

# Preventive effects of statin therapy in coronary artery diseases: Current controversy

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The role of statins for primary and secondary prevention of coronary artery disease (CAD), is extensively investigated. This review of literature highlights the current controversies of the research regarding this role. Despite the great impact of statins on outcomes during management of CAD, many issues need further investigation. A debate remains about the biomarkers of cardiovascular pleiotropic effects, stratification of high-risk persons eligible for therapy, evaluating cost-effectiveness, patient factors enhancing benefit-based therapy, long-term benefits, combination therapy, and residual risk after coronary revascularization. Coronary artery calcium (CAC) scoring is a useful tool, when combined to clinical cardiovascular risk scores, in order to guide the shared decision for prescription of statins in asymptomatic persons. A balance approach remains to reserve high-doses of statins for patients with ACS and when the therapeutic target of LDL-C at 70 mg/dl could not be obtained with moderate-doses. Future powered studies are required to detect biomarkers of statin therapy, eligibility for the prophylactic use, reasons for real-life non-adherence with statins, predictors of the statin effects in combination with other lipid-lowering agents, factors enhance the benefit-based therapy, ideal therapeutic doses, and the reasons of the residual risk. and respiratory systems, cardiac anomalies should be considered. Our case

of congenital pulmonary vein stenosis presented with refractory wheezing from pulmonary venous obstruction. Unfortunately, this disorder has an unrelenting course. Even with early diagnosis and current surgical management, the outcome is poor.

**Key Words:** Coronary artery disease; statin; prevention; acute coronary syndrome; coronary revascularization

**Abbreviations:** ACC/AHA: American College of Cardiology/American Heart Association; ACS: Acute Coronary Syndrome; AF: Atrial Fibrillation; Akt: Protein Kinase B; CABG: Coronary Artery Bypass Grafting; CAC: Coronary Artery Calcium; CAD: Coronary Artery Disease; DES: Drug-Eluting Stent; DM: Diabetes Mellitus; eNOS: Endothelial-Type Nitric Oxide Synthase; EPA: Eicosapentaenoic Acid; EPC: Endothelial Progenitor Cells; ESC: European Society of Cardiology; HDL-C: High Density Lipoprotein Cholesterol; HMG-CoA: 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A; hsCRP: High Sensitivity C-Reactive Protein; IL: Interleukin; LDL-C: Low-Density Lipoprotein-Cholesterol; Lp (a): Lipoprotein (a); MACE: Major Adverse Cardiovascular Event; MESA: Multi-Ethnic Study of Atherosclerosis; MI: Myocardial Infarction; mTOR: Mammalian Target of Rapamycin; NC: Necrotic Core; NSTEMI: Non-ST Elevation Acute Coronary Syndrome; PCI: Percutaneous Coronary Intervention; PI3K: Phosphoinositide 3-Kinase; QALY: Quality-Adjusted Life Year

Statin inhibit hepatic biosynthesis of cholesterol where they prevent mevalonate formation, and inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) (1-2). Through the last decades, research targets the protective cardiovascular effects of statins (3-4). Statins have desired roles preventing primary and secondary all-cause death and major cardiovascular events of coronary artery disease (CAD) (5). Protecting against atherosclerotic cardiovascular disease, statin therapy is effective with modification of risk factors (6).

The favorable pleiotropic effects occur through increasing expression of atheroprotection genes, inhibiting inflammatory markers, protecting endothelium, enhancing plaques stability, inhibiting platelets aggregation, increasing nitric oxide bioavailability, decreasing circulating oxidative stress and inflammatory biomarkers, and inhibiting thrombogenesis (2,7).

Variable recommendations of statins in high-risk CAD patients exist. Many guidelines recommend low-density lipoprotein-cholesterol (LDL-C) goal at 70 mg/dl (8-9), but the guideline of American College of Cardiology/American Heart Association (ACC/AHA) supports high-intensity statins and repeated lipid measures (10).

A debate exists about prescribing patterns, eligible patients, high-intensity doses (11-13), combined lipid-lowering therapy, improved outcomes following coronary surgery or intervention (14-15). Therefore, our review of the contemporary literature concerns contemporary status and debates of statin therapy in CAD patients. Our methods of constituting this narrative review include searching MEDLINE with a limit of publication dates between January and December 2017, using search terms of (statins) and (coronary artery disease) which yield 319 trials, of which 104 studies were relevant to the aim of our review.

## Impact of Statins on Biomarkers

The current research proceeds to investigate the role of statins in repairing, stabilization, and regression of coronary artery lesions, which form a

cornerstone in inhibition of cardiac events (16). However, the mechanisms rather than lowering LDL-C to produce beneficial cardiovascular pleiotropic effects, remain multifactorial and unclear.

