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Review

Management Strategies to Lower Risk of Atherosclerotic Cardiovascular Disease (ASCVD) in High-Risk South Asians

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Abstract

The review focuses on South Asians (SA) with lipoprotein abnormalities and addresses risk stratification and management strategies to lower atherosclerotic cardiovascular disease (ASCVD) in this high-risk population. SAs have lower low-density lipoprotein cholesterol (LDL-C) compared with Whites and at any given LDL-C level, higher risk of myocardial infarction (MI) and coronary artery disease (CAD) are seen in SA ethnicity when compared with other non-Asian groups. SAs have higher triglycerides and lower high-density lipoprotein cholesterol (HDL-C) with smaller particle sizes of HDL-C compared with Whites, which strongly indicates high prevalence of metabolic syndrome in SAs. Compared with other ethnic groups SAs have higher lipoprotein (a) (Lp(a)) levels and this unique Lp(a) profile plays a vital role in the elevated risk of ASCVD in SAs. Studies which evaluate dietary patterns of SAs in the U.S show high consumption of carbohydrates and saturated fats. SA ethnicity has a high-risk lipoprotein profile and multifactorial lipid abnormalities play a central role in the pathogenesis of CAD. To understand the impact of the various lipoproteins and their contribution to increasing ASCVD in SAs more studies are desired. In high-risk groups aggressive lowering of LDL-C by using lifestyle modification including dietary changes and medications, such as statins, are essential in overall CAD risk reduction.

Keywords: Lipids, South Asians, dyslipidaemia, low-density lipoprotein, high-density lipoprotein

Introduction

South Asians (SAs), individuals who originate from countries including India, Pakistan, Nepal, Bangladesh, Sri Lanka, and Bhutan, comprise approximately 1.8 billion or one-quarter of the world's population.[1-4] Higher ASCVD risk in SAs may be explained, in part, by a higher prevalence of traditional risk factors such as diabetes, dyslipidaemia, hypertension, obesity, and tobacco use.[5,6] Additionally, SAs experience premature coronary artery disease (CAD) with 3–5-fold higher risk of morbidity and mortality from heart disease as compared with individuals from other countries.[6-9] SAs are a heterogeneous population arising from various religions and racial and cultural backgrounds; however, they share several characteristics.[10-14]

In the Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction (INTERHEART) case-control study of 14,820 individuals from 52 countries that included acute myocardial infarction (AMI) cases and controls from 5 different SA countries, it showed an association between hypertension, diabetes, smoking, waist/hip ratio, diet, physical activity, and apolipoprotein levels with AMI among all populations including SAs.[15] The risk factors associated with the highest population attributable risk among SAs were elevated Apo B100/Apo A-I ratio (46.8%), waist to hip ratio (37.7%), and smoking (37.5%).[5,6,15] Dyslipidaemia was found to have the strongest association with AMI in SAs, indicating that it is vital in understanding the pathogenesis and evolution of ASCVD in SAs. Kalhan *et al.* demonstrated that SAs that migrate to the U.S have an adverse metabolic profile with an abnormal plasma lipid profile, higher plasma insulin levels, and truncal skin-fold thickness in their young adulthood compared with their European counterparts.[16] In addition, the SHARE study evaluated disease risk factors and its relationship to subclinical atherosclerosis in 985 participants of SA, European, and Chinese descent residing in Canada. SAs were found to have higher total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and lipoprotein (a) (Lp(a)) levels, as well as increased prevalence of glucose intolerance and other risk factors compared with Europeans and Chinese.[17,18]

Dyslipidaemia

Total Cholesterol, LDL-C, and VLDL-C

Elevated cholesterol, particularly LDL-C, is a well-established risk factor for coronary artery disease (CAD) and a target for therapy to decrease ASCVD risk. Elevated LDL-C is also a risk factor for CAD in SAs with risk of AMI increasing with rising LDL-C levels.[19] Karthikeyen *et al.* demonstrated a large variation in LDL-C levels among different Asian subgroups in the INTERHEART study. SAs had lower mean LDL-C levels compared with people from Southeast Asia (Singapore, Malaysia, Thailand, and the Philippines) and Japan (LDL-C 125 mg/dL compared with 150 mg/dL in Southeast Asians and 134 mg/dL in Japanese).[15]

