

Insight

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Coronary Artery Disease in South Asians

EPIDEMIOLOGY

The term South Asians refers to people who are originally from the Indian subcontinent, that is, from India, Pakistan, Nepal, Bangladesh, and Sri Lanka. As a result of worldwide migration (Figure 1) standardized comparisons among different ethnic groups have provided valuable information regarding clinical outcomes in South Asians with CAD. The traditional CAD risk factors occur at a younger age with higher mortality rates from CAD. Over the past 30 years, the incidence of CAD among South Asians has doubled, and has exponentially risen for South Asians who have immigrated to the United States. Contemporary data from the United States suggest the proportional mortality ratio for South Asians with CAD is at least two times that of any other ethnicity (Figure 2). Although CAD affects only 3% to 4% of the rural population in South Asia, it affects 10% of South Asian urban populations who live in South Asia, and who have immigrated to western countries. As such, environmental factors related to urbanization play a role in the premature development of CAD among the South Asian community.

The CAD burden of South Asians is projected to worsen in the next decade to more than half of the global CVD. The current control measures that have proven effective in other ethnic groups may not be optimal in the South Asian population.

Are All South Asians the Same?

Variations in the distribution of CAD and associated risk factors have been observed among South Asian countries, with Bangladesh

having the highest prevalence of risk factors and the lowest prevalence of risk modification (ie, regular exercise and daily consumption of fruits and vegetables) with the lowest mean age of acute myocardial infarction (MI). When South Asian migrant groups living in the United Kingdom were studied, similar heterogeneities in cardiovascular risk factors have been observed among Bangladeshi migrants compared with Indian and Pakistani migrants. Furthermore, the metabolic profiles of Bangladeshi migrants demonstrate higher levels of triglycerides, low-density lipoprotein (LDL), and fasting glucose, and the lowest levels of high-density lipoprotein (HDL) when compared with Pakistanis, Indians, and Europeans. These exaggerated differences in Bangladeshis are of particular concern and require further investigation.

Future Generations

Unfortunately, South Asian children are showing increased susceptibility to the metabolic syndrome and CAD. A comparative study done in the United Kingdom between white and South Asian children showed higher mean fasting and postglucose load insulin concentrations, increased mean heart rate, and elevated mean serum triglyceride and fibrinogen levels among South Asian children. A higher incidence of adiposity was seen in South Asian children compared with white children, yet an increased prevalence of insulin resistance persisted after adjusting for adiposity and pubertal status.

In addition to the children from native and migrant South Asian populations who have been reported to have such tendencies, children of South Asian descent born and raised in Western societies have altered metabolic profiles when compared with





their white counterparts. Case Western Reserve University (Cleveland, OH) compared metabolic and anthropometric measures of young adults of South Asian ethnicity, who were born and raised in the United States. Men had significantly higher total cholesterol (TC), LDL, TC: HDL ratios, triglycerides, and fasting insulin levels and lower HDL than their white counterparts. Women demonstrated higher plasma insulin levels than their white counterparts. The entire South Asian group had higher truncal skin-fold thickness and lower insulin-like growth factor-binding protein-1 levels. Plasma leptin levels were also significantly higher in the South Asian cohort, whereas no differences were observed in lean body mass, homocysteine, or serum lipoprotein(a) [Lp(a)]. These findings point to an altered metabolic profile that supports a genetic predisposition to altered body fat pattern (thin muscle/visceral fat phenotype), and contributes to the deleterious consequences of the metabolic syndrome.

TRADITIONAL RISK FACTORS

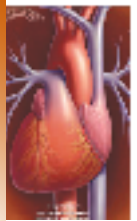
Traditional risk factors for atherosclerotic vascular disease, which had been described by the Framingham study were mainly assessed in white subjects. Although they play a part in the South Asian population, they cannot fully explain the excess risk. South Asians seem to have a combination

of traditional and novel risk factors, which contribute to their heightened risk of CAD. In general, traditional risk factors are noted to be rare with the exception of diabetes mellitus. In fact, the contribution of insulin resistance plays a major role in the higher prevalence of CAD and may be associated with the contribution of excessive central abdominal obesity/visceral fat. In fact, when compared with other ethnicities of comparable body mass index, South Asians have higher visceral fat mass, thicker truncal skin fold, and lower lean body mass with the distribution focused in the abdominal visceral space (thin muscle/visceral fat phenotype). Central adiposity has been correlated with insulin resistance and hyperinsulinemia, and has been noted to have a direct relationship with increased risk of CAD. The International Diabetes Federation utilizes ethnic-specific waist circumference, which helps better identify South Asian patients having the highest cardiovascular risk factors. For the South Asian population, the waist circumference cutoff for men was 90 cm or more and for women was 80 cm or more (Table 1).