Statin can modify the number and function of endothelial progenitor cells (EPC) which has a critical role in vascular repairing. The currently main proposed mechanisms include: (1) reduction of micro non-coding RNAs in EPC, helping its differentiation and mobilization; (2) enhancing endothelial-type nitric oxide synthase (eNOS) associated with EPC mobilization; and (3) stimulating the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway to activate eNOS, and hence enhancing mobilization and number of EPC (17).

Statin exhibit potent anti-inflammatory effects on atherogenesis, resulting in reduction of the circulating levels of high sensitivity C-reactive protein (hsCRP) and adhesion molecules (18). A possible mechanism underlying plaque stabilization is reduction of hsCRP with decreased necrotic core (NC), and hence reinforced fibrous cap, 12-month after rosuvastatin therapy (19). Interesting findings demonstrated a beneficial effect of statins on depression, one year following ACS due to attenuated pro-inflammatory cytokines; interleukin (IL)-6 and IL-18 (20).

A debate exists concerning Lipoprotein (a) [Lp (a)] as a biomarker for long-term statin effects on atheroma volume. A recent study indicates modifying long-term statin therapeutic effects on Lp (a) by traditional risk factors including primary hypertension, diabetes mellitus (DM), LDL-C and high density lipoprotein cholesterol (HDL-C) (21). Also, the recent insights from [Study of coronary atheroma by intravascular ultrasound: Effect of Rosuvastatin Versus Atorvastatin] (SATURN) revealed no association of Lp (a) levels with progression of coronary atheroma in patients with CAD using intensive statins and have low on-treatment LDL-C levels (22).

The increased vitamin D levels and reduced platelet reactivity are potential indicators of the pleiotropic high-intensity statins benefit during dual

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antiplatelet therapy receiving high-intensity statins following ACS or elective percutaneous coronary intervention (PCI) (23). Another emerging biomarker of CAD, namely omentin-1, has a dose-dependent increase with atorvastatin therapy. A dose of 40 mg has a greater effect on levels of omentin-1 than does atorvastatin at 20 mg (24).

### Prescription Strategies and Eligibility for Therapy

**Primary Prevention of Cardiovascular Disease:** Low and moderate-dose statins have a confirmed benefit for individuals aged 40-75 years old with a cardiovascular risk factor and 10-year event risk of 7.5-10% (25). The ACC/AHA guideline-based class-I recommendations include persons have 10-year risk of CVD  $\geq$  7.5%, DM, and LDL-C  $\geq$ 190 mg/dL (26). A recent Multi-Ethnic Study of Atherosclerosis (MESA) considers these indications as a superior screening tool for subclinical and clinical CVD (27). The cost-effectiveness analysis revealed that 10-years universal statin use, starting at 2016, vary moderately considering different risk indications and statin toxicity, and affected greatly by pill burden (28).

An interesting point of the current research is to determine possible markers that may help identify individuals eligible for statin therapy. Coronary artery calcium (CAC) score  $>$ 100 has a useful role in decision making for statin therapy. It can help identify individuals at high risk for cardiovascular disease (CVD) and target guideline-based statin therapy to persons likely to have the most benefit (29). Moreover, CAC score  $>$ 100 associated with mortality whether statins recommended, considered, or non-recommended (30). In addition, when high-intensity statins required in asymptomatic individuals, elevated CAC score  $\geq$  300 associated with age, male gender, and fasting blood glucose, thus, individualization of therapy and lifestyle modification will be useful in this instance (31).

Recent studies reported CAC score  $<$ 100 common in persons taking statins in accordance to AHA/ACC and European Society of Cardiology (ESC) guidelines. This may change decision-making of statin therapy, by matching clinical risk to atherosclerotic plaque burden (32), with reclassification of the risk in 50% of people with estimated 10-year CVD risk of 5% to 20% (33). Thereafter, measuring CAC score gains its significance to find the real risk and then avoiding subjects with low 10-year risk for CVD (32-33). This may support individual-physician discussion when decide long-term statin therapy.

A cost-effectiveness study of using CAC score to guide long-term statin therapy compared with treating all patients eligible for statins according to 2013 ACC/AHA guidelines, suggesting that the economic value of both approaches are similar. Therefore, clinicians should account for each preference in context of shared decision-making when choosing good strategy to guide statin decisions (34).