Moreover, for a given LDL-C level, the risk of MI and CAD is higher among SAs compared with other groups.[15,20,21] This indicates that SAs have a high risk of AMI even at normal to low LDL-C levels. This heightened risk among SAs is likely secondary to smaller LDL particle sizes that are denser and therefore more atherogenic.[22] In a study by Kulkarni *et al.*, the prevalence of small dense LDL (sdLDL) particles was higher in Asian Indians compared with Whites (44% versus 21%; $p< 0.05$).[23] SAs with high levels of small dense LDL particles also have high fasting insulin levels, further suggesting that insulin resistance may be playing an important role in the increased prevalence of small, dense LDL particles.[23,24] Overall, data suggest that smaller, denser LDL particles and higher concentrations of apolipoprotein B (ApoB) may be the driving factor in the elevated risk of CAD even at lower LDL-C concentrations.

HDL-C

High-density lipoprotein cholesterol (HDL-C) concentrations are generally inversely associated with ASCVD.[25] Compared with other ethnic groups, SAs tend to have lower HDL-C and apolipoprotein A (ApoA) levels.[2,15,26] However in SAs, HDL particles may be dysfunctional with pro-inflammatory and pro-oxidant effects, therefore contribute to increased ASCVD risk.[27,28] In a small cross-sectional study by Dodani *et al*., 50% of the participants had dysfunctional HDL particles with HDL inflammatory index of ≥1.0, and dysfunctional HDL-C was significantly correlated with higher intimal medial thickness in the common carotid artery (CCA-IMT).[29]

This pattern of low HDL-C levels and dysfunctional HDL particles has been linked to insulin resistance and the increased prevalence of multiple sclerosis (MS) in SAs.[30,31] In a study that evaluated MS and its association with HDL function, APOA1 gene polymorphisms and subclinical CAD, there was an association between MS and ApoA1 levels as well as APOA2 polymorphisms. The researchers postulated that this could lead to dysfunctional and low HDL in SAs predisposing them to an increased ASCVD risk.[32]

SAs tend to have HDL particles that are smaller in size, which could also be contributing to the abnormal function of HDL. Superko *et al*. studied metabolic disorders linked to CAD in Asian Indian men compared with age-matched men not of Indian descent; the Asian Indian group had a higher prevalence of low HDL2b ($p<0.0002$), even among the subgroup with HDL-C >40 mg/dL.[33] They suggested that this could explain impaired reverse cholesterol transport in SAs. In a study comparing concentrations of large and small HDLC in Asian Indian men to white men in the Framingham Offspring Study, the Asian Indian men had higher concentrations of small HDL-C, lower concentrations of large HDL-C, and smaller particle size compared with Whites.[30]

Triglycerides

SAs tend to have a higher prevalence of hypertriglyceridemia. In a study by Misra *et al.*, SAs had higher plasma triglycerides than Whites, with dyslipidaemia occurring at lower levels of BMI in SAs.[34,35] Another comparative study revealed that Asian Indians in the Unites States compared with Whites have 2-fold higher hepatic triglyceride content (1.94 vs. 0.75%, respectively; $p<0.001$.[36] SAs may be predisposed to increased levels of ectopic fat (deposition of triglycerides in non-adipose tissue such as the liver and muscle) that disrupts glucose-insulin metabolism resulting in MS and insulin resistance that contribute to elevated triglycerides. Shah *et al.* found higher hepatic fat, intermuscular fat, and visceral fat in SAs compared with other ethnicities (Whites, African Americans, Chinese Americans and Latinos).[37] SAs also have a less favourable adipokine profile which could potentially play a vital role in their predisposition to cardiometabolic disease.[37] In a study evaluating dyslipidaemia patterns in various races, Asian Indians had a higher risk of having combined dyslipidaemia which

included high triglycerides. They were found to be twice as likely to have higher triglycerides compared with Whites (55.3% vs. 42.5%) with OR 2.12 for women and 2.67 for men; p<0.001.[38]

Cholesteryl ester transfer protein (CETP) is a plasma protein that mediates the transfer of triglycerides from triglyceride-rich lipoproteins to HDL and LDL particles in exchange for cholesteryl esters resulting in low HDL-C and small dense LDL.[39] Abnormalities in CETP are linked to accelerated atherosclerosis. SAs have higher CETP activity compared with Whites and this in turn is positively associated with higher triglycerides and LDL-C, but inversely related to HDL-C.[40]

Lp(a)