One of the modifiable risk factors, smoking, is low in South Asians, and virtually nonexistent in women. However, a high intake of dietary fats and little or no exercise contributes to characteristic lipid profiles, including higher triglyceride levels, higher Lp(a) levels, increased ratio of

Figure 1. South Asian migration patterns from the Indian subcontinent to different areas across the world.





apolipoprotein B to apolipoprotein A-1 (ApoB/ApoA-I), smaller HDL and LDL particle size, and lower levels of HDL. ApoB 100 is the major apolipoprotein found in LDL, intermediate-density lipoprotein, and very LDL, and it is the primary ligand for the LDL receptor. ApoA-I is the major protein constituent of HDL. The ApoB 100/ApoA-I ratio provides an atherogenic to antiatherogenic lipoprotein ratio that has been shown to be a better predictor of CVD than LDL level, HDL level or LDL/HDL ratio. Furthermore, the ApoB 100/ApoA-I ratio can identify individuals with a preponderance of small dense LDL particles, but with seemingly normal LDL levels. The landmark International Heart (INTERHEART) study was among the first studies to demonstrate that elevated ApoB100/ApoA-I ratio was the risk factor associated with the highest population-attributable risk for MI (46.8%), with waist-to-hip ratio (37.7%), and smoking (37.5%) also being important risk factors in the South Asian population.

EMERGING RISK FACTORS

Although contributory, traditional risk factors do not fully explain the heightened risk of CAD in South Asians. Thus, novel and emerging risk factors have been explored. This

is particularly important as testing for these parameters (if available) will certainly help risk stratification in South Asian patients.

Lipoprotein (a)

The National Cholesterol Education Program Adult Treatment Panel III considers Lp(a) an important and emerging risk factor for CAD. Lp(a) has been implicated in the development of premature atherosclerotic disease in the South Asian cohort. It represents a class of LDL particles that contains the plasminogen-like apolipoprotein A moiety attached to the ApoB100 protein. Unlike other lipids that are influenced by diet, age, sex, and other environmental factors, Lp(a) levels are primarily driven by genetics and ethnicity. In whites, Lp(a) levels more than 30 mg/dL are considered a risk factor for premature CAD. In South Asians, levels less than 20 mg/dL are considered optimal. There is a two- to threefold increased risk of acute myocardial infarction and restenosis after coronary angioplasty or coronary artery bypass grafting in those South Asian patients with Lp(a) levels between 20 and 30 mg/dL. When Lp(a) levels are more than 55 mg/dL with low HDL and high TC/HDL ratio, MI risk increases 100-fold.

Due to its homology to plasminogen, Lp(a) is highly thrombogenic and antifibrinolytic.

Homocysteine

Mager et al acknowledges that treating hyperhomocysteinemia (>15 μ M) in CAD as both primary and secondary strategies have failed to show benefit. However, they also noted that all the prior studies have focused on white cohorts, which questions ethnic variation. Hyperhomocysteinemia is also known to occur due to alcohol abuse, and seems to be a novel risk factor in South Asian patients. It contributes to cardiovascular risk and tends to be higher in South Asians compared with the white population. Boushey et al reported that a 1- μ M increase in hyperhomocysteinemia level is associated with an increase in

TABLE 1. New Metabolic Syndrome (MS) Criteria

Measures (Any 3 of 5 Constitutes Diagnosis of MS)	Categorical Cutoff Points
Elevated waist circumference*#	Men: ≥ 102 cm (≥ 40 inches) Women: ≥ 88 cm (≥ 35 inches)
Elevated triglycerides (TGL)	≥ 150 mg/dL (≥ 1.7 mM) Or on drug therapy for elevated TGL
Reduced HDL-cholesterol (HDL-C)	Men: ≤ 40 mg/dL (1.03 mM) Women: ≤ 50 mg/dL (1.3 mM) Or on drug therapy for reduced HDL-C
Elevated blood pressure	≥ 130 mm Hg systole (or) ≥ 85 mm Hg diastole (or) on antihypertensive therapy for history of hypertension
Elevated fasting blood glucose	≥ 100 mg/dL (5.6 mM) or on drug therapy for hyperglycemia

*To measure the waist circumference, locate top of right iliac crest. Place measuring tape in a horizontal plane around abdomen at the level of iliac crest. Ensure tape is snug, does not compress abdomen skin and is parallel to the floor. Measurement is made at the end of normal expiration.

