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Lipids in South Asians: Epidemiology and Management

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Abstract

Purpose of Review—This review focuses on lipoprotein abnormalities in South Asians (SA) and addresses risk stratification and management strategies to lower atherosclerotic cardiovascular disease (ASCVD) in this high-risk population.

Recent Findings—South Asians (SAs) are the fastest growing ethnic group in the United States (U.S) and have an increased risk of premature coronary artery disease (CAD). While the etiology may be multifactorial, lipoprotein abnormalities play a key role. SAs have lower low-density lipoprotein cholesterol (LDL-C) compared with Whites and at any given LDL-C level, SA ethnicity poses a higher risk of myocardial infarction (MI) and coronary artery disease (CAD) compared with other non-Asian groups. SAs have lower high-density lipoprotein cholesterol (HDL-C) with smaller particle sizes of HDL-C compared with Whites. SAs also have higher triglycerides than Whites which is strongly related to the high prevalence of metabolic syndrome in SAs. Lipoprotein a (Lp(a)) levels are also higher in SAs compared with many other ethnic groups. This unique lipoprotein profile plays a vital role in the elevated ASCVD risk in SAs. Studies evaluating dietary patterns of SAs in the U.S show high consumption of carbohydrates and saturated fats.

Summary—SAs have a high-risk lipoprotein profile compared with other ethnicities. Lipid abnormalities play a central role in the pathogenesis of CAD in SAs. More studies are needed to understand the true impact of the various lipoproteins and their contribution to increasing ASCVD in SAs. Aggressive lowering of LDL-C in high-risk groups using medications, such as statins, and lifestyle modification including dietary changes is essential in overall CAD risk reduction.

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Compliance with Ethical Standards

Conflict of Interest Minhal Makshood, Wendy Post, and Alka Kanaya declare that they have no conflicts of interest.

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Keywords

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Introduction

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. The U.S is home to about 5.1 million SAs (2017, American Community Survey-Census Bureau [1]) who are at increased risk of atherosclerotic cardiovascular disease (ASCVD) compared with other ethnicities in the United States [2–4].

Higher ASCVD risk in SAs may be explained, in part, by a higher prevalence of traditional risk factors such as diabetes, dyslipidemia, 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. This includes higher rates of acute myocardial infarction (AMI) at younger ages largely attributed to the impact of risk factors earlier in life [6–9].

SAs are a heterogeneous population arising from various religions and racial and cultural backgrounds; however, they share several characteristics. SAs living in the U.S have distinct dietary patterns, a low prevalence of smoking, modest alcohol use, and low levels of exercise [10–14].

In the INTERHEART case-control study of 14,820 individuals from 52 countries that included 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 $ApoB_{100}$/ApoA-I ratio (46.8%), waist to hip ratio (37.7%), and smoking (37.5%) [5, 6, 15]. Dyslipidemia 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]. This indicates that the metabolic syndrome (MS) plays an important role at a younger age in SAs. 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].

When SAs are grouped together with Asian Americans, there is a falsely low ASCVD risk as a result of the lower risk in East Asian subgroups [18]. Given the rising population of SAs in the U.S, there is a need to understand risk factors and to better characterize ASCVD risk

in SAs to provide effective management recommendations. Dyslipidemia and insulin resistance play important roles in the risk ASCVD in terms of strength of association and occurring at a younger age.

This article will serve as a review of the literature regarding dyslipidemia in SAs, including the different components of the abnormal lipid profile and its individual effects on ASCVD and dietary influences and recommendations on approach to management.

Dyslipidemia

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]. SAs generally have either similar or lower LDL-C levels when compared with other race/ethnic groups. 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 particles was higher in Asian Indians compared with Whites (44% versus 21%; $P < 0.05$) [23]. In INTERHEART, SAs had a higher concentration of apolipoprotein B (ApoB) indicating a larger atherogenic particle load and possibly smaller LDL-C particle size [15]. 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 ApoB may be the driving factor in the elevated risk of CAD even at lower LDL-C concentrations, although this is not completely understood.

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, and therefore contribute to increased ASCVD risk [27, 28]. The overall prevalence of dysfunctional HDL is unknown in SAs. In a small cross-sectional study by Dodani et al [29], 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 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. Large HDL particles like HDL2b are more effective in reverse cholesterol transport compared with the smaller particles. Superko et al [33] 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. They suggested that this could explain impaired reverse cholesterol transport in SAs. In a study comparing concentrations of large and small HDL-C 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].