Elevated Lp(a) levels are an independent risk factor for ASCVD.[41-44] Some but not all studies have shown that SAs have high Lp(a) levels.[45,46] Palaniappan *et al.* compared 210 women <30 years old from three different ethnic groups (Whites, African Americans, and Asian Indians) in the United States. Asian Indian women had higher Lp(a) levels than Whites but lower than African American women (0.3 g/L in SAs, 0.5 g/L in African Americans, and 0.2 g/L in Whites, p<0.0001).[47]

There are some data to suggest that there is an association between Lp(a) and atherosclerosis in SAs. In a study looking at the association between Lp(a) and subclinical atherosclerosis by measuring CCA-IMT in diabetic South Indians, Lp(a) levels had a strong association with CCA-IMT.[48] In another study that evaluated Lp(a) levels in young north Indian patients with MI, the mean Lp(a) was 22.3±5.4 mg/dL in MI patients compared with 9.3±22.6 mg/dL in the healthy control group.[49] In the INTERHEART study, Lp(a) levels and risk of MI were studied among seven ethnic groups. Higher Lp(a) concentrations were associated with an increased risk of MI and a high population burden was noted in SAs with the population attributable risk of high Lp(a) for MI to be 9.5% in SAs compared with 0% in Africans.[50]

The Mediators of Atherosclerosis in South Asians Living in America (MASALA) study was a prospective observational cohort study of 906 SA men and women aged 40–84 years living in the U.S, designed to study cardiovascular risk factors and subclinical CVD.[51,52] In the MASALA, Lp(a) had no association with subclinical atherosclerosis including coronary artery calcium (CAC) (p=0.98), internal carotid IMT (ICA-IMT) (p=0.46), and CCA-IMT (p=0.97).[53] Additionally, Lp(a) had no association with progression or incidence of CAC in the MASALA.[4]

Management of Dyslipidaemia

Risk Assessment Tools

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) ASCVD risk assessment guidelines included the Pooled Cohort Equations (PCE) to estimate the 10-year risk by race/ethnicity (Whites or African American) and sex for the first ASCVD event. For other ethnicities including SAs, the guidelines suggest using the equation for Whites and SA ancestry is now included as a "risk-enhancing factor" in the new cholesterol guidelines; therefore, after calculation of PCE, this risk-enhancing factor may favour initiation of statin or if already on statin intensification of therapy.[54]

Use of Statins

A consensus statement on dyslipidaemia management in SAs was published by Chandra *et al.*[55] According to this statement, statins are the mainstay in treatment of dyslipidaemia in SAs to lower LDL-C with a goal of LDL-C <100 mg/dL in high-risk and LDL <70 mg/dL in very high-risk patients.

A study by Gupta *et al*. evaluated statin effects on LDL-C and HDL-C in SAs and whites.[56] They found one large trial that included SAs was the Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial, with India being one of the participating countries. HOPE-3, a primary prevention trial looking at patients with intermediate risk, demonstrated that treatment with rosuvastatin 10 mg daily resulted in a significantly lower risk of cardiovascular events than placebo.[57] A small study looking at pharmacokinetics and pharmacogenetics of statins in Asian Indians compared with Whites revealed higher peak plasma concentrations in Asian Indians, indicating possible increased risk of side effects at higher doses of statins in SAs.[58] The SLCO1B1 C allele is a risk factor for statin-induced myopathy by causing lower statin uptake by the liver. A study done in Kerala, a region of southern India, revealed the presence of this variant in 15% of the population further postulating increased propensity for statin-induced myopathy in certain groups of SAs.[59,60]

Based on the current guidelines, it is reasonable to treat SAs on maximally tolerated statins like other ethnic groups while closely monitoring for side effects. Management strategies for dyslipidaemia in SAs are largely based on the new guidelines published by AHA/ACC and other societies in 2018 **(Figure 1)**.[54]

- In SAs aged 40–75 years without diabetes mellitus who have LDL-C >70 mg/dL and intermediate risk (7.5%–19.9%), initiate moderate intensity statin therapy and consider initiating statin therapy for those at borderline (5.0%–7.5%) risk, as being SA is a risk-enhancing factor.
- If risk-based decisions remain uncertain, among the intermediate risk group with an ASCVD score ≥7.5%–19.9% or among select borderline risk (5.0%-7.5%), it is reasonable to measure CAC to guide decisions to start a statin.
- In SAs with severe hypercholesteremia (LDL-C ≥190 mg/dL) start high-intensity statin—no need to calculate the ASCVD risk score.
- Since being SA is a risk-enhancing factor, if risk <5%, we recommend consideration of measuring CAC.