**Secondary Prevention of Cardiovascular Events:** Statins are still recommended as the first-line for secondary prevention after ACS, as the early intensive therapy with atorvastatin 80 mg daily decreases the burden of atherosclerotic plaques, with reduced time to first occurrence of death, non-fatal myocardial infarction (MI), resuscitated cardiac arrest, or hospitalization for unstable angina, hard cardiovascular events, and the need for revascularization in symptomatic patients (35-37). Moreover, statins can decrease morbidity during the acute phase of ACS in patients on chronic pre-treatment, as they can decrease plaque rupture particularly in those with non-ST segment elevation ACS (38). On the other hand, patients with ACS on no-statin therapy have an increased risk of CVD-related death overtime, which remains constant for those on high-intensity statins (39).

Statin effects after ACS correlated with accumulated dose and therapy duration (40), and it is proportional to the achieved LDL-C (41). The influences on lipid levels and cholinesterase activity further confirm the beneficial effects of intensive statin therapy in patients with CAD (42). Moreover, the highest overall quality-adjusted life year (QALY) gain against acceptable costs confirmed the cost-effectiveness of intensive lipid-lowering therapy with statins (43).

Despite the beneficial effects of statins, a dichotomy exists between intention to prescribe and real prescribing of therapy (44). Less than 40% of CAD statin-treated patients attained their recommended LDL-C and non-HDL-C goals due to irregular use and unscheduled dosage (45), with discontinuation rates of 53.7 and 84.3% at one and three-year follow-up, respectively, after ACS (46).

Suboptimal statin use is common early after non-ST elevation acute coronary syndrome (NSTE-ACS) due to muscular symptoms, therefore, keep, and enhance use of high-potency statin therapy can improve outcomes (47). Good

adherence to statin therapy through 6 months after ACS without declined dosage is important to prevent major adverse cardiovascular events (MACEs), with recommendations to give higher tolerable dosage (48).

Patient factors associated with non-use of high-potency statins after ACS include age older than 75 years, female gender, renal dysfunction, heart failure during hospital admission, and lower LDL-C (49). In addition, statin intolerance is an important factor that affect adherence to statins after hospitalization for MI and associated with an increased risk for recurrent MI and CAD events over the year following hospital discharge, in comparison to those on high-intensity statins (50).

### Effects of Combined Therapy

**Combination with Ezetimibe:** Ezetimibe is a non-statin lipid-altering drug reduces intestinal cholesterol absorption. Combination of statins with ezetimibe could help attainment of guideline LDL-C and non-HDL-C goals (45). The greater effects of combination therapy explained partly by its more significant anti-inflammatory effect than mono-therapy (51). Other investigated mechanisms underlying the effects of combination therapy are ameliorating endothelial dysfunction in stented coronary arteries, and larger decreases in oxysterol levels (52). However, the anti-atherosclerotic mechanisms of ezetimibe and ezetimibe-statin combination therapy remains controversial in a recent randomized trial, as it did not result in a significant change in coronary plaque regression compared with statin alone (53).

In a recent 6-year population-based cohort study, using both agents together for patients with ACS and multiple comorbidities associated with lower risks of re-hospitalization for ACS and revascularization (54). Moreover, adding ezetimibe to simvastatin reduces the risk of ischemic stroke after ACS, particularly in patients with a prior stroke (55).

In comparison to intensive statin therapy in patients with ACS, statin-ezetimibe combination therapy has a greater effect on lowering LDL-C, drug-related adverse events, percentage of non-high density lipoprotein-cholesterol (non-HDL-C), and cholesterol absorption (56-58).

Examining effects of statin-ezetimibe combination in special patient groups revealed similar response for both men and women (59), less liver dysfunction than double-dose statin in very elderly patients with ACS (60), and better role than mono-therapy associated with reducing blood lipid levels and improving plaque stability in diabetic patients with CAD (61).

**Combination with Eicosapentaenoic Acid:** Eicosapentaenoic acid (EPA), an omega-3 fatty acid, lowers plasma triglycerides, reduces levels of pro-inflammatory cytokines and chemokines, and may decrease coronary plaque vulnerability and prevent plaque progression (62). In comparison to statin monotherapy, combination of statins with EPA therapy during the first 24 hours after PCI reduces inflammation and ventricular arrhythmia, and reduces cardiovascular events after primary PCI if early initiated in patients with ACS (63).

Combination therapy reinforces plaque stabilization particularly in patients with stable angina, and appears a promising option in patients under intensive and strong statin therapy to decrease residual CAD risk (64-65), particularly in patients with a higher baseline risk for residual disease (66).

**Combination with Nutraceuticals:** Nutraceuticals are combination of natural components. Similar to ezetimibe, nutraceuticals are alternative therapy to statins in patients intolerant to high-dose statins, as they lower LDL-C concentration when used alone or in association with other agents (67).