#Non-Asian adults (black, Hispanic and white) with marginally increased waist circumference, men: 94 cm to 101 cm (37-39 inches), women: 80 cm to 87 cm (31-34 inches) may have a strong genetic contribution to insulin resistance and should benefit from lifestyle changes similar to those in the categorical cutoff group. Asian adults have a lower waist circumference cut off, men: ≥ 90 cm (>35 inches) and women: ≥ 80 cm (31 inches).

TGL indicates triglycerides; HDL, high-density lipoprotein.



CAD risk of 12% in men and 16% in women. Refsum et al reported a high prevalence of hyperhomocysteinemia (15 μ M) in Indians. They also observed that dietary difference made no difference, and that hyperhomocysteinemia strongly correlated with cobalamine deficiency. Further ethnic-specific studies are needed to fully understand the contribution of hyperhomocysteinemia to CAD in South Asians.

Adipokines

Adipokines or adipose-tissue-derived circulating hormones seem to link insulin resistance and premature atherosclerosis, particularly in South Asians given the propensity toward central abdominal obesity. Certainly proinflammatory adipokines, such as leptin, PAI-1, tumor necrosis factor- α , interleukin-6, and C-reactive protein, contribute to endothelial dysfunction and the development of atherosclerotic disease. Adipose tissue also produce anti-inflammatory substances such as adiponectin (a cytokine with insulin sensitizing, antiatherogenic, and antiinflammatory properties), but seem to be suppressed in individuals with central obesity. In fact, studies support the direct association between hypoadiponectinemia (both total adiponectin levels and high molecular-weight adiponectin levels) and the development of CAD in South Asians. Yet, this association has not been observed in whites.

Other Novel Cardiac Biomarkers

Abnormalities in markers of endothelial dysfunction, such as

vascular-cell adhesion molecule-1, impaired endothelium dependant dilation, proinflammatory HDL, and Apo A-I polymorphisms, have been described in the South Asian population. Further research is needed to delineate the magnitude of cardiovascular risk these novel risk factors will confer upon this high-risk patient population.

NOVEL CONSIDERATIONS

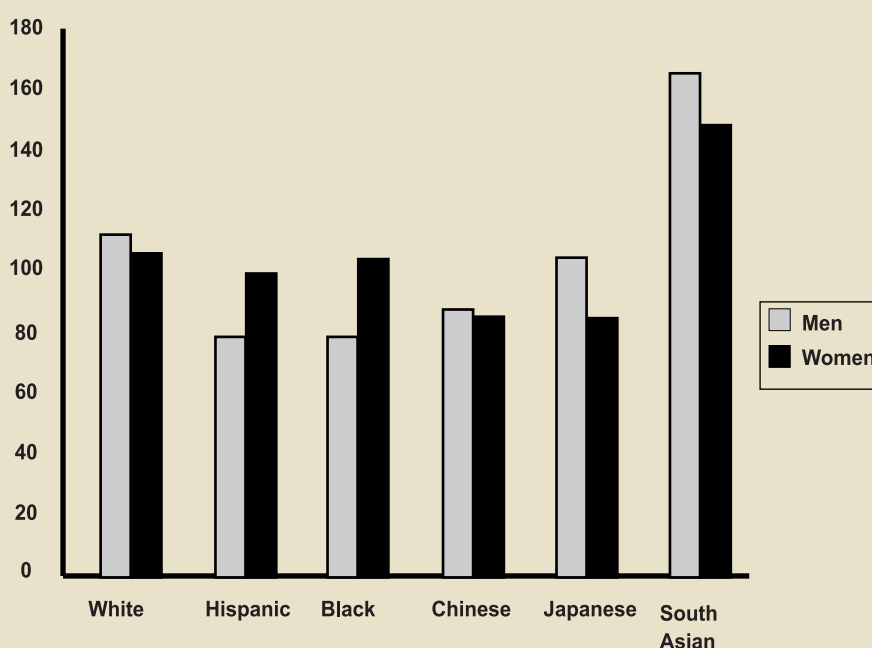
Genetics

The Coronary Artery Disease Genetic Consortium (C4D) recently reported the discovery of five new loci for CAD. They focused on two populations, whites and South Asians, and found the same five loci were implicated in the development of CAD in both populations. Yet, there may be other genes causing premature CAD in South Asians, which remain undiscovered. Currently, the best available genetic information is one of the Lp(a) variants, which occur in approximately one in every six persons, and confers a 50% increase in risk, and the 9p21 gene, which confers an approximate 25% increase in risk. Still, this does not entirely explain the heightened risk of CAD in the South Asian population. As such, two major genome-wide association studies are currently being performed in the United Kingdom (the London Life Sciences Prospective Population Study) and Pakistan (the Prosecutor's Management Information System).

Coronary Artery Size

Currently, there is a lack of consensus regarding the contribution of coronary artery size in South Asian patients. Nonetheless, the South Asian cohort still has a higher prevalence of both severe diffuse and three-vessel CAD. Vascular remodeling based on ethnic differences has been implicated because, in comparison with whites, the South Asian cohort exhibits a greater narrowing of the proximal left anterior descending artery in association with more advanced atherosclerosis. Another small retrospective study using strict inclusion/exclusion criteria showed that proximal coronary artery size and the number of significant coronary stenoses did not differ between

Figure 2. Mortality of different ethnic groups from ischemic heart disease.





matched pairs of South Asian and white men. Dhawan and Bray compared coronary angiograms from a consecutive series of South Asian men with those from randomly selected white men and found a smaller mean total coronary artery diameter in the South Asian group than in the white cohort. They also demonstrated a correlation between body surface area and coronary artery size. However, when the investigators adjusted total coronary artery diameter for body surface area, the interethnic difference in coronary artery size between South Asian and white patients was negligible. A recent article by Hasan et al used quantitative coronary angiography to assess the coronary size and distribution of disease between South Asians and whites, and concluded that South Asians have smaller coronary artery luminal diameters compared with whites, which reiterates a possible role of coronary artery size in affecting increased CAD risk and mortality among South Asians. Furthermore, they noted the observation that South Asians exhibit heightened CAD at an earlier age when compared with whites. Intravascular ultrasound may be a worthwhile investigative modality, although this has not been currently explored.

Alcohol

Regular alcohol consumption (\geq once per week) is noted to be cardioprotective in some ethnicities. The beneficial effects are dependent on the amount of alcohol consumed and the pattern of drinking. In their meta-analysis, Di Castelnuovo et al reported the beneficial effects of alcohol when limited in the light-to-moderate drinkers who have less risk than abstainers. Heavy drinkers are at the highest risk. They also showed that consumption of one drink daily by women and one or two drinks daily by men was associated with a reduction in total mortality of 18%. Conversely, intakes of more than two drinks daily in women and three drinks daily in men were associated with increased mortality in a dose-dependent fashion. Alcohol consumption was not cardioprotective in the South Asian group, and was actually harmful in the Indian subgroup. Perhaps this could be related to the lower prevalence or the pattern of drinking (binge vs daily drinking) in South Asians.

FUTURE DIRECTIONS

Is it Time to Revise the Framingham's Risk Factor Profile Score?

Traditionally, the Framingham's risk factor profile score (FRFPS) includes age, cholesterol levels, blood pressure,

smoking, and diabetes mellitus to help determine the 10-year risk of nonfatal MI or coronary death. The FRFPS underestimates the CAD risk in South Asians. Certainly the metabolic syndrome is contributory in South Asians and should be included in risk stratification. Figure 3 provides a modified FRFPS in South Asians at risk for CAD and may be a useful tool in risk stratification.

Are We Missing Something?

Despite conventional and novel risk factors, it has been shown that the beliefs and attitudes of South Asian patients have a direct result on their health outcomes. Health beliefs are important in influencing health behaviors. The ability to embrace or reject lifestyle modifications could possibly be influenced by a lack of appreciation for CAD and the consequences of the disease. Various studies based in the United Kingdom and the United States have identified a general deficit in knowledge concerning CAD, its prevention and health promotion. Furthermore, Rankin and Bhopal identified that the lack of knowledge was influenced by the country of birth, noting that the Bangladeshi community fared the worst.

This lack of knowledge of CAD is linked to poor dietary habits, low levels of physical activity, and social support. Beishon and Nazroo noted that despite healthy-eating campaigns, there was a definite lack of information among the South Asian community regarding dietary intake and its correlation with CAD. Most South Asians believe in a healthy diet, yet few adhere to dietary constraints. Reddy and Yusuf highlighted the global availability of vegetable oils and fats, which resulted in increased fat consumption among low-income countries. The usual diet for South Asian countries consisted of high carbohydrates and low fat. This has been replaced with a decline in complex carbohydrates and a high intake of dietary fat. As well, South Asians are unaware of the varied types of oils and fats (saturated and unsaturated) and their effects on CVD. This deficit in dietary knowledge, along with urbanization, has translated to poor dietary habits for Indians immigrating to the United Kingdom, leading to central obesity and a predisposition to accelerated atherosclerotic disease.

In general, South Asians have lower levels of physical activity. Many South Asians do believe it is important, yet it seems only younger men actually engage in regular physical activity. Women and children believe daily activity is sufficient, whereas elderly South Asians believe physical activity over a certain age would be detrimental to their

health. Overall, Beishon and Nazroo found little awareness among South Asians regarding types of activities and their respective health benefits, especially in the presence of CAD. A study conducted by Williams et al found ethnicity to be the most significant risk factor for physical activity rates. This echoes the point of ethnicity affecting knowledge levels, and once again the Bangladeshi community has the worst rate of physical activity. It was also identified that urbanization and psychological distress for those South Asians who immigrated to the United Kingdom, partially explains the difference in physical activity. As a result, Bainey et al found South Asians with CAD exhibit poor health-related quality of life when compared with whites with CAD (Table 2).

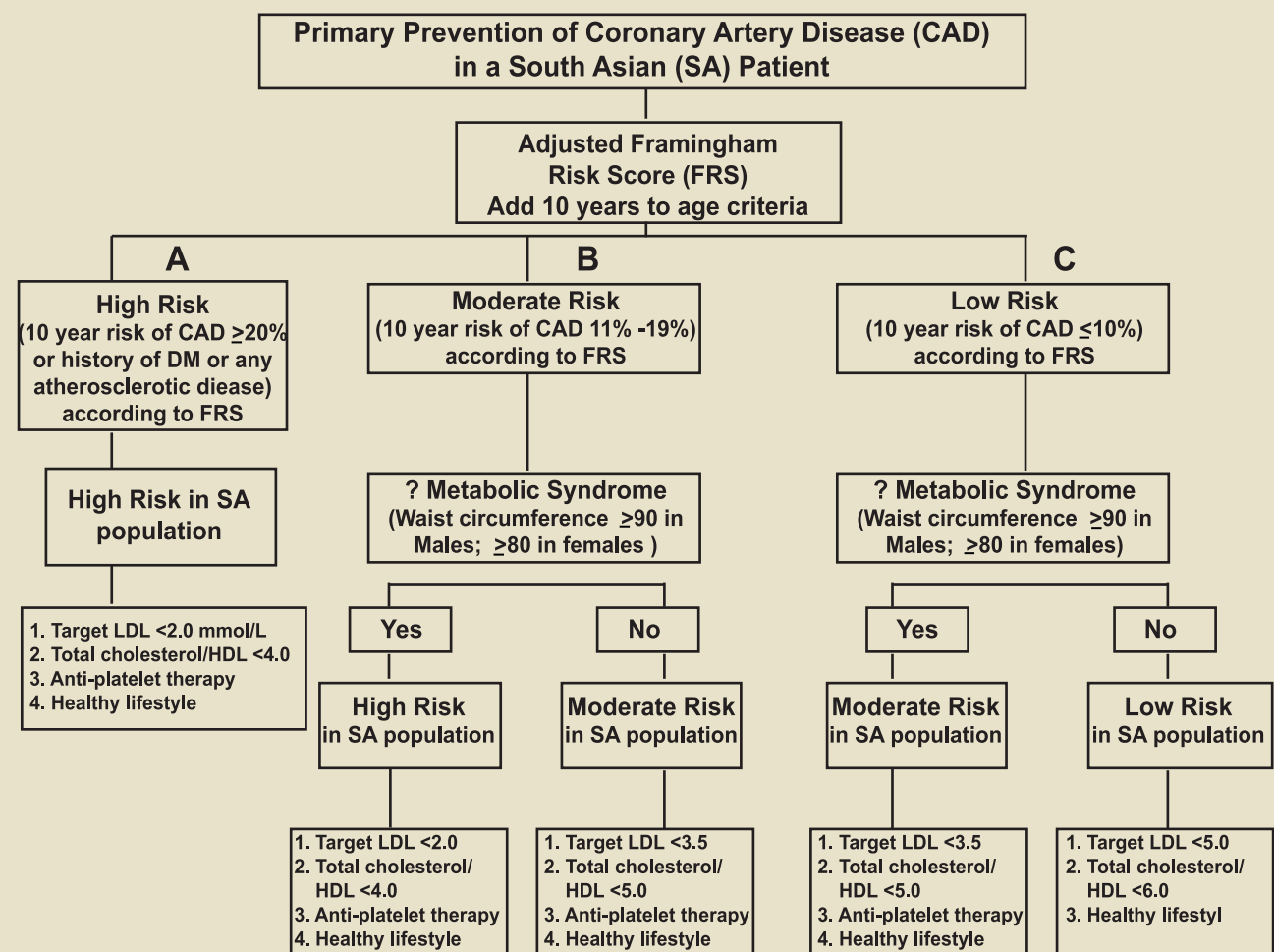
Another important factor that is overlooked is social support. For those South Asians who immigrated to the United Kingdom, there is evidence to suggest poor social support outside of the home and religious communities,

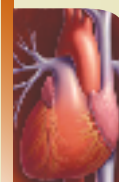
where Pakistanis and Bangladeshis fared worse than Indians. Pollard et al found there was no clear evidence of social networks having a protective effect for abdominal obesity, blood pressure, and serum lipid profiles. Barnett et al identified that poor use of resources may be linked to an increase in CAD in UK South Asians. It was also highlighted that South Asians are less likely to be prescribed statins and other cardioprotective treatments.

How Do We Alter Health Beliefs Among South Asians?

As there is a general deficit in knowledge regarding health, and more specifically CAD, health information, and education is essential. Rankin and Bhopal believe that there is an urgent need for culturally appropriate education programs, especially for the Bangladeshi community. The information required to decrease the prevalence of CAD needs to be culturally sensitive and accessible to patients. Tailoring and delivering the information on individual and

Figure 3. A proposed cardiovascular risk stratification tool for patients of South Asian descent.





community levels can improve outcomes. The information in its varying forms must be language specific and appropriate for effective communication. Additionally, extra support should be given to complement the information that is available. This could be in the form of healthy-cooking methods as an adjunct to dietary education. Accessibility can be accomplished by providing information from a wide variety of sources, including primary-care physicians, media, schools, the home, community centers, and family and friends.

South Asians and health professionals alike need to be educated primarily on the predisposition of CAD. Additionally, health professionals should be aware of the increased prevalence and risk of CAD, and the prominent role of risk factors and metabolic dysfunction. Education will promote optimal standards of care. As an adjunct to education, appropriate screening, which includes measuring waist circumference, waist-to-hip ratios (appropriate for South Asians), and frequent fasting glucose and lipid levels, need to be provided.

An example of a health-promotion program that led to a decrease in cardiovascular risk factors was the Khush Dil (Happy Heart) intervention. The program aimed to develop and test methods for locally based and culturally sensitive CAD prevention and control services for South Asians. In addition to decreasing the cardiovascular risk factors, it changed the motivational status of the participants, increasing the adherence to diet and lifestyle modifications.

CONCLUSIONS

It is well established that South Asian migrants living in the western world have a higher burden of CVD than do other ethnic groups. In addition, South Asians develop CVD at a younger age, and have a higher cardiovascular mortality. This epidemic is multifactorial, which includes a combination of traditional and emerging risk factors, a lack

of awareness, and an absence of ethnic-specific prevention/control measures. Future direction points toward ongoing research with the aim of discovering technology for earlier detection. Additionally, CAD in South Asians could be attenuated by increasing awareness, modifying health beliefs through health-promotion strategies, and instituting ethnic-specific control measures including appropriate pharmacological intervention.

CLINICIAN'S TAKE-HOME POINTS

1. South Asians have an increased risk for early onset of CVD. Among this population, they have the youngest mean age for MI with poor clinical outcomes.
2. Besides the traditional risk factors (particularly diabetes mellitus), physicians should be aware of the emerging risk factors to aid risk stratification in their South Asian patients. These include the metabolic syndrome, visceral adiposity, hyperinsulinemia, elevated ApoB100/ApoA-I ratio, LP(a), homocysteine, and low adiponectin levels. Of importance is the elevated Lp(a) levels in the presence of normal TC and low HDL levels. Lp(a) levels less than 20 mg/dL are considered optimal. A raised ApoB100/ ApoA-I ratio was the risk factor associated with the highest population-attributable risk for MI.
3. Ethnic-specific targets should be utilized with the waist circumference cutoff for men being 90 cm or more and women, 80 cm or more in the definition of the metabolic syndrome.
4. The FRFPS underestimates CAD risk in both South Asian males and females. Along with the established risk factors, the metabolic syndrome could help risk stratify South Asian patients.
5. Raising awareness of this phenomenon through education and health promotion among both physicians and patients is vital. It is important to not only initiate appropriate and early pharmacological therapy, but also include strategies to modify health beliefs and improve lifestyle interventions to ensure continued success.

TABLE 2. Propensity Score-Matched Analysis of SAQ Scores at 1 Year

	SA SD (n = 632)	EN SD (n = 2681)	P
Physical limitation	75 (23)	80 (23)	0.011
Angina stability	77 (28)	77 (27)	0.627
Angina frequency	86 (23)	80 (20)	<0.001
Treatment satisfaction	86 (19)	89 (16)	<0.001
QOL	71 (24)	76 (21)	<0.001
SAQ indicates Seattle angina questionnaire; SD standard deviation; SA, South Asian; EN, European; QOL, quality of life.			

Source:

Coronary Artery Disease in South Asians.
Seshasayee Narasimhan, MBBS, MRCP,
Katrina McKay, and Kevin R. Bainey.
Cardiology in Review 2012;20: 304–311

Cardiology News

Beta-Blockers Not Equal in LQTS, Metoprolol Appears Least Effective

Propranolol and nadolol are nearly four times better than metoprolol at preventing breakthrough cardiac events in symptomatic patients with long QT syndrome (LQTS), a retrospective study suggests. The multicenter study also found that propranolol is significantly better at shortening heart rate-corrected QT interval (QTc), compared to metoprolol and nadolol, especially in patients with prolonged QTc. Among the 101 previously symptomatic subjects, there was an overall significant difference ($p=0.018$) in rates of breakthrough events: 8% on propranolol, 7% on nadolol and 29% on metoprolol. The authors noted that the incidence of first breakthrough event was rather low and did not include lethal events. (All 15 events were syncope.) 1 years on beta-blocker therapy, the cumulative event-free survival for propranolol or nadolol users was 91%, versus 60% for metoprolol users. Among patients whose QTc was prolonged (more than 480 ms), QTc shortening was significantly better with propranolol than with either of the other two drugs.

J Am Coll Cardiol 2012.

Monitoring Could Be Best for Spontaneous Coronary Artery Dissection

Watchful waiting may be the best therapeutic strategy for patients with spontaneous coronary artery dissection (SCD), a Spanish group says. Whenever possible a conservative approach should be attempted as the initial strategy. First, according to the researchers experience prognosis in stable (or stabilized patients) is excellent. Second, many of these patients heal spontaneously at follow-up and the coronary wall is fully and completely recovered. Finally, coronary interventions and coronary surgery is challenging in this scenario.

J Am Coll Cardiol Interv 2012;5:1062-1070.

Drug-Eluting Stents May Curb Mortality in Elderly

In elderly patients with chronic total coronary occlusion, drug-eluting stents (DES) are better than bare-metal stents (BMS) for reducing mortality, registry data suggest. DES were used in 80% and BMS in the remaining 20%. There were several statistically significant differences between the groups: on average, the DES patients were younger (74.0 vs 75.5 years) and had longer lesions (18.8 vs 16.5 mm), and they were significantly more likely to receive at least two stents (45.7% vs 37.9%) and to require multivessel interventions (18.9% vs 15.1%). At 30 months of follow-up, DES implantation was associated with a significantly reduced risk of mortality (hazard ratio, 0.72). A number of other outcome measures, including risk of myocardial infarction, subsequent revascularization and need for hospitalization for bleeding, were similar between the groups.

J Am Coll Cardiol Interv 2012;5:1054-1061.

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Editorial Note

Dear Doctor,

We are happy to present the 27th issue of "Insight Heart". It is a small endeavor to provide you compiled & updated information on cardiovascular diseases and its management. This issue is focused on "**Coronary Artery Disease in South Asians**". We will appreciate your thoughtful comments.

Thanks and regards.