Overall, larger prospective studies are needed to understand the functionality of HDL and if dysfunctional HDL particles play an important role in the pathogenesis of dyslipidemia in SAs. Even at high HDL-C levels, SAs still demonstrate elevated ASCVD risk and although there is some evidence to suggest that MS may be playing a role, we need larger studies to further understand its effects on HDL function. More evidence is needed to understand the true effects of HDL size on reverse cholesterol transport and its contribution to increased CAD risk.

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 dyslipidemia occurring at lower levels of BMI in SAs [34, 35]. In INTERHEART, SAs had slightly higher levels of fasting triglycerides compared with SA (163 mg/dL compared with 160 mg/dL) [15]. 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. [37] found higher hepatic fat, intermuscular fat, and visceral fat in SAs compared with other ethnicities (Whites, African Americans, Chinese Americans, and Latinos). SAs also have a less favorable adipokine profile which could potentially play a vital role in their predisposition to cardiometabolic disease [37]. In a study evaluating dyslipidemia patterns in various races, Asian Indians had a higher risk of having combined dyslipidemia 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]. High prevalence of insulin resistance and MS appears to be strongly associated with abnormalities in CETP, high plasma triglycerides, elevated ectopic fat, and overall, the atherogenic dyslipidemia pattern in SAs.

Lp(a)

Elevated Lp(a) levels are an independent risk factor for ASCVD [41–44]. Lp(a) is a subclass of low-density lipoproteins distinguished by their apolipoprotein(a) component and is highly heritable. There are differences in Lp(a) concentrations between ethnic groups largely attributed to the differences in frequency of Lp(a) genetic variants [41].

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 U.S. 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]. Anand et al. [45] studied Lp(a) in SAs in the U.S in 3 different studies. The first study group included Indian participants aged 40–57 years, who were physicians from India visiting the U.S. Lp(a) levels were compared between these participants with White physicians, and the median Lp(a) values for SAs was 15 mg/dL vs. 11 mg/dL in Whites ($P = 0.17$). The second study was a cross-sectional study of 255 SA churchgoers in Chicago, Illinois. Lp(a) levels in this group were compared with 246 White individuals who participated in the San Antonio Heart Study in Texas. SAs had a median Lp(a) concentration of 16.1 mg/dL vs 9.1 mg/dL in Whites ($P < 0.0001$). In the third study, 30 South Asians and 21 whites from a Canadian community were randomly sampled. Lp(a) median concentrations were 28.4 in SAs vs. 11.3 mg/dL in whites ($P < 0.014$) [45]. In conclusion, several studies have shown elevated Lp(a) in SAs compared with Whites.

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. The prevalence of carotid atherosclerosis with Lp(a) levels > 20 mg/dL was higher than Lp(a) levels ≤ 20 mg /dL (26.9% vs. 16.3%, $P = 0.003$), which stayed robust in adjusted analyses [48]. In a small study that comprised Asian Indians < 40 years of age, median Lp(a) was measured in people with CAD and compared with age-matched healthy controls. The median Lp(a) in the angiographically proven CAD group was 26.7 mg/dL, higher than the control group 13.8 mg/dL ($P < 0.015$). Multiple regression analysis showed that Lp(a) levels were an independent risk factor (OR 3.06, $P < 0.001$) for premature CAD [44]. 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 INTERHEART, 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 is 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. This cohort was designed with protocols similar to the Multi-Ethnic Study of Atherosclerosis (MESA), another study of characteristics of subclinical CVD which includes 6814 participants from multiple racial/ethnic groups (Whites, African American, Hispanic, and Asians, predominantly Chinese) [51, 52] in MASALA compared with MESA, median Lp(a) levels was higher in SA (17 mg/dL) compared with Whites (13 mg/dL), Hispanics (13 mg/dL), and Chinese Americans (13 mg/dL), but significantly lower than in African Americans (35 mg/dL). However, in 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 MASALA [4].

Existing evidence suggests that SAs have higher Lp(a) levels compared with Whites; however, the evidence with regard to its impact on atherosclerosis is conflicting. A recent study using Mendelian randomization found a causal relationship between Lp(a) and ASCVD [41]. In the Pakistani PROMISE study, SNPs of Lp(a) were associated with MI using Mendelian randomization indicating that Lp(a) is a causal factor for CAD; however, the Pakistani cohort has a high prevalence of consanguinity making the results less generalizable to all SAs [54]. Lp(a) could potentially contribute to the elevated ASCVD risk in SAs.

