Coronary Artery Disease In Asian Indians: An Update And Review

E Enas, A Senthilkumar

Abstract
Coronary artery disease (CAD) rates vary 10-fold among populations. The CAD rates among overseas Asian Indians worldwide are 50% to 400% higher than people of other ethnic origin irrespective of gender, religion, or social class. India is now in the middle of a CAD epidemic with urban Indians having CAD rates similar to overseas Indians, which is 4-fold higher than Americans. Whereas the CAD rates halved in the West in the past 30 years, the rates doubled in India with no signs of a downturn yet. The average age of first myocardial infarction (MI) has decreased by 20 years in India. Among Asian Indian men, about half of all MI occur under the age of 50 and 25% under the age of 40. Apart from glucose intolerance, they have no excess of conventional risk factors such as cigarette smoking, hypertension, and high cholesterol levels. Nearly half of them are life-long vegetarians. This excess burden of premature CAD in Asian Indians is due to a genetic susceptibility, mediated through elevated levels of lipoprotein(a) (Lp(a)), which magnifies the adverse effects of lifestyle factors associated with urbanization, affluence, and changes in diet. It appears that at a given level of any single or combination of conventional risk factor(s), the CAD rates among Asian Indians are at least double that of Whites. A more aggressive approach to prevention and treatment of both conventional and emerging risk factors is warranted in the Asian Indians. Although CAD is a fatal disease with no known cure, it is also highly predictable, preventable, and treatable with the existing knowledge.

INTRODUCTION
The term “Asian Indians” will be used in this review to denote people originating from the Indian subcontinent and to distinguish them from American Indians (native Americans). CAD among Asian Indians can be broadly categorized into 3 distinct forms: Type I or malignant type occurs in young individuals (<50 years) with marked prematurity and severity; this type is accompanied by the absence or low levels of conventional risk factors and the presence of high levels of emerging risk factors. Type II occurs in older individuals (>65 years) with high levels of conventional risk factors and low levels of emerging risk factors. Type III or mixed variety occurs between the ages of 50 and 65 and is accompanied by varying combinations of conventional and emerging risk factors. This review will focus primarily on the Type I or malignant form of CAD.

The CAD rates vary more than 10-fold among populations (Graph 1). The CAD rates among first generation immigrants are usually intermediate between those of the country of origin and the country of immigration. In virtually all populations, the CAD rates blend with those of the adopted country in two to three successive generations, depending upon the degree and speed of acculturation, as well as the prevailing rates in the respective countries.

Asian Indians have been a singular exception in having higher rates of CAD than the native population of the adopted country. Asian Indians residing in different countries have higher rates of incidence, hospitalization, prevalence, morbidity, mortality, and case fatality from CAD than people of other ethnicity.

The CAD rates in urban India over the past 40 years have increased dramatically and are now similar to that of overseas Indians and several times higher than in other Asian countries. This review initially discusses the magnitude of CAD among Asian Indians in various countries. Then, we discuss the crucial role of genetic susceptibility mediated by Lp(a) and its synergistic effects with other emerging as well as conventional risk factors. Finally, we offer recommendations for testing and treating to reduce the morbidity and mortality from malignant CAD in young Asian Indians.
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Figure 1

OVERVIEW OF CAD AMONG OVERSEAS ASIAN INDIANS

PREVALENCE:
In the U.K, which has one of the highest mortality rates of CAD, the prevalence of symptomatic CAD in Asian Indians is similar to Whites (8.5% versus 8.2%), but the asymptomatic or silent CAD is higher. In the US, the prevalence of CAD in Asian Indians is 4-fold higher than Whites (10% versus 2.5%) as shown in Graph 2.

The prevalence data underestimate the incidence when case fatality rates are higher, as is the case in the U.K. Therefore, the burden of CAD in Asian Indians is much higher than that reflected by the prevalence data.

Figure 2

MORTALITY RATE:
The relative risk (RR) of CAD mortality in Asian Indians is 20% to 50% higher than Whites in Canada, South Africa, and U.K., 300% to 400% higher than Chinese in Canada and Singapore, and 20 times higher than Blacks in South Africa (Graph 3). Other countries, which have reported substantially higher CAD mortality among Asian Indians, include Fiji, Mauritius, Trinidad, Uganda, Malaysia, and Qatar. In the U.S., only the state of California has reported CAD mortality data among Asian Indians. This report showed that CAD mortality among Asian Indians is 3-fold higher in men <45 years of age.

Figure 3

The excess CAD mortality among Asian Indians is greater in women than in men (Graph 3). In the U.S., CAD mortality rates are 2-fold higher in Asian Indian women 45-64 years of age than in Whites. In Singapore, CAD mortality among Asian Indian women 30-39 years of age is 8-fold higher than Chinese women of the same age. The excess burden of CAD among Asian Indian women has been recently reviewed.

Case Fatality Rate: The U.K. has universal access to high quality medical care. In a comparative British study, the hospitalization rate for acute MI was 2-fold higher among Asian Indians than Whites, despite a lower age and a greater proportion of non-smokers among the former. There was no difference in the management of the two groups, except that a higher percentage of Asian Indians received aspirin and thrombolytic therapy (75% versus 64%), yet, the Asian Indians had a 2-fold higher case fatality over the ensuing six months. Likewise, Asian Indians undergoing coronary artery bypass grafting (CABG) have almost twice the mortality of Whites. In the U.K. the CAD deaths among Asian Indians is expected to double in the next 30 years and the National Health Service is exploring strategies to tackle this burden.