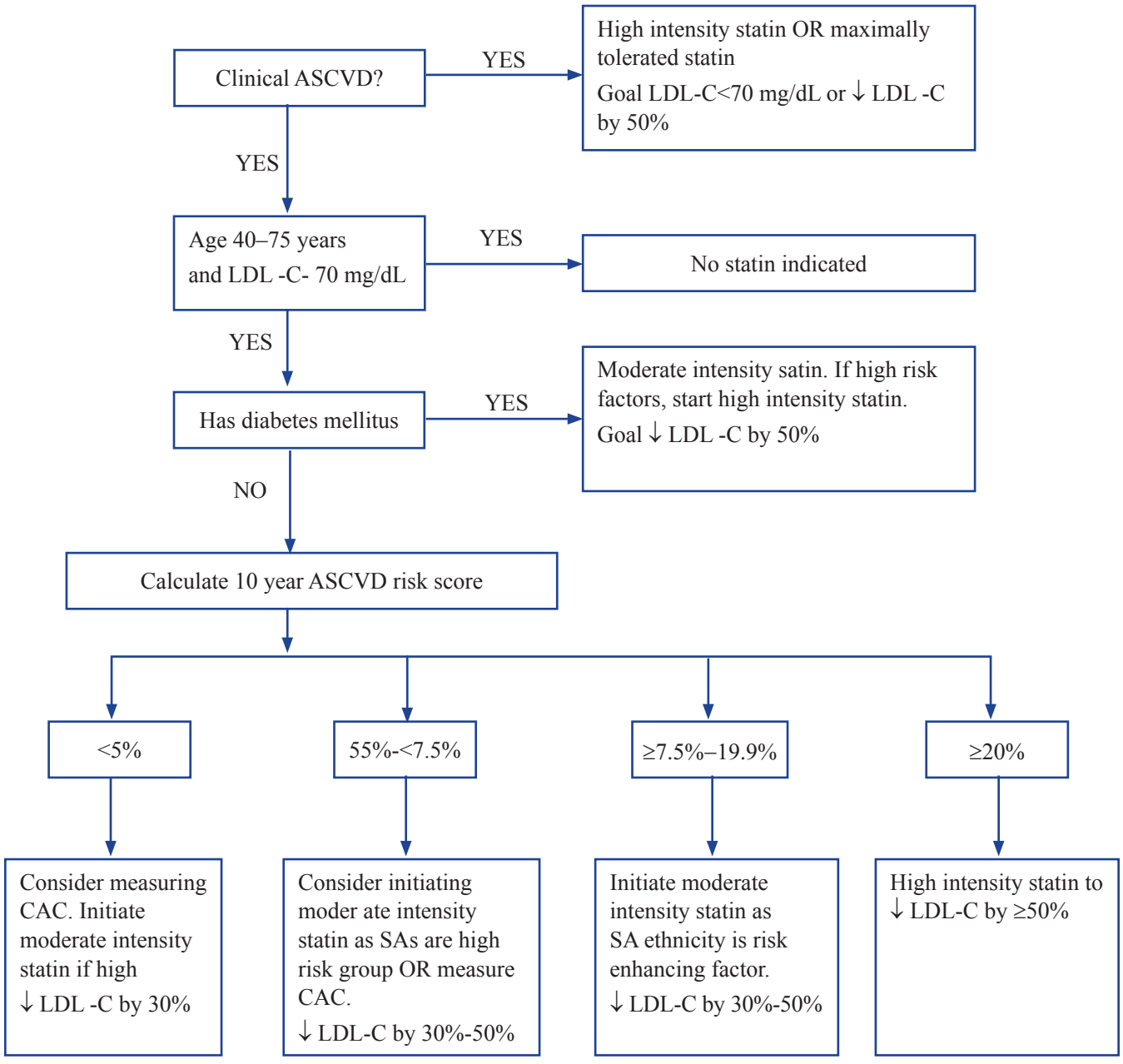

Figure 1. Management of lipids in SAs based on AHA/ACC 2018 guidelines and Chandra *et al.* consensus statement [54,55]

Combination Drug Therapy

Addition of Ezetimibe

Ezetimibe is a non-statin medication used to treat hyperlipidaemia. It is an inhibitor of intestinal cholesterol absorption and reduces total cholesterol, LDL-C, apolipoprotein B, and non-HDL-C. Ezetimibe lowers LDL-C by inhibiting the activity of Niemann-Pick C1-like 1 (NPC1L1) protein.[61]