Dietary Effects on Dyslipidemia

SA cuisine is diverse with significant variation not only between countries but within countries like India, which is multicultural and multi-religious. SAs in the U.S have a combination of preserved food habits from their native culture and Western food habits adopted by living in the U.S. Diet plays a major role in the prevalence and impact of dyslipidemia on cardiovascular health.

In general, the SA diet has large amounts of carbohydrates and saturated fats which include rice, refined grains, saturated oils, starchy vegetables and animal fat. In MASALA, a longer length of residence in the U.S was associated with higher intake of alcohol, carbohydrates (pizza and pasta), and fats including saturated and trans fats, cholesterol, and n-6 fatty acids [11] The MASALA study also found three dietary patterns (animal protein; fried snacks, sweets, and high-fat dairy; and fruits, vegetables, nuts, and legumes) that were consumed among SAs in the U.S. The animal protein and the fried snacks, sweets, and high-fat dairy patterns were associated with adverse metabolic risk factors in SAs whereas, the fruits, vegetables, nuts, and legumes pattern was linked with lower prevalence of hypertension (OR 0.63) and metabolic syndrome (OR 0.53) [10, 12].

Vegetarian diets are prevalent among SAs (38% in MASALA) and Jin et al. looked at the association of vegetarian diets with selected cardiometabolic risk factors and found that consuming a vegetarian diet is associated with lower BMI, total cholesterol ($P = 0.02$) and LDL-C ($P = 0.004$) [55]. Half of the vegetarians consumed the sweets, fried snacks, and high-fat dairy pattern which were associated with low HDL-C and high insulin resistance, and the other half consumed the fruits, vegetables, nuts, and legume pattern [12].

The overall emphasis needs to be on understanding different types of diets among SAs and using that knowledge to provide culturally sensitive counseling to effectively decrease the deleterious effects of elevated cholesterol, insulin resistance, and MS.

Management of Dyslipidemia

Risk Assessment Tools

The 2013 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 favor initiation of statin or if already on statin intensification of therapy [56].

A study comparing MASALA with MESA evaluated the relationship between 10-year ASCVD risk estimates in SAs (using the PCE for Whites) to CAC burden. The results posed that the PCE may overestimate risk in low and intermediate risk SAs even to a greater extent than in Whites. This could be because the MASALA population is generally comprised of lower-risk, healthy SAs from high-income groups, highly educated, with no clinical ASCVD with 27% taking statins at baseline compared with prior studies conducted in Europe and Canada that demonstrated higher ASCVD prevalence in SAs compared with Whites [57]. In the low and intermediate risk ASCVD risk strata, SAs had higher odds of CAC = 0 compared with Whites (ORs 1.26, 95% 0.91–1.76 and 1.73, 95% CI 1.00–2.99, respectively) [58]. The authors suggested that CAC could be a valuable tool to refine risk estimation in SAs with intermediate risk. Ten year and lifetime predicted CVD risk with subclinical CAD in SAs were studied in MASALA, and it was found that SA men and women with high 10-year predicted risk had significantly greater CAC burden than those with lower 10-year risk. SAs with high lifetime predicted risk had a greater odds of having CAC (OR: men 1.97; 95% CI, 1.2 to 3.2; women 3.14; 95% CI, 1.5, 6.6) [14]. This study was the first to provide evidence that contemporary ASCVD risk assessment algorithms derived from data in Whites and African Americans can identify differences in subclinical ASCVD burden in SAs in the U.S. Caveats to the PCE also include that it starts at age 40 and SAs are at increased risk of premature heart disease which further adds to the possibility of underestimation of risk.

There are many other risk tools available but a majority of them are derived from Whites in developed countries [59], and may not adequately assess risk in SAs in the U.S given differences in socioeconomic status, lifestyle, and acculturation factors. Some examples of risk tools from Europe include the UK QRISK2, UKPDS, ETHRISK, and WHO risk tables.

Since age is the driving factor in most tools, the higher prevalence of premature CAD in South Asians may be underestimated in younger patients with these scores that are developed in older populations [60].This stands true for PCE as well that starts at age 40.