Incidence: Data for incidence of CAD in Asian Indians is sparse except for the St. James Survey and the Singapore MI Registry. In the 10-year prospective follow-up of the St.
James Survey in Trinidad, the age-standardized RR of CAD incidence in Asian Indians was 2-fold higher than Whites and 7-fold higher than Blacks. In Singapore, where all MI in the country are systematically entered in the registry, the incidence of MI has been 3-fold higher among Asian Indians than Chinese men and women (Graph 4). This difference is maintained in 2001. Even developed countries including the U.S. have limited data on the incidence of CAD, since it is very difficult and expensive to collect detailed morbidity and mortality figures over an extended period of time.

**OVERVIEW OF CAD IN INDIA**

**CAD RATES IN RURAL INDIA:**

Despite higher rates of smoking, CAD rates in rural India are about one-half those in urban India (Table 1). A cross-sectional survey done in rural Haryana in 1998 revealed a CAD prevalence rate of 6% in rural Indians aged 35-64 years. This rate is 2-fold higher than contemporary U.S. rates and 3-fold higher than the 2.1% reported in 1974 from the same village.

**Figure 6**

Table 1: Prevalence of CAD in India

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**CAD RATES IN URBAN INDIA:**

The prevalence of CAD in urban India is about double the rate in rural India, and about 4-fold higher than in the U.S. The rates appear to be higher in south India with Kerala having a prevalence of 13% in urban areas, and 7% in rural areas (Table 1). The CAD rates in urban India are similar to those among the generally more affluent overseas Indians. For example, the prevalence of CAD in New Delhi is 10% and Chennai 11%. Overall there has been a >3-fold increase from 3% prevalence 30 years ago in urban India. In Sri Lanka, between 1980 and 1988, the CAD mortality rates have doubled and now have a prevalence of 10%, similar to India. CAD in India appears to follow the same pattern that was observed in the U.S., where high rates of CAD first appeared in the urban and affluent, followed by the poor and rural Americans.

Higher rates of CAD in urban India compared to rural India suggest important roles for nutritional and environmental factors, or nurture. There is a significantly higher body mass index (BMI) in urban India compared to rural India (BMI, 24 versus 20 in men and 25 versus 20 in women). There is also a higher rate of abdominal obesity among the urban
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BMI – Body Mass Index
Waist Hip Ratio > 0.85 in female and > 0.95 in male
*TC – total cholesterol

CONTRASTING CAD TRENDS IN INDIA AND U.S.:
During the past 3 decades, CAD rates doubled in India, whereas these rates have halved in most developed countries, especially the U.S. (Graph 6). CAD rates were identical in India and the US in 1968. As a result of these opposing trends, CAD rates are now 4-fold higher in India compared to the U.S. Though contemporary mortality data from India are unavailable, the totality of the data reviewed above suggests that an epidemic of CAD is already underway. Furthermore, the urban population in India is projected to double by the year 2020. Therefore, the CAD burden in India will greatly increase in parallel with affluence and urbanization of villages.

PREMATURITY OF CAD:
The excess risk of CAD in Asian Indians appears to be greater at younger ages. In the U.K, the RR of CAD mortality in Asian Indian men compared with Whites is 3.3 between the ages of 20-29 as opposed to 1.36 overall. In Singapore, compared with Chinese, the RR of CAD mortality in Asian Indian men between ages 30-39 is 12.5 in
contrast to 3.0 between the ages of 60-69.13 In an angiographic study in Malaysia, Asian Indians under 40 years of age had a 15-fold higher rate of CAD compared to Chinese and a 10-fold higher rate compared to Malays. About 25% of acute MI in India occur under the age of 40 and 50% under the age of 50.40 About 25% of acute MI in India occur under the age of 40 and 50% under the age of 50.44 In general, MI develops 5-10 years earlier in Asian Indians than in other populations,43,44 and its occurrence in patients under 40 is 5 to 10-fold higher.45

SEVERITY OF CAD:
The earliest report of high rates of CAD in Asian Indians was based on 9,568 autopsies undertaken between 1950 and 1954 in Singapore.46 This study showed a 7-fold higher rate of coronary atherosclerosis in Asian Indians compared to Chinese.46 Among those studied by coronary angiogram, three-vessel disease is seen among half of all Asian Indians and one third of premenopausal women.47-48 Unlike in Whites, CAD in young Asian Indians is known to be severe, extensive, and malignant.44,49,50 This is attributed to an accelerated atherosclerotic process that begins early in life. Contrary to common belief, the size of the coronary arteries is not different in Asian Indians when adjusted for BMI.51

CONVENTIONAL RISK FACTORS
All conventional risk factors are significantly associated with the risk of CAD in Asian Indians, as in all other populations. However, compared with Whites, Asian Indians have a lower prevalence of hypertension, hypercholesterolemia, obesity, and smoking, but a higher prevalence of high triglycerides (TG), low high density lipoprotein (HDL), glucose intolerance, and central obesity. Although the conventional risk factors do not fully explain the excess burden of CAD, these risk factors appear to be doubly important in Asian Indians, and remain the principal targets for prevention and treatment.

TOBACCO ABUSE:
Smoking rates in Asian Indian men are lower than in Japan, China, and other Asian countries and are very low in Asian Indian women.2 Smoking is however common among Bangladeshi men.52 Tobacco use (both cigarettes and beedi) is strongly related to CAD. Current smoking of >10 cigarettes or beedi a day is associated with a 6.7-fold increase in the risk of MI.53 Non-smoking men, women and children may be harmed by passive smoking which increases platelet activity, accelerates atherosclerosis, reduces exercise tolerance, and increases the risk of both fatal and nonfatal cardiac events.54 The risk of CAD begins to decline within months of smoking cessation and disappears within 3-5 years.