Low-dose statin combination with nutraceuticals such as Armolipid Plus (red yeast rice, policosanol, berberine, folic acid, coenzyme Q10 and astaxanthin) represents a valuable therapeutic option in patients with CAD and high-dose statin intolerance (68).

### Impact on Outcomes after Coronary Revascularization

**Impact on Outcome after Percutaneous Intervention:** In the current actual practice, long-term statin therapy before primary PCI improves epicardial perfusion in patients with stable angina (69) and treatment outcomes of acute MI (70). Both rosuvastatin and atorvastatin are suitable and well tolerated to control lipid levels and prevent risk of cardiovascular events after PCI (71). The benefit of high-dose atorvastatin to decrease the risk of MI and cardiovascular adverse events supports its current use as an adjunct to aid PCI (72).

The loading high-dose of rosuvastatin before PCI in patients with ACS has more beneficial effect than the conventional dose, however, the limited quality of studies indicates further evidence (73). In addition, a high-dose of

rosuvastatin can delay ventricular remodeling, inhibit malignant remodeling, improve left ventricular systolic function, and decrease the prevalence of adverse events, 3 months after emergent PCI (74).

A controversy exists about the effect of gender on long-term outcomes of statin therapy after PCI. In a recent study with a median follow-up period of 6.3 years, the cumulative rate of MACE were higher in women than in men, however, there was no significant association of female gender with MACE after adjusting for age and other risk variables (75).

The primary targets for maximizing the beneficial effects of statin therapy after PCI are elderly patients and those with chronic kidney disease (76). Even in patients older than 80 years, statin therapy through 5 years after PCI associated with significant reduced risk for cardiovascular events (77). In patients with ACS, received either 40mg simvastatin or 20mg atorvastatin daily, for at least 6 months after PCI, the rate of declined renal function was similar in both drug groups (<27%) (78), however, comparative renoprotective effects of statins need further evaluation.

In patients with diabetes mellitus, which affects the prognosis of PCI, a high intensity statin therapy increases EPC levels, decreases in-stent neointima area and volume, and does not affect the degree of stent re-endothelialization at 3 months after drug-eluting stent (DES) implantation (79). Interestingly, pitavastatin therapy (4 mg daily) has more favorable effects than atorvastatin (20 mg daily) on glucose control in patients with non-ST elevation ACS received successful PCI (80).

In summary, literature shows favorable outcomes after PCI whether statins prescribed as long-term pretreatment or as an adjunct to PCI. However, a controversy exists on the use of high-dose rosuvastatin and the proper type of loading dose before PCI. Despite the beneficial effects of statins after PCI in elderly, chronic kidney disease and diabetics, there is a need for further studies to compare the effects of different statin types and doses.

**Impact on Outcome after Coronary Artery Bypass Grafting:** Preoperative statin therapy has a beneficial effect to decrease risk of mortality after coronary artery bypass grafting (CABG). However, little data exists on optimal dose and timing of statin therapy. A recent study demonstrated that both preoperative statin use <24 hours and a dose of >20 mg associated with decreased 30-day all-cause mortality after CABG (81). In contrary, another recent study reported dose-independent pattern of statin therapy to decrease in-hospital mortality and MACE in patients undergoing CABG for ACS (82).

The biggest beneficiary of statin pretreatment in CABG is reduction of postoperative atrial fibrillation (AF), attributed to modulation of systemic inflammatory markers (cytokines, C-reactive protein) (83). A controversy remains about the effect of preoperative statin therapy on renal outcomes after isolated CABG. In a recent study, although preoperative statin therapy associated with lower risk of postoperative renal dysfunction and the need for renal replacement, it did not decrease the risk of acute kidney injury (84). Interestingly, pretreatment with atorvastatin reduced the risk of bleeding and blood products use after on-pump CABG, probably due to a reduction in the postoperative inflammatory response. A recommendation remains for statin continuation at the highest tolerable dose before cardiac surgery (85), although further well-designed studies required.

#### Predicting Residual Risk for CAD

The vascular response to statin therapy in patients with CAD, due to stabilization of thin-cap fibroatheroma, associated with favorable cardiovascular outcomes. Residual risk for CAD remains due to lack of the favorable vascular response. Chronic kidney disease is an independent clinical predictor for unfavorable vascular response to statin therapy (86).

Recent investigated biomarkers associated with residual risk of CAD following coronary revascularization despite statin treatment determined that increased cholesterol absorption marker and apoB48 concentration lead to de-novo lesions (87). In addition, higher levels of Lp(a) carries a residual cardiovascular risk for adverse events among CAD patients receiving intensive statin therapy after PCI (88), however, correlation of measured Lp(a) levels and coronary atheroma progression was absent in CAD patients prescribed long-term maximally intensive statin therapy who have low on-treatment LDL-C levels (22).