Dietary Modification

To effectively improve dietary changes in SAs, it is important to have a good understanding of the variety of foods in the SA diet. SAs who have adopted a Western/non-vegetarian diet should be counseled on reducing the consumption of saturated fats, by opting for leaner meats like chicken and turkey as opposed to red meats, reduce oil, butter, and ghee-based products as well as fried foods and other trans fats while incorporating more vegetables [10, 61]. SAs with vegetarian diets tend to have a more favorable cardiometabolic profile; however, they do need to be counseled on higher quality of plant-based foods and reducing simple carbohydrate consumption such as sugar, bread, and rice and incorporating more whole grains [62].

Taking a good nutrition history and providing personalized culturally sensitive counseling and education will be key in reducing the harmful effects of poor diet on dyslipidemia and cardiovascular health [63]. Besides individualized counseling, there is a need for targeted interventions that take into account sociocultural belief systems centered on food [64].

Medications

The guidelines for treatment of SAs with dyslipidemia are based on the general guidelines by the AHA/ACC. There is a paucity of studies that include SAs evaluating the effectiveness of various therapies. The AHA released a scientific statement in 2018 with management recommendations for dyslipidemia in SAs. In 2018, the AHA/ACC also released new lipid guidelines emphasizing SAs as a risk-enhancing factor. For those at borderline or intermediate risk by the PCE, South Asian ancestry may favor initiation of statin, or intensification of statin therapy if already on a statin. In SAs, if risk-based decisions for preventive therapies remain uncertain, for the intermediate ASCVD risk group (7.5–19.9%) or select borderline risk (5–7.5%) individuals, additional testing with CAC can be considered to determine if initiation of statin therapy is warranted [14, 56, 65].

Use of Statins

A consensus statement on dyslipidemia management in SAs was published by Chandra et al. [66] According to this statement, statins are the mainstay in treatment of dyslipidemia 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. These recommendations were derived largely from Western guidelines mainly studied in Whites.

A study by Gupta et al. [67] evaluated statin effects on LDL-C and HDL-C in SAs and whites. They found that atorvastatin (median dose 20 mg/dL) produced similar decreases in LDL-C in SAs (43%) and Whites (41%) and raised HDL-C by 19% in SAs and 12% in Whites [67]. The results of this study suggest that SAs should be treated with statins in doses similar to Whites.

One large trial that included SAs was the 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 [68]. In the IRIS trial, patients of SA origin with hypercholesteremia without CAD were treated with either rosuvastatin 10 or 20 mg or atorvastatin 10 or 20 mg. LDL-C decreased by 45% with rosuvastatin 10 mg versus 40% with atorvastatin 10 mg ($P = 0.002$) [69]. The ACTFAST study was a prospective study looking at the effects of atorvastatin in patients of SA versus European descent at high risk of atherosclerosis. Atorvastatin lowered LDL-C to a similar extent in both SAs and people of European descent (34% in SAs vs 38% in European descent, $P = 0.22$) [70].

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 [71]. 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 [72, 73]. However, larger prospective studies are needed to further understand the role of genetics and pharmacokinetics in the use of statins in SAs. Based on current guidelines, it is reasonable to treat SAs on maximally tolerated statins similar to other ethnic groups while closely monitoring for side effects.

Statins are effective in lowering LDL-C in SAs and therefore decreasing overall ASCVD risk. Management strategies for dyslipidemia in SAs are largely based on the new guidelines published by AHA/ACC and other societies in 2018 [56]. Figure 1 summarizes the guidelines for lipid management in SAs.

- 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.–7.5%) risk, as being SA is a risk-enhancing factor.
- If risk-based decisions still remain uncertain, among the intermediate risk group with an ASCVD score ≥ 7.5–19.9% or among select borderline risk (5.–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.

The single asterisk denotes that for high-risk ASCVD patients, if LDL ≥ 70 mg/dL despite being on maximally tolerated statin, initiate ezetimibe [74].

The double asterisk suggests calculating the ASCVD risk score using the PCE for Whites as SA ancestry not included in PCE. After PCE calculation, the presence of SA ethnicity and the CAC score, if measured, can help further refine risk to guide treatment decisions.