HYPERTENSION:
High blood pressure (BP) is a stronger risk factor for stroke than for CAD. Recent data show that even high normal levels (systolic BP 130-139 mm Hg and/or diastolic BP 85 to 89 mm Hg) are associated with doubling of CAD risk.55 Hypertension is closely correlated with salt and alcohol intake and obesity. A 5% increase in weight is associated with a 20% to 30% increase in the odds of developing hypertension. Conversely, a weight reduction of 9 kg can lower systolic BP by 6 mm Hg and diastolic BP by 3 mm Hg in hypertensive patients.56 In the U.K., hypertension is more common and associated with greater morbidity and mortality in Asian Indians than Whites but less than in Blacks.57,58

GENERALIZED OBESITY:
Obesity is associated with increased risk of hypertension, diabetes, dyslipidemia, and CAD. BMI, defined as the weight in kilograms divided by height in squared meters (kg/m2) is now accepted as the single best measure of obesity.59 The cut points for BMI in Asian Indians are lower than for Whites by 2 units for overweight and 5 units for obesity for both men and women (Table 4). For Asians, the optimum BMI is <23, whereas 23 to 25 is considered overweight and >25 obese.60 The weight cut points for different heights are given in Table 5. An even lower BMI cut point of 21.5 for males and 19 for females has been suggested recently from India. Height is inversely associated with CAD in both men and women.61,62,63,64

Figure 10
Table 4: Co-morbidities Risk with Different Levels of BMI in Asian Indians - Influence of Waist Circumference 60
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Figure 11
Table 5: Body Mass Index (BMI) and Weight Cut points for Overweight and Obesity at Different Heights in Asian Indians*

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Adapted from NHLBI Obesity Task Force, 199859 & diabetes.com.au/research/report_obesity.htm Feb 200060

APPLE-TYPE AND PEAR-TYPE OBESITY:

The distribution of fat is at least as important as the total amount of fat in the body. Marked adverse metabolic consequences are seen with central (android or apple-type), but rarely with gluteo-femoral (gynoid or pear-type) obesity. The usual measure of central obesity is the WHR. Since the excess fat is usually concentrated in the hip in women and the waist in men, the optimum value for the WHR is lower in women (<0.85) than in men (<0.95).60 Central obesity is not only more common but also more dangerous in Asian Indians.66

WAIST CIRCUMFERENCE:

Recently, waist circumference has been found to be an even better marker of central obesity than WHR.63 For Asian Indians, the optimum waist circumference is <80 cm in women and <90 cm in men. These values are about 8-10 cm lower than that recommended for Whites (Table 4).66 and underscore the need for early institution of weight management programs. At any given level of WHR or waist circumference, CAD rates are identical in men and women. It is plausible that sex differences in central obesity are the key to the gender gap in CAD.66

The recognition of the significance of central obesity should not divert attention from the metabolic consequences of noncentrally obese individuals who need to reduce weight. Among Asian Indians, as in other populations, both BMI and WHR are related to CAD risk factors in a graded manner; the maximum risk occurs in apple-shaped overweight and minimum in pear-shaped lean individuals.70

SOCIOECONOMIC STATUS (SES):

CAD has now become a disease of the poor in rich countries and of the rich in poor countries.71 Asian Indians with low SES have a higher prevalence of CAD and risk factors such as smoking and hypertension.72 However, differences in SES do not explain the excess burden of CAD among Asian Indians. Asian Indians have a 3 to 4-fold higher odds ratio for a high-risk lipid profile (despite having a lower level of TC), after controlling for SES, age, and sex.73

PSYCHOSOCIAL FACTORS:

Depression, hostility, anger, and low social support are associated with CAD, after controlling for adverse health behaviors, in some but not all studies.74-75 Contrary to common belief, type A personality is not associated with an excess of CAD.76 Moreover, the prognosis of CAD among type A persons is better than in type B patients.

DIABETES MELLITUS:

Abnormalities of glucose metabolism are particularly common and important in Asian Indians and often occur without significant obesity.9,77,78 A recent study in India showed an age-standardized prevalence of diabetes and impaired glucose tolerance of 12.1% and 14.0% respectively, with no gender difference.77 About 50% of diabetes remains undiagnosed. Both diabetes and impaired glucose tolerance are associated with increased risk of CAD even within the ranges considered normal.53,80 Approximately 80% of deaths in diabetic patients are attributable to cardiovascular disease (CVD), which in turn is highly correlated with dyslipidemia.41 Diabetic dyslipidemia consists of elevated TG, low HDL, and an increased proportion of small dense LDL. Among diabetics, Asian Indians have no higher risk of MI than Whites, but Blacks have only half the risk.82

METABOLIC SYNDROME (INSULIN RESISTANCE SYNDROME):

This syndrome is a precursor of diabetes and a common pathogenic mechanism for the development of CAD.83,84 This syndrome consists of hyperinsulinemia, atherogenic dyslipidemia, glucose intolerance, prothrombotic state, central obesity, and hypertension.85 For comparable age, BMI, and WHR, Asian Indians are more insulin resistant.
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than Whites. Metabolic syndrome is particularly common among Asian Indians. There is controversy as to whether cardiac risk in this syndrome exceeds that of the constituent risk factors.

The excess of diabetes and metabolic syndrome among Asian Indians worldwide has led many investigators to erroneously attribute virtually all the excess of CAD in this population to this entity. A recent prospective study involving 1,515 European and 1,420 South Asian men 40-49 years of age has convincingly demonstrated that diabetes and metabolic syndrome cannot fully explain the excess burden of CAD. In this study, there were 34 CAD deaths among South Asians and 20 deaths among Europeans during a median follow-up of 6.8 years. The age-adjusted RR for CAD death in Asian Indians was 2.0, which increased to 3.1 after adjusting for smoking and TC. Adjusting for glucose intolerance reduced this RR to 2.4. Further adjustments for insulin level, WHR, BMI, hypertension, fasting TG, and HDL failed to reduce this RR any further. These results underscore the need for studying other emerging risk factors such as Lp(a) (to be discussed below).

