The current research proceeds to investigate the role of statins in repairing, Impact of Statins on Biomarkers relevant to the aim of our review. (coronary artery disease) which yield 319 trials, of which 104 studies were between January and December 2017, using search terms of (statins) and statin therapy in CAD patients. Our methods of constituting this narrative A debate exists about prescribing patterns, eligible patients, high-intensity statin therapy 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 congential 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; statins; prevention; acute coronary syndrome; coronary revascularization

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

Yasser Ali Kamal1, Seham Abdel-Wakeel Abdel-Gaber2

Statins inhibit hepatic biosynthesis of cholesterol where they prevent mevalonate formation, and inhibit 3-hydroxy-3-methylglutaryl-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 allcause 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 constructing 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.

Statins 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).

Statins exhibit potent anti-inflammatory effects on atherogenesis, resulting in reduction of the circulating levels of high sensitivity Creatine 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) 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
antiplaque 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 ≥ 7.5%, DM, and LDL-C ≥ 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-year 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 ≥ 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 decision when decide longterm statin therapy.

A cost-effectiveness study of using CAC score to guide longterm 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 they intensify intensive therapy with atorvastatin 50 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 reduce 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 cholesteraese 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 the acceptable costs confirmed the cost-effectiveness of intensive lipolysering therapy with statins (43).

Despite the beneficial effects of statins, a dichotomy exists between intention to prescribe and real prescripting 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 musclar 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-lowering 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 angora, 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, longterm 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
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 controversy exists about the effect of gender on long-term outcomes of statin therapy in patients with CAD, due to de-novo lesions (87). In addition, higher levels of Lp(a) carries an increased cholesterol absorption marker and apoB48 concentration 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 subbing high-intensity 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.

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

Statin therapy has 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 be 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, preprocedural factors enhancing benefit-based therapy, ideal doses of statins before revascularization, and reasons underlying the residual risk after therapy.

Curr Res Integr Med Vol 3 No S1 Winter 2018 7
REFERENCES

Preventive effects of statin therapy