Combination Drug Therapy

The newer guidelines recommend thresholds for considering additional LDL-C lowering in high-risk patients, particularly patients with clinical ASCVD as described above. To achieve lower LDL-C levels, statins alone may not be sufficient and some people do not tolerate statins requiring additional agents. Below are examples of other drugs that can be used in conjunction with statins to achieve goal LDL-C. Some smaller studies have studied other agents in conjunction with statins in SAs. Most of the larger trials did not include SAs and therefore, the efficacy of these drugs on SAs is largely unknown. However, SAs are a high-risk group and aggressive lowering of LDL-C may be required to decrease overall risk.

Addition of Ezetimibe—Ezetimibe is a non-statin medication used to treat hyperlipidemia. 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 [75]. Stitziel et al. [76] sequenced the exons of NPC1L1 in 7364 patients with CAD compared with 14,728 controls without disease. The participants were of European, African, and SA ancestry. They found that naturally occurring mutations, which disrupt NPC1L1 function, were associated with lower plasma LDL-C levels and a lower risk of CAD [76]. This study showed that ezetimibe, an inhibitor of NPC1L1 can reduce plasma LDL-C levels in SA and therefore reduce CAD risk.

The INFINITY study [77], comprising SA Canadians, assessed the effectiveness of ezetimibe in patients with CAD or diabetes who were already on statin therapy in a randomized trial.

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 [77].

The IMPROVE-IT [78] randomized controlled trial, in a predominantly White population with a few SAs, evaluated the potential benefit of the addition of ezetimibe to simvastatin on cardiovascular outcomes among patients with acute coronary syndrome. Addition of ezetimibe reduced LDL-C levels by around 24% compared with simvastatin alone. The primary end point of cardiovascular death, MI, unstable angina, coronary revascularization beyond 30 days, and stroke was lower in the ezetimibe and simvastatin group compared with simvastatin alone (32.7% vs. 34.7%, hazard ratio [HR] 0.94, 95% CI 0.89–0.99; $P = 0.016$) [78]. 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 LDL-C threshold ≥ 70 mg/dl despite maximally tolerated statin would favor the additional initiation ezetimibe as a second-line agent.

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 FIELD [79] and ACCORD [80] studies. 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 [79]. In ACCORD, fenofibrate and simvastatin did not reduce the rate of fatal CVD events, non-fatal MI, or non-fatal stroke compared with simvastatin alone. Subgroup analyses of the fibrate trials revealed that in those with high triglycerides (> 200 mg/dL) and low HDL-C (< 35 mg/dL), there was benefit in treating with fibrates in men after statin therapy has reduced LDL-C ($P = 0.057$). Overall, there is no evidence to suggest that adding fibrates has any benefit on CVD mortality. Given the pattern of dyslipidemia in SAs, theoretically, fibrates could have some benefit but larger studies in SAs are needed to investigate this hypothesis.

PCSK-9 Inhibitors—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 FOURIER [74] 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. 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; $P < 0.001$) [77].

The ODYSSEY OUTCOMES [81] trial showed the use of alirocumab, taken every other week, significantly reduces ischemic events, including all-cause mortality and MI compared with placebo among patients with an acute coronary syndrome in the preceding 1–12 months. 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, $P < 0.001$ [81].

Both of 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 despite being on maximal tolerated statin plus ezetimibe, PCSK-9 inhibitors should be considered to help LDL-C reduction to achieve goal levels.

Conclusions

SAs comprise a rapidly growing population in the U.S and have unique characteristics in the pathogenesis of dyslipidemia and elevated ASCVD risk. The abnormal lipid profile in SAs include low but more atherogenic LDL-C, 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. SAs are also at increased risk for premature heart disease that limit the use of most existing ASCVD risk prediction tools such as PCE that starts at age 40. For management of dyslipidemia, the Western guidelines

including AHA/ACC/Multi-Society 2018 lipid guidelines that included SAs as a risk-enhancing factor along with the consensus statement from Chandra et al. [66] serve as an updated guide to manage SAs with abnormal lipid profiles and elevated ASCVD risk.

Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
ACCORD	Action to Control Cardiovascular Risk in Diabetes
AMI	Acute myocardial infarction
ASCVD	Atherosclerotic cardiovascular disease
CAC	Coronary artery calcium
CAD	Coronary artery disease
CCA-IMT	Carotid artery–intima media thickness
CETP	Cholesteryl ester transfer protein
CVD	Coronary vascular disease
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
HDL-C	High-density lipoprotein cholesterol
ICA-IMT	Internal carotid artery intima-media thickness
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein a
MASALA	The Mediators of Atherosclerosis in South Asians Living in America
MESA	Multi-Ethnic Study of Atherosclerosis
MS	Metabolic syndrome
PCE	Pooled cohort equation
PCSK-9	Proprotein convertase subtilisin/kexin type 9
SAs	South Asians
VLDL-C	Very low-density lipoprotein cholesterol

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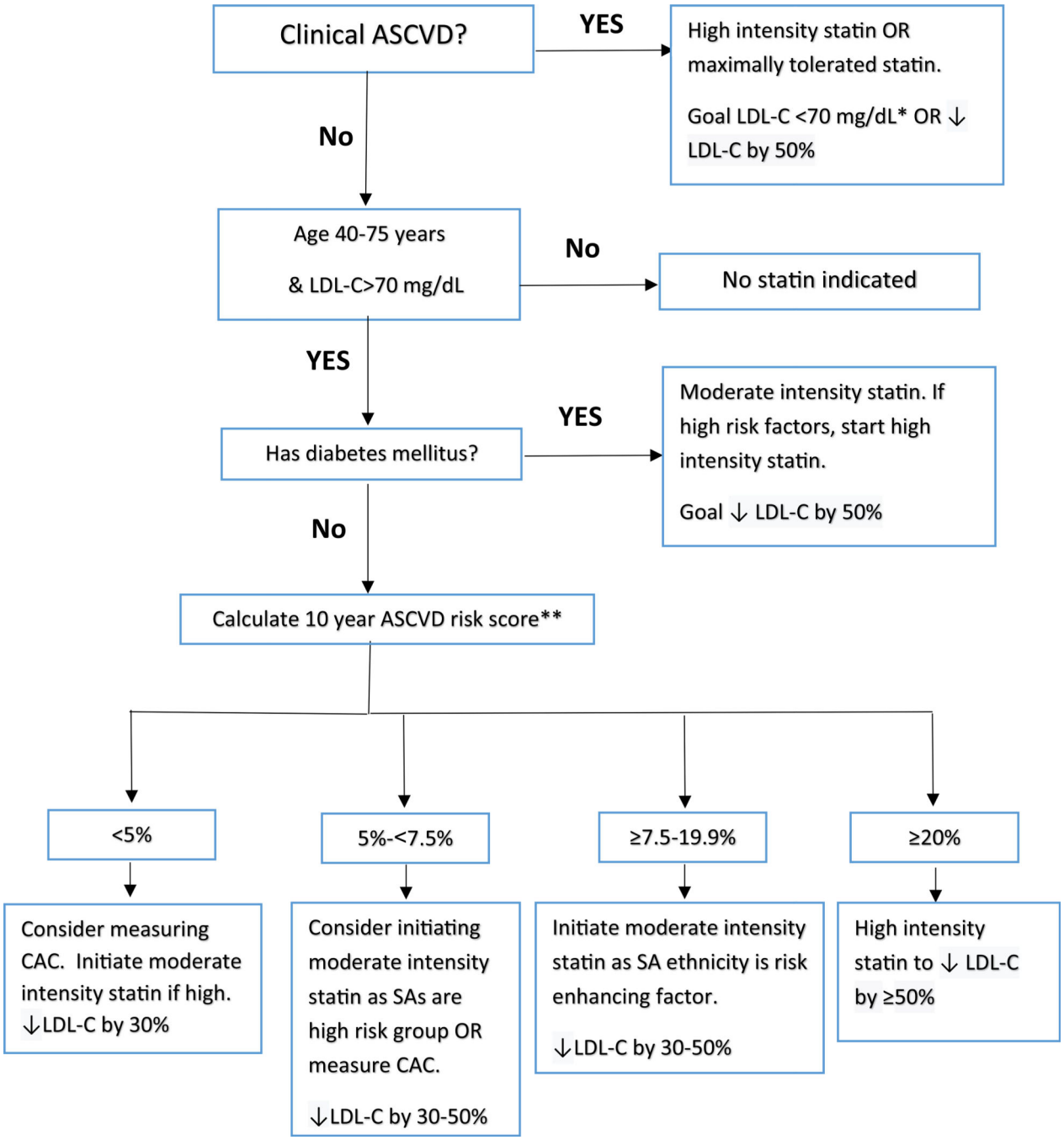

Fig. 1.
Management of lipids in SAs based on AHA/ACC 2018 guidelines and consensus statement by Chandra et al. [66, 68]