LOW HDL AND HIGH TG:
An 88 mg/dL increase in TG levels significantly increases the RR of CAD by 30% in men and 75% in women. Low HDL is associated with increased risk of CAD even if TG and TC levels are not elevated. A 10 mg/dL decrease in HDL confers the same risk for CAD as a 30 mg/dL increase in LDL. Low HDL with or without high TG is very common among Indians and genetic factors may be involved. Conversely, people with low TG-high HDL levels have a low risk of CAD, but this profile is uncommon among Asian Indians.

TOTAL CHOLESTEROL:
An elevated level of TC is the strongest risk factor for CAD. The mean level of TC in cord blood of newborns worldwide is 75 mg/dL, which rises to 120 mg/dL in two weeks and remains at that level until approximately 20 years of age, when it starts to gradually rise again. TC levels correlate well with the presence and severity of CAD in Asian Indians similar to Whites. Even though TC levels among Asian Indians are lower than in Whites, the levels are higher than other Asians. A recent large study has shown an 8-fold higher CAD mortality with an increase in TC from <160 to >280 mg/dL among young Americans. The optimum level of TC appears to be 150 mg/dL, especially for Asian Indians, much lower than the 200 mg/dL considered desirable in the Western society. TC levels < 150 mg/dL are not associated with increased risk of stroke or cancer.

Figure 12

ASIAN INDIAN ETHNICITY:
In the Seven Countries Study, the CAD mortality varied more than 5-fold among populations with the Japanese having the lowest and Finns having the highest mortality. Further analysis of the data has demonstrated that compared to Americans, the CAD risk is 50% lower among southern Europeans but 50% higher among northern Europeans at any given level of conventional risk factors. For example, the risk of hard CAD events (MI, revascularization procedures or death) among northern Europeans with a TC of 160 mg/dL is similar to southern Europeans with a TC of 240 mg/dL even when adjusted for smoking and hypertension. It appears that at any given level and/or combination of conventional risk factors, the risk of CAD among Asian Indians is the highest - higher than in northern Europeans, double that of Americans and several-fold higher than other Asians. A recent landmark study in Canada has found Asian Indian ethnicity to be a risk factor by itself. The failure of conventional risk factors to explain the 10-fold difference in CAD rates among populations is shown in Table 7.
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Figure 13
Table 6

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Figure 14
Table 7: Ethnicity and Paradox Galore

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| The Japanese cohort of the Seven Countries Study had the lowest age-standardized 25-year CAD mortality among all 16 cohorts, although 74% of the Japanese were smokers (Graph 8). 109 CAD rates in Japan are about 5-fold lower than the U.S. (Graph 1). Despite its affluence (second largest economy) and rapid urbanization, Japan has reduced its already low CAD rate by 60% and continues to have the lowest rates of CAD upon international comparison. The factors contributing to the low rates of CAD among Japanese include high HDL levels (55 mg/dL in men and 65 mg/dL in women vs 39 mg/dL and 43 mg/dL in Asian Indian men and women), low TC, low TC/HDL ratio and high consumption of fish and soy proteins. 113

| CHINESE PARADOX:                |
| The Chinese also have a very low rate of CAD, despite having high rates of hypertension and smoking (60%-75% in men) and the third largest economy. 114 The incidence and mortality from CAD in Chinese is 5-fold lower than the U.S. 114-116 In addition, the mortality rates among Chinese have been 3 to 4-fold lower than Asian Indians in many countries (Graph 2). 20,117,118 The low rates of CAD in China are attributed to their highly anti-atherogenic lipid profile. 115 The typical lipid levels in rural China are: TC 127 mg/dL; LDL 63 mg/dL; TG 100 mg/dL; HDL 44 mg/dL and TC/HDL ratio 2.9. 119

| ASIAN INDIAN PARADOX:           |
| Asian Indian physicians in the U.S. have a 4-fold higher prevalence of CAD compared to Americans. This high rate is in sharp contrast to the 4-fold lower rate of CAD among American physicians who participated in the Physicians’ Health Study. 120 The high rates of CAD in Asian Indians are accompanied by low rates of conventional risk factors. This was particularly true in the Coronary Artery Disease in Indians (CADI) study, which revealed a similar or lower prevalence of all major conventional risk factors, except for diabetes (Graph 9). 10 Physical activity was high (136 minutes/week) and saturated fat consumption was low (8% of the calories). 121 CAD rates and lipoprotein levels were similar among vegetarians and non-vegetarians. The high rate of CAD among Asian Indians despite these enviable levels of risk factors suggest an important role of a genetic risk factor, unrelated to, and possibly not amenable to even the maximum modification of lifestyle. |
LIPOPROTEIN (A) – A GENETIC RISK FACTOR FOR PREMATURE CAD AMONG ASIAN INDIANS

LIPOPROTEIN(A), THE “DEADLY CHOLESTEROL”:

Lp(a) is a variant of LDL particle which has in addition to apolipoprotein B, apolipoprotein(a). Lp(a) is a strong independent risk factor for premature CAD in many populations including Whites, Chinese, and Japanese. Lp(a) is often the link between atherosclerosis and thrombosis. The atherogenicity of Lp(a) is 10-fold higher than LDL. Lp(a) is also highly thrombogenic and antifibrinolytic, by virtue of its homology to plasminogen. Therefore, the term “deadly cholesterol” may be used to describe Lp(a) and to distinguish it from the “good cholesterol” or HDL, the “bad cholesterol” or LDL, and the “ugly cholesterol” or TG. Its levels are genetically determined with environmental factors having only a negligible impact. Childhood levels of Lp(a) are a better predictor and marker for future CAD in young adult life than any other lipoproteins. Although the relationship of Lp(a) to CAD is continuous and graded, a level of 15-20 mg/dL is now considered the threshold.

