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EDITORIAL COMMENT

Statin Adherence and Effects on Outcome in Premature Coronary Artery Disease*

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Lipid lowering therapy with statins is the cornerstone of treatment of coronary artery disease (CAD). Meta-analysis of secondary prevention trials showed an average 21% reduction of major cardiovascular events for every 1 mmol/L (39 mg/dL) reduction in low density lipoprotein (LDL) cholesterol. Recent national guidelines recommend earlier age of lipid screening and treatment, intensification of LDL-lowering goals, and maintaining that target long term to prevent recurrent CV ischemic events.[1]

Adherence to statin therapy in real world stands is in sharp contrast to the guidelines with only 30% adherence at 2 years after acute coronary syndrome.[2] There is a graded inverse association between statin adherence and intensity with mortality in stable atherosclerotic CV disease. Adherence has been found to be lower in women, younger and older adults, Blacks and Hispanics vs Whites, and best compliance rates are seen in the 65- to 74-year-old adults.[3]

In this issue of the journal, the study in patients with premature CAD (defined as >50% angiographic stenosis) in men <50 years and women <55 years by Vikulova et al[4] is an important addition to the subject of statin adherence. This observational study evaluated longitudinal average achievement of LDL and non-high density lipoprotein (HDL) target (<70 mg/dl LDL cholesterol and <92 mg/dL non HDL cholesterol), its relationship with adherence to statin therapy and effects of both on CV outcome over a 3 year period in a cohort of 476 patients—68% with acute coronary syndrome and 28% stable angina. At index event, surgical coronary revascularization was performed in 21%, percutaneous in 62% and angiography alone in 17%. The authors used treatment from pharmacy dispensation records and adherence as proportion of days covered, defined by the number of doses dispensed in relation to a dispensing period, with proportion of days covered ≥80% as optimal. Majority of patients received high intensity statin therapy (73%) at baseline and achieved guideline recommended lipid level at least on 1 occasion (74%). However, consistent LDL target at 1, 2, and 3 years was achieved in only 39, 31 and 27% respectively. 27% of patients were never at target. Numbers were worse for non-HDL-cholesterol target. 18% of patients discontinued lipid lowering and adherence decreased over time with only 43.5% of patients continuously treated at 3 years. Higher intensity statins did not achieve lower LDL goal. Adherence to statins was lower than for ezetimibe or PCSK9 inhibitor and antihypertensives or diabetic medications. Time weighted average exposure to LDL of 1 mmol/L but not the lowest LDL achieved was associated with a higher risk of combined major adverse cardiac events (MACE) of death, myocardial infarction, coronary revascularization, or unstable angina, which occurred in 15.5% of study cohort. Each 1 mmol/L increase in time weighted LDL exposure increased MACE risk 2-fold (after adjustment for age, sex, hypertension diabetes, and continued smoking) whereas the lowest achieved LDL had no effect on outcome.

The study raises provocative questions on lipid lowering adherence following a cardiac event in patients with premature CAD and its effect on MACE. The dichotomy between 43.5% adhering to therapy

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and only 27% consistently achieving LDL goals at 3 years, indicates suboptimal dosing or lack of up titration of dosing due to physician or patient related or social factors. The authors propose to use time weighted exposure to LDL (or non-HDL-cholesterol) in addition to isolated lipid levels as a metric of lipid control.

Besides premature CAD, the study cohort had high prevalence of risk factors, 26% were active smokers, 36% had markedly elevated Lpa, 70% had familial hypercholesterolemia, and 39% had family history of premature CAD. Seventeen percent of patients had prior CVD or chronic kidney disease which was not used in multivariable analysis. In addition, the impact of prior lipid use on adherence was not evaluated. Lipid levels were not available in 11% and were imputed from statin dose. Target LDL and MACE among patients with elevated Lpa were not reported.

Poor adherence to statins is very prevalent and is related to multiple factors at patient, provider and health system level. Studies have found a U-shaped relationship for age with those <50 years or >70 years less adherent. Women, Blacks and Hispanics, those with poor socio-economic status have high non adherence rate,[5] whereas higher socioeconomic class, increased health literacy, and presence of chronic CV conditions such as history of myocardial infarction, CAD, diabetes, and hypertension are associated with increased adherence. Self-perceived adverse effects of statins on cognition, muscles and development diabetes are the commonest cause of nonadherence besides "present bias" in the young (long time interval before beneficial statin effects), denial of health issues, lack of symptoms, pill aversiveness, suspicion on manufacturing practices, poor health insight, and poor understanding of statin effects have been identified as barriers to statin adherence.[6] Complexity of medical regimen, high intensity statins from the start, decreased frequency of visits with care provider, or lipid testing as well as disregard of the care provider to patients' perceived side effects from statins, poor socioeconomic status and health literacy, and other chronic illnesses are other identified factors.

The study findings among patients with premature CAD are sobering especially as the LDL target in high risk subjects is now <55 mg/dL. Better adherence to nonstatin therapies Ezetimibe and PCSK-9 inhibitors in the study suggests that earlier initiation of combination therapy particularly in younger adults may help to improve adherence and LDL lowering. Improved physician patient partnership including explanation of benefits of statins to patients on health outcomes,[4] follow-up communication by allied health professionals to determine side effects and other barriers to statin intake may improve compliance. Education by pharmacists during drug dispensation as well as input from behavioral therapists may help, although modifying behavioral risk factors without patient motivation is quite challenging. Obtaining coronary artery calcium score has been shown to increase medication adherence probably due to more aggressive physician medical management more so than patient motivation. Over 70% of subjects in the current study had attended university or college and compliance for nonstatin drugs was better than for statins suggesting that education or health literacy had lesser role in nonadherence.

Improving adherence to statin therapy is also important for health care stakeholders due to the cost associated with suboptimal target lipid goals in treating recurrent CV events. The study highlights the need for novel methods of improving adherence to medical therapy and life style modification. Creative studies incorporating widely used technologies like smart phones with specially designed apps to allow better disease insight (education on CAD and statin benefits in primary and secondary prevention setting), visualization of atherosclerotic plaque in the coronaries or in carotids (by coronary artery calcium or carotid ultrasound) and remote monitoring for health behaviors such as exercise, smoking cessation, calorie counting etc,[7] besides frequent communications with patients and follow up to encourage and confirm adherence are needed.

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