

48. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. "The relationship of reduction in incidence of coronary heart disease to cholesterol lowering". *Journal of the American Medical Association* 251 (1984): 365.

49. Frick MH., *et al*. "Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease". *The New England Journal of Medicine* 317 (1987): 1237.

50. Ford I., *et al*. "Long-term follow-up of the West of Scotland Coronary Prevention Study". *The New England Journal of Medicine* 357 (2007): 1477.

51. Packard CJ and Ford I. "Long-term follow-up of lipid-lowering trials". *Current Opinion in Lipidology* 26 (2015): 572.

52. Ford I., *et al*. "Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol with Statin Therapy: 20-Year Follow-Up of West of Scotland Coronary Prevention Study". *Circulation* 133 (2016): 1073.

53. Vallejo-Vaz AJ., *et al*. "Low-Density Lipoprotein Cholesterol Lowering for the Primary Prevention of Cardiovascular Disease Among Men With Primary Elevations of Low-Density Lipoprotein Cholesterol Levels of 190 mg/dL or : Analyses From the WOSCOPS (West of Scotland Coronary Prevention Study) 5-Year Randomized Trial and 20-Year Observational Follow-Up". *Circulation* 136.20 (2017): 1878-1891.

54. Cholesterol Treatment Trialists' (CTT) Collaborators., *et al*. "The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials". *Lancet* (2012).

55. Ray KK., *et al*. "Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants". *Archives of Internal Medicine* 170 (2010): 1024.

56. Taylor F., *et al*. "Statins for the primary prevention of cardiovascular disease". *Cochrane Database of Systematic Reviews* (2013): CD004816.

57. Chou R., *et al*. "Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force". *Journal of the American Medical Association* 316 (2016): 2008-2024.

58. Silverman MG., *et al*. "Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis". *Journal of the American Medical Association* 316 (2016): 1289.

59. Butowski PF and Winder AF. "Usual care dietary practice, achievement and implications for medication in the management of hypercholesterolaemia. Data from the U.K. Lipid Clinics Programme". *European Heart Journal* 19 (1998): 1328.

60. Jenkins DJ., *et al*. "Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein". *Journal of the American Medical Association* 290 (2003): 502.

61. Stefanick ML., *et al*. "Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol". *The New England Journal of Medicine* 339 (1998): 12.

62. Multiple risk factor intervention trial. "Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group". *Journal of the American Medical Association* 1982 248 (1982): 1465.

63. Grundy SM., *et al.* "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice" (2019).

Volume 16 Issue 1 January 2020