Enas et al. were the first to report high levels of Lp(a) in Asian Indians. Elevated Lp(a) level was the most common risk factor in the CADI Study. Subsequent studies have reported elevated Lp(a) levels in Asian Indians in the U.S., Canada, Singapore, U.K., and India. Numerous case control and angiographic studies have shown Lp(a) to be a powerful risk factor for CAD among Asian Indians.

A genetic determination of Lp(a) levels in Asian Indians is strongly supported by reports of identical levels in several countries, with a mean level of 20 mg/dL. The Lp(a) levels in Asian Indian newborns are significantly higher than in Chinese in Singapore and the differences in Lp(a) levels in cord blood parallel the 3 to 4-fold differences in adult CAD mortality between these two populations, observed over the past 40 years. In the U.K., Lp(a) levels in Asian Indians are significantly higher than Whites but identical to their siblings living in India. Also, Asian Indians with CAD and their offspring in the U.K. had higher Lp(a) levels than White CAD patients and their offspring. More than 10 angiographic and case-control studies in India have shown elevated Lp(a) levels to be a powerful risk factor for premature CAD, especially under the age of 40.

A recent case control study involving Asian Indians in India and the U.S. showed similar results. Higher levels as well as low molecular weight isoforms of Lp(a) were found in patients with CAD than in controls. Of particular importance, the Lp(a) level was inversely related to the molecular weight of the more abundant Lp(a) isoforms. This was the first report implicating Lp(a) isoform size as a predictor for development of premature CAD in Asian Indians. The Asian Indian control subjects in the U.S. and India had similar levels of Lp(a). These data suggest that elevated levels of Lp(a) confer genetic predisposition to CAD in Asian Indians. However, U.S. controls had higher levels of LDL and apo B, and lower levels of HDL, than their counterparts in India. This suggests that nutritional and environmental factors (affluence, urbanization and/or immigration) can further increase the risk of CAD by virtue of acquired dyslipidemia in these genetically predisposed individuals.

Asian Indians have Lp(a) levels intermediate between Whites and Blacks. However, Blacks have a lower rate of CAD despite having the highest levels of Lp(a) due to the presence of high molecular weight isoforms and high HDL levels. Conversely, Asian Indians have heightened risk from Lp(a) due to the presence of low molecular weight isoforms, as well as low HDL. Superko et al. have reported abnormalities of HDL subclasses in Asian Indians. Even among Asian Indians without low HDL, HDL 2b, the most protective subclass of HDL was low. In this study, 42% of Asian Indians had Lp(a) >20 mg/dL and 92% had low HDL 2b.

MULTIPLICATIVE EFFECTS OF LP(A) WITH CONVENTIONAL AND EMERGING RISK
FACTORS:

Lp(a) is an independent risk factor for CAD with a relative risk of 2.7 at levels >20 mg/dL. However, the pathophysiological effects of Lp(a) are exponentially increased by concomitant unfavorable concentrations of other lipoproteins, especially low HDL. Recent studies indicate that the CAD risk in patients with high Lp(a) is much greater with low HDL than with high LDL. For example, the relative risk of CAD from high Lp(a) increases to 8.3 when HDL is <35 mg/dL versus 2.6 when LDL is >160 mg/dL (Graph 10).

Lp(a) levels >40 mg/dL (versus <40 mg/dL) increase the risk of CAD associated with other risk factors by a factor of 2 to 10 (smoking by a factor of 2, diabetes and hypertension 4, high TC/HDL ratio 7, and high homocysteine 10) (Graph 11). More importantly, subjects with high levels of Lp(a), homocysteine and TC/HDL ratio have a 122-fold risk of CAD if any one of the conventional risk factors is also present. For comparison, the CAD risk is only 20-fold in patients with all five major risk factors combined. Certainly, the presence of additional risk factors can further double or triple the risk from Lp(a). These multiplicative effects of conventional and emerging risk factors appear to provide a plausible explanation for the excess burden of CAD among Asian Indians.

HOMOCYSTEINE:

Recently homocysteine has been identified as a novel risk factor for CAD in Indians. Homocysteine levels are higher among Asian Indians than Whites in several countries. A 1 micromol/L increase in homocysteine level is associated with an increase in CAD risk of 12% in men and 16% in women. Refsum et al have recently reported a very high prevalence of hyperhomocysteinemia (>15 micromol/L) in 75% of subjects in India, which was strongly correlated with cobalamin deficiency (and not folic acid deficiency, which was rare). Total cobalamin of <150 pmol/L was found in 47% of subjects. There was no difference between vegetarians and non-vegetarians. Also, about 75% of the subjects had signs of cobalamin deficiency. Although a few small studies showed no relationship of homocysteine with CAD in India, no biological explanation other than small sample size has been provided.