#### SUMMARY

A controversy exists regarding biomarkers of the pleiotropic effects associated with statin therapy in CAD patients. The investigated mechanisms include vascular repairing by enhanced endothelial progenitor cells, plaque

stabilization due to reduction of hs-CRP and necrotic core, and attenuated cytokines effect on depression following ACS. Emerging biomarkers of statin effects include lipoprotein (a), vitamin D levels, and serum omentin-1 levels.

The targeted universal statin use for primary prevention of CVD may depend on the inutility caused by pill burden. Quantification of coronary artery calcium score in addition to the guidelines improves stratification of subjects at high risk for cardiovascular events. The CAC score is an important complementary tool for risk stratification in asymptomatic persons need high-intensity statins. The role of each preference for approach of therapy in context of shared decision-making with clinicians supported by the similar economic values of CAC scoring and guideline-based primary prevention for all eligible persons.

Statins are the first-line treatment for the secondary prevention after ACS. In patients on chronic pre-treatment, statins have beneficial effects on morbidity during the acute phase of ACS. The beneficial effect of statins for secondary prevention in CAD patients correlated with its dose and therapy duration. The cost-effectiveness results with the highest overall quality-adjusted life year (QALY) gain against acceptable costs adds an economic benefit of intensive statin therapy. A contrast exists between intention to prescribe and real prescribing behaviors of high-intensity dose statin for patients with CAD that may affect guideline recommended cholesterol goals. Discontinuation of statins or non-adherence carries an adverse prognosis after discharge of patients with ACS. Non-use of high-potency statins after ACS associated with elder age, female sex, renal dysfunction, heart failure during admission, lower LDL-C, and statin intolerance.

The combination of statins with other agents such as ezetimibe, eicosapentaenoic acid, and nutraceuticals is a promising option to increase benefits of lipid lowering agents or subsiding high-dose statins. However, the mechanisms of subsequent effects due to combination with ezetimibe remain unclear. Adding ezetimibe to statins is beneficial for patients with ACS and multiple comorbidities, and may replace intensive statin therapy. Very elderly and diabetic patients are good targets for combination therapy. Early initiation of statins with eicosapentaenoic acid after ACS has a significant role to decrease intensive statin therapy and residual CAD risk. Nutraceuticals is a valuable therapeutic option allowing the use of low-dose statins instead of intolerable high-doses.

The beneficial effects of preoperative statin therapy on outcomes after CABG are widely reported. A controversy remains about optimal dose and timing of therapy, in addition to the effect of statins on renal outcomes. Modulation of systemic inflammatory markers may explain the beneficial effect of statin pretreatment on occurrence of AF after CABG. An emerging benefit of statin therapy is reduction of bleeding risk after on-pump CABG but it requires more evidence.

The residual risk remains for CAD despite statin therapy. Debate remains on proper clinical factors and biomarkers associated with the residual risk for CAD undergoing coronary revascularization despite statin therapy. The current investigated factors underlying residual-risk include chronic kidney disease, increased cholesterol absorption marker, apoB48 concentration, and higher serum levels of lipoprotein (a).

#### CONCLUSION

Statins have a great impact on primary and secondary prevention of CAD, however, many issues need an investigation. The points of debate and inconclusive data may be related to variation in study design, presence of scant randomized trials comparing the effects of statin therapy, variation in dose and type of statins, and absence of universal biomarkers of statin cardiovascular effects.

As proved in the contemporary literature that CAC scoring can reclassify asymptomatic individuals at risk for ASCVD before initiating statin therapy, we recommend more application of CAC scoring for shared decision making in adherence to clinical scoring systems, particularly in moderate risk persons (5-20% 10-year ASCVD risk) and in those with a family history of premature CAD. As a controversy exists about the adverse events of high-dose statins, a recommendation for balance therapy remains to reserve these doses for patients with ACS and when the therapeutic target of LDL-C at 70 mg/dl could not obtained with moderate-doses.

Moreover, we recommend future studies to detect the emerging biomarkers of statin pleiotropic effects, persons eligible for therapy, reasons for the gap between recommendations of guidelines and real-life prescription of statins, predictors of the statin effects in combination with ezetimibe, pre-procedural factors enhancing benefit-based therapy, ideal doses of statins before revascularization, and reasons underlying the residual risk after therapy.

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**CONFLICT OF INTEREST**

The authors declare that they have no competing interests.

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