High rates of CAD in Asian Indians in the United States despite intense modification of lifestyle: What next?

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Asian Indians around the globe have the highest rates of coronary artery disease (CAD), even though almost half of them are life-long vegetarians. When compared to Whites, Blacks, Hispanics and other Asians, the CAD rates in Asian Indians worldwide are 2–4 times higher at all ages and 5–10 times higher in those under 40 years of age. The prevalence of CAD in New Delhi is 4-fold higher than in Framingham (US). The unifying hypothesis, considering all the data available today, suggests the combined role of nature and nurture in the development of malignant atherosclerosis in young Asian Indians. Nature is provided by elevated levels of lipoprotein(a), the levels of which are genetically determined. Urbanization, affluence, and mechanization provide nurture. Since conventional risk factors do not explain this excess burden of CAD in Asian Indians, conventional approaches to prevention and treatment may also be insufficient. Asian Indian physicians in the US have made maximum modification of lifestyle and yet their CAD rates are 4-fold higher than White Americans and 6-fold higher than Chinese Americans. Dyslipidemia characterized by the 'Lipid tetrad' appears to offer the best plausible explanation. Therefore, an aggressive approach to treatment of dyslipidemia seems not only justified, but warranted in this population. The overall risk of CAD in Asian Indians appears to be similar to that of other populations with known CAD. Therefore, high-risk Asian Indians should be treated for an low density lipoprotein (LDL) goal < 100 mg/dl, the level recommended for patients with CAD, if maximum modification of lifestyle fails to achieve this goal.

AMONG the one million Asian Indians settled in the United States (US), thirty thousand are physicians, including two thousand cardiologists[1]. About one in forty Asian Indians in the US is a doctor, and one in five hundred is a cardiologist. These Asian Indians enjoy a high socio-economic status and nearly half of them are life-long vegetarians, two factors generally considered protective against coronary artery disease (CAD). The Asian Indian physicians in the United States are not only aware of the major coronary risk factors but appear to have made maximum modification of lifestyle to reduce their risk of CAD. Yet, they have the highest rates of CAD among all Americans[2].

In the Coronary Artery Disease in Asian Indian (CADI) Study of 1131 men, aged 30–69, the prevalence of CAD was 10.2% (ref. 3) (80% angiographically documented) compared with 2.5% in White men of the same age group in the Framingham Offspring Study[4]. The rates were similar among subjects born in different states in India as well as among those settled in different states in the US. Vegetarians and non-vegetarians had similar rates. Among the Asian Indians studied, 75% were physicians and they had CAD rates similar to non-physicians.

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The 4-fold higher rates of CAD in Asian Indian physicians are in sharp contrast to the 5-fold lower rates of CAD among other physicians in the US[5]. Among the participants in the Physicians' Health Study, the CAD mortality (prevalence data not available) was only 22% that of the general US population[6]. The high rates of CAD in Asian Indians in the US are not limited to physicians[7]. The hospitalization rates for CAD in Asian Indians are 4-fold higher than Whites and 6-fold higher than Chinese in California[8]. Although their overall mortality is low, young Asian Indian men and middle-aged Asian Indian women in the US have a substantially higher proportionate mortality ratio (PMR) for CAD[9]. For example, with 100 as the standard for Whites, the PMR for CAD is 350 in Asian Indian men under 45 years of age and 210 for Asian Indian women between the ages of 45 and 65. Thus, Asian Indians in the US have considerably higher rates of incidence, prevalence, and mortality from CAD than the general population.

The high rates of CAD among Asian Indians are in sharp contrast to the low rates of CAD among other Asians. Despite very high rates of smoking and hypertension, the CAD rates in Japan[10] are 4-fold lower than in the US (Japanese paradox). The same is true in China (Chinese paradox)[11]. Serum cholesterol levels in Japan,

China as well as other Asian countries are much lower than in the West (150 mg/dl to 170 mg/dl) and account for their low rates of CAD[12]. Though these Asians experience an increase in CAD upon immigration and acculturation to the US, the CAD rates among other Asian Americans remain substantially lower – about half that of White Americans[7].

The high rates of CAD in Asian Indians appear to be a global phenomenon, shared by the inhabitants of the four countries of the Indian subcontinent (India, Pakistan, Bangladesh and Sri Lanka) as well as immigrants from these countries to various regions of the world[13]. The CAD mortality rates among overseas Asian Indians are 2- to 4-fold higher compared to compatriots of other ethnic origins[14]. Women have an even greater excess of CAD than men, even though smoking is uncommon among them (Table 1).

Those living in the urban areas of the Indian subcontinent have CAD rates similar to Indians living overseas[15]. The CAD rates in rural India are one-half that of urban India, though smoking is more common in Indian villages[16]. However, these rural rates are double that of the overall US rates[17] and 4-fold higher than in rural China and Japan.

The three remarkable features of CAD in the Asian Indian population are extreme prematurity, marked severity and low prevalence of conventional risk factors. Asian Indians develop CAD 5- to 10 years earlier than in other populations and the chance of the first MI occurring under 40 years of age is 5 to 10-fold higher. Coronary angiographic studies have consistently shown severe, extensive multi-vessel disease even among nonsmoking premenopausal women. This suggests the development of a malignant atherosclerosis in Asian Indians at a much earlier age than in other populations.

Table 1. Standardized coronary mortality rate in Asian Indians compared with other population groups/100 000 (1980–1985)

Population Group	Men	Women
Singapore		
Asian Indians	613	214
Chinese	162	57
Malays	306	133
Canada		
Asian Indians	469	182
Chinese	144	53
Whites	386	131
South Africa		
Asian Indians	573	279
Blacks	25	15
Whites	453	179
England and Wales		
Asian Indians	433	137
Whites	318	94
Caribbeans	143	71
General population (for comparison)		
Scotland	398	142
USA	235	69
France	94	20
China	49	27
Japan	37	9

Adapted from refs. 16, 21.

Conventional risk factors and paradox galore

These high rates of CAD among Asian Indians are accompanied by low rates of conventional risk factors (Asian Indian paradox). Among the participants in the CADI Study, only 3% smoked cigarettes, 3% had obesity, 14% had high blood pressure, 17% had high cholesterol (> 240 mg/dl), 19% had high triglycerides (>200 mg/dl) and 24% had low HDL