OTHER EMERGING RISK FACTORS:

Asian Indians also have higher levels of most of the other emerging biochemical risk factors such as apolipoprotein B, plasminogen activator inhibitor (PAI-1), fibrinogen, and C-reactive protein (CRP). Although Indians are expected to have a preponderance of small dense LDL, the results have not been conclusive. The relative contributions of various risk factors to CAD in Asian Indians are shown in Graph 12. The effect of diet and physical activity is mediated through glucose and lipid metabolism.
The high rates of CAD in Asian Indians are due to a combination of nature (genetic predisposition) and nurture (lifestyle factors). The nature is attributed predominantly to elevated levels of Lp(a), a common but often ignored risk factor in Asian Indians. With a prevalence >40%, elevated Lp(a) appears to be the most common risk factor in this population. Given this genetic predisposition, the harmful effects of lifestyle factors are magnified exponentially (Graph 11). The lifestyle factors include those associated with affluence and urbanization as well as immigration and acculturation. Urbanization is accompanied by decreased physical activity and increased consumption of fat and calorie dense food, resulting in abdominal obesity, insulin resistance, and atherogenic dyslipidemia. These acquired metabolic abnormalities appear to have a synergistic effect on the development of CAD in genetically susceptible individuals such as those with elevated levels of Lp(a).

Singapore was the first country to report a >3-fold higher CAD incidence and mortality among Asian Indians than in Chinese.46 The overall CAD mortality rate doubled in Singapore from 1959 to 1983 (107 to 205/100,000 men and from 31 to 72 in women) but the ethnic differences in CAD incidence and mortality were maintained. 20 Since 1983, the differences in CAD rates between these two populations have not narrowed and the latest incidence data (2001) shows a 3-fold higher incidence in Asian Indians.21,22 The Singapore experience highlights the disproportionate impact of lifestyle factors on Asian Indians and underscores the need for lower target goals for all risk factors.

**IMPLICATIONS**

**EARLY MODIFICATION OF LIFESTYLE:**
Increasing physical activity and decreasing consumption of calories as well as saturated fat are the foundation of this strategy and should begin early in life. Avoidance of abdominal obesity is very important, even when BMI is normal. Every effort should be undertaken to discourage children and adults from using tobacco products. The consumption of all types of tobacco products should be reduced and eventually eliminated. The roles of lifestyle modification at the individual and population levels have been recently reviewed.54,159

**PHYSICAL ACTIVITY:**
Atherogenic risk factor clustering is common in Asian Indians and worsens with weight gain.160 Age-related increase in weight and waist circumference is closely related with decrease in physical activity. Most studies have shown a reduced level of physical activity among Asian Indians,161 with the notable exception of Asian Indian physicians in the CADI study.121 Whereas daily walking of 45-60 minutes is sufficient to prevent weight gain, walking of fifty-six kilometers per week is necessary for weight loss. However, even walking two to three kilometers (1 hour) per week produces a favorable risk factor profile, especially fibrinogen and insulin levels.162

**DIETARY MODIFICATION:**
The National Cholesterol Education Program (NCEP) III recommends >50% of total calories from carbohydrates, <20% from protein and 25-35% from fat. Diets of any type containing more energy than needed or expended will lead to obesity and dyslipidemia.163 Asian Indian physicians in the U.S. follow a heart healthy diet with 32% fat and 8% saturated fat similar to that recommended by NCEP.164 This appears to be an exception rather than the rule. In a Canadian study, Asian Indians consumed more fried foods and high-fat dairy products such as homogenized milk than Whites.165 Although the intake of fat is 20-25% in most Asian countries, many affluent Indians receive >50% of their calories from fat.

**SATURATED FAT (SAFA):**
The quality of the fat is perhaps more important than the quantity. Saturated fat (SAFA) intake is the principal determinant of TC and CAD.109 Contrary to popular belief, dietary cholesterol intake plays only a minor role in TC levels. Kerala, renowned for the universal use of
coconut, not only has the highest level of TC in India, but also the highest rate of CAD in India (Table 1). The proportion of subjects with high TC (>239 mg/dL) in Kerala, which also has a very high rate of CAD, about 80% of the fat in the habitual diet comes from coconut. Other foods containing SAFA should also be severely restricted to limit the total intake of SAFA to <7% of the energy. Major sources of SAFA include red meat, coconut (meat, milk and oil), palm oil, butter, ghee (clarified butter), vanaspathi (vegetable ghee), and most dairy and bakery products. In Mauritius, a regulated change in the SAFA content of the widely used cooking oil (from palm oil to soybean oil) resulted in a dramatic fall in TC by 32 mg/dL. These data underscore the crucial role of cooking oils in levels of TC. The role of cooking oil in TC level and CAD has been recently reviewed. TRANS-UNSATURATED FATTY ACIDS (TRUFA): Consumption of TRUFA, formed by the partial hydrogenation of vegetable oils increases LDL and decreases HDL, resulting in a higher TC/HDL ratio. For example, replacement of 9% of calories from SAFA with TRUFA results in a 15 mg/dL decrease in HDL. The major sources of TRUFA include vanaspathi, margarines, vegetable shortening, biscuits, cake, donuts, and white bread and virtually all “crispy foods”. SAFA calories should not be replaced by TRUFA calories. MONOUNSATURATED FATTY ACIDS (MUFA) AND POLYUNSATURATED FATTY ACIDS (PUFA): Substitution of 1% carbohydrate calories by SAFA increases TC by 1.5 mg/dL whereas PUFA and MUFA lower it by 0.5 mg/dL. Replacing SAFA with MUFA and PUFA may be more effective in preventing CAD than reducing overall fat intake. The NCEP III has recommended up to 20% of total calories from MUFA. A higher intake of MUFA is particularly beneficial among Asian Indians as it is very effective in lowering LDL and does so without raising TG or lowering HDL. Since all fats are high in calories, the addition of MUFA should be at the expense of SAFA and carbohydrates. Olive oil and Canola oil are high in MUFA. Nuts and avocado are excellent sources of MUFA and are recommended provided the quantity is no more than 30 grams. Meats are high in MUFA but also high in SAFA and should be used sparingly. REUSE OF OIL USED FOR DEEP FRYING: Reuse of such oil may be particularly dangerous. The repeated use of such oil is a cause for concern in India where this practice is common. The consumers need to be educated about the atherogenic and anti-atherogenic effects of various cooking oils, as well as animal and vegetable ghee. There is little awareness and even some controversy about the atherogenic effects of certain foods and oils, especially in regions where sale or consumption of such products has a profound impact on the regional economy. CONTAMINATED VEGETARIANISM: About 50% of Asian Indians are vegetarians, but their rates of diabetes and CAD are as high as non-vegetarians. Unlike the Western vegetarians, the lipoprotein levels among Asian Indian vegetarians are not different from non-vegetarians. This phenomenon is due to contaminated vegetarianism, wherein vegetarians consume liberal amounts of butter, ghee, cheese, dairy, and bakery products, all of which are major sources of SAFA and/or TRUFA. Contrary to popular belief, dairy products (and not meat) are the major source of SAFA, even in the Western diet. Recent research indicates that a diet very low in fat and very high in carbohydrate can aggravate dyslipidemia by increasing TG and decreasing HDL levels. There appears to be a threshold for carbohydrate consumption. Intake of carbohydrates >282 g/day often leads to high TG and atherogenic dyslipidemia. SHOULD ASIAN INDIANS BE TESTED DIFFERENTLY? Since conventional risk factors do not explain the excess burden of CAD among Asian Indians, conventional approaches to testing and treatment are insufficient. The most important aspect of prevention of CAD is to identify individuals at high risk of developing CAD at an early age. Since Lp(a) is fully expressed in the first year of life, tracking Lp(a) from childhood may be better than focusing on other dyslipidemias which are not expressed until later in life. It seems reasonable to test all Indians for elevated levels of Lp(a) and homocysteine. Lp(a) and homocysteine levels need not be repeated if the levels are in the optimum range. Other lipoproteins must be tested before the age of 20 and repeated every 5 years and/or following every 5 kg weight gain.
SHOULD ASIAN INDIANS BE TREATED DIFFERENTLY?