The Intensive Versus Standard Blood Pressure Lowering to Prevent Functional Decline in Older People (INFINITY) study, comprising SA Canadians assessed the effectiveness of ezetimibe in patients with CAD or diabetes who were already on statin therapy in a randomized trial.[62] At 6 weeks, patients that took ezetimibe plus statin were more likely to achieve goal LDL-C <77 mg/dL compared with the statin doubling group (68% vs. 36%; p=0.03) with an OR (95% CI) of 4.0 (1.2, 13.2). At 12 weeks, 76% of ezetimibe plus statin patients achieved target LDL-C compared to 48% (p=0.047) of the statin doubling group (adjusted OR (95% CI)=3.31 (1.01, 10.89)). The ezetimibe plus statin was generally well tolerated.[62] The 2018 AHA/ACC guidelines stated that in patients who are very-high risk, we should aim to reduce LDL-C by 50% and that an LDLC threshold ≥70 mg/dL despite maximally tolerated statin would favour the additional initiation ezetimibe as a second-line agent.[54]

Role of Fibrates

Fibrates increase HDL-C, lower triglycerides, and increase the LDL particle size. This pattern can potentially benefit SAs as they are prone to higher triglycerides, dysfunctional HDL, and smaller LDL particles. There are no clinical outcome trials in SAs looking at effects of fibrates. There were two large studies in the U.S which evaluated whether fibrates reduce CVD risk in diabetic patients, including the Fenofibrate Intervention and Endpoint Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) studies.[63,64] Both included participants who were predominantly White. In the FIELD study, fenofibrate did not significantly reduce the primary outcome of coronary events, but it did reduce total CVD events due to non-fatal MI and revascularizations, but benefits were seen in specific subgroups i.e., with triglycerides >204 mg/dL and HDL-C <34 mg/dL.[63] In the ACCORD study, fenofibrate and simvastatin did not reduce the rate of fatal CVD events, non-fatal MI, or non-fatal stroke compared with simvastatin alone.[64] Post hoc analysis of the ACCORD study reported exactly similar findings to subgroup analysis of the FIELD study.[65]

PCSK-9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK-9) is a protease that promote the degradation of LDL receptors. PCSK-9 inhibitors are a newer class of drugs that effectively lower LDL-C levels. The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk (FOURIER) trial used evolocumab, a monoclonal antibody that inhibited PCSK-9 and evaluated its effects on clinical outcomes in patients with CVD in a predominantly white population.[66] Compared with placebo, the mean percent reduction in LDL-C levels in patients taking evolocumab was 59%. Evolocumab treatment reduced the risk of CVD death, MI, stroke, hospitalization for unstable angina, or revascularization (9.8% vs. 11.3%; hazard ratio, 0.85; 95% CI, 0.79 to 0.92; p<0.001) and the key secondary end point which included CVD death, MI, or stroke (5.9%vs. 7.4%; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; p<0.001).[62] The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial where alirocumab, taken every other week, reduced ischemic events significantly, including myocardial infarction and all-cause mortality when compared with placebo among patients with an acute coronary syndrome in the preceding 1–12 months.[67] The primary outcome (CAD death, MI, ischemic stroke, unstable angina) for alirocumab compared with placebo was 9.5% vs. 11.1%, hazard ratio (HR) 0.85, 95% CI 0.78–0.93, p<0.001. Both these large studies included participants that were predominantly White. Further studies in SAs are needed to evaluate if similar reductions in LDL-C and overall mortality benefit are seen with use of PCSK-9 inhibitors. SAs are a high-risk group so for those patients with LDL-C >70 mg/dL despite being on maximal tolerated statin plus ezetimibe, PCSK-9 inhibitors should be considered to help LDL-C reduction to achieve goal levels.

Conclusions

The abnormal lipid profile in SAs include more atherogenic LDL-C even without significant elevations in LDL-C levels, low and dysfunctional HDL, elevated triglycerides related to insulin resistance, and high Lp(a) levels compared with whites. For

any given LDL-C, SAs exhibit a higher risk for CAD. For management of dyslipidaemia, the Western guidelines including AHA/ACC/Multi-Society 2018 lipid guidelines that included SAs as a risk-enhancing factor serve as an updated guide to manage SAs with abnormal lipid profiles and elevated ASCVD risk.

Declaration of conflicting interests

The author declares no conflict of interest.

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