The database to support treatment recommendations is derived primarily from studies of White populations. Therefore, the risk calculation is likely to underestimate or overestimate in non-White populations. Moreover, genetic factors determine individual variations in disease susceptibility in response to environmental factors. The risk of CAD from all known risk factors is graded and continuous. For any given level of risk factors, the CAD risk among Asian Indians is at least double that of Whites. Therefore, the threshold of intervention and goals of treatment should be lower in Asian Indians than in Whites by 10% to 20%, akin to those recommended for patients with diabetes (Table 8). In the NCEP III, diabetes is regarded as a CAD risk equivalent, with an LDL goal of <100 mg/dL, irrespective of the presence or absence of CAD. The goal of treatment for hypertension in diabetics is <130/85 mm Hg. In the Hypertension Optimal Treatment (HOT) study, patients with diabetes mellitus had a 51% reduction in major cardiovascular events when diastolic blood pressure was reduced to <80 mm Hg compared to <90 mm Hg.

Table 8: Threshold of Intervention and/or Targets of Treatment in Indians

Table 9: Proposed Cut-points for LDL, Non-HDL Cholesterol, and Total Cholesterol Levels (mg/dL) for Asian Indians*

<table>
<thead>
<tr>
<th>Category</th>
<th>LDL</th>
<th>Non-HDL Cholesterol</th>
<th>Total Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimum</td>
<td>&lt;80</td>
<td>&lt;110</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Near or above optimal</td>
<td>80-99</td>
<td>110-129</td>
<td>150-169</td>
</tr>
<tr>
<td>Borderline high</td>
<td>100-114</td>
<td>130-144</td>
<td>170-184</td>
</tr>
<tr>
<td>High</td>
<td>115-129</td>
<td>145-159</td>
<td>185-199</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt;130</td>
<td>&gt;160</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

* Modified from NCEP164; goals for Asian Indians are about 20% less than NCEP. Non-HDL cholesterol is more important than LDL when the TG is >150 mg/dL.

THE TRIGLYCERIDE ISSUE:

Although TG is an important risk factor, lowering TG has not been shown to reduce CAD risk. However, in patients with levels >400 mg/dL, lowering TG is necessary to prevent pancreatitis. Lowering LDL and raising HDL remain primary proven therapies in CAD prevention, for patients with elevated triglyceride levels. In subjects with TG >250 mg/dL, significant and dose-dependent reductions in triglyceride of 22-45% (identical to LDL reduction) were seen with all statins. It is often ignored that for a given level of TC, LDL decreases by 20 mg/dL for every 100 mg/dL increase in TG, spuriously lowering the apparent CAD risk.

NON-HDL CHOLESTEROL:

Non-HDL cholesterol eliminates the false sense of security from low LDL in patients with high TG. Although the primary target of treatment remains LDL, non-HDL cholesterol appears to be an even better target, especially for Asian Indians known to have high TG. Non-HDL
cholesterol is obtained by subtracting the HDL from TC and reflects the total burden of atherogenic lipoproteins. The various cut-points for non-HDL cholesterol level are given in Table 9. When non-HDL cholesterol is used as a target for treatment, more patients would qualify for aggressive drug treatment.

**RELEVANCE OF NCEP III TO ASIAN INDIANS:**

People with diabetes, subclinical atherosclerosis, and multiple risk factors with 10-year risk >20% are considered CAD equivalents, under the new NCEP guidelines. The lipid goals are the same for patients with known CAD and CAD equivalents. Since the data needed for risk prediction in Asian Indians is not available, Asian Indians with multiple emerging and conventional risk factors may be treated as CAD equivalent with an LDL goal of <100 mg/dL. This is particularly true of those with HDL <50 mg/dL, Lp(a) >15-20 mg/dL, homocysteine >10 mmol/L and/or TG >150 mg/dL. In our opinion, the LDL level should be reduced to <80 mg/dL in Asian Indians with CAD. In the Heart Protection Study of 20,536 patients (age 40-80 years and TC >135 mg/dL) simvastatin 40 mg/day reduced LDL by 60 mg/dL. This resulted in a 24% reduction in major acute coronary events (MACE) in men, women and the elderly in 5 years, with virtually no major side effects. The results of this study have clearly demonstrated that there is no threshold below which lowering TC doesn’t lower the risk. In other words, lower the TC the better it is.

**EXPANDING USE OF STATINS IN THE PREVENTION AND TREATMENT OF CAD:**

Statins have now become the foundation of treatment of elevated LDL, the principal causative factor for CAD. For every 10% of LDL-lowering with statins, CAD mortality would be reduced by 17% and total mortality by 11%. In contrast to dietary interventions, which reduce LDL by only 5-10%, statins can reduce LDL levels by up to 60%, an effect seen with no other therapy. Randomized clinical trials, which did not use the maximum doses of statins, have achieved an LDL reduction of 25 to 35%. This was accompanied by up to 37% reduction in MACE, 42% reduction in coronary death, and 30% reduction in total mortality (Table 10). Benefits are seen in a broad range of patients with and without CAD and with TC levels that are high, average, or low. Striking benefits are also seen in patients with low HDL and high TC/HDL ratio, even when the LDL level is not elevated. The results of AFCAPS/TexCAPS are particularly relevant to Asian Indians (Graph 13). In this study, all participants had HDL <50 mg/dL and TC/HDL ratio >5; only a few had other risk factors and none had CAD. The risk of a first MI was reduced by one-third by lowering the LDL to <115 mg/dL. The CAD risk reduction in AFCAPS patients (HDL <50 mg/dL) was 13 times greater than that observed from treatment of diastolic hypertension (90-109 mm of Hg) in the medical research council (MRC) trial. Thus, the benefit of lipid-lowering therapy appears to exceed that of treatment of hypertension and diabetes, both having only a modest effect in reducing the risk of CAD.

**Figure 22**

Table 10: Reduction in Morbidity and Mortality in Landmark Statin Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>MACE* (%)</th>
<th>CAD death (%)</th>
<th>All cause death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>4444</td>
<td>34</td>
<td>42</td>
<td>30</td>
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<tr>
<td>CARE</td>
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<td>9</td>
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<td>WOSCOPS</td>
<td>6595</td>
<td>31</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>6605</td>
<td>37</td>
<td>NS**</td>
<td>NS**</td>
</tr>
</tbody>
</table>

*MACE - major acute coronary events (unstable angina, MI and death)*

**Figure 23**

Statins also have numerous beneficial effects beyond lipid lowering. The reduction in CVD morbidity and mortality with statins is rapid, profound, universal, and not defined by age, sex, or the type of vascular bed. Statins can delay or avoid the need for expensive coronary revascularization procedures. Statins alter the natural history of CAD and are the most potent antiatherosclerotic agents available currently. Meeting the LDL goals can now be considered a
surrogate for decreasing CAD morbidity and mortality. The safety and benefits of statins for CVD risk reduction is at least as great as that of aspirin, if not more. Therefore, statins should remain the foundation of preventive cardiology and first line drugs in the treatment of dyslipidemia.

**MANAGEMENT OF SUBJECTS WITH ELEVATED LP(A) LEVELS:**

In people with elevated Lp(a), the preventive and therapeutic goals consist of diligently searching and drastically reducing all concurrent modifiable risk factors. Lowering LDL with statins is the initial strategy for patients with elevated Lp(a). Moderate lowering of TC to <200 mg/dL or LDL to <122 mg/dL was not sufficient to reduce atherogenicity in patients with elevated Lp(a) in the 4S. Therefore, aggressive lowering of LDL with potent statins in high doses may be necessary in patients with elevated Lp(a). The safety and benefits of lowering of LDL to <80 mg/dL have been demonstrated in three recent trials. Once the LDL is lowered sufficiently, niacin may be used to lower Lp(a) levels. The newer extended release preparation, Niaspan, reduces the Lp(a) levels by 30% and can be given in combination with statins. Niaspan has also been shown to selectively increase the cardioprotective sub-fraction of HDL. In the Coronary Drug Project, niacin reduced CAD and total mortality. In postmenopausal women, estrogen replacement therapy can lower Lp(a) substantially. In the Heart and Estrogen/Progestin Replacement Study, the recurrent MACE were reduced by 50% among women with elevated Lp(a) without any early harm or adverse effects.

**CONCLUSION**

India is currently in the middle of a CAD epidemic that was initially observed among overseas Asian Indians. Although the conventional risk factors do not fully explain the excess burden of CAD, these risk factors are doubly important in Asian Indians, and remain the principal targets for prevention and treatment. Due to the genetic susceptibility mediated primarily by Lp(a), the adverse effects of the conventional risk factors are magnified several-fold. Therefore, the threshold of intervention and goals of treatment for various risk factors in Asian Indians should be 20% lower than Whites for LDL and 10% lower for all other risk factors (Tables 8 and 9). It seems appropriate to begin preventive strategies at an earlier age than in other populations because of the extreme prematurity and malignant nature of CAD. The benefit of statin therapy appears to exceed that of treatment of hypertension or diabetes. Therefore, lipid-lowering therapy with statins should be considered among the first line of treatment rather than the last thing we do for our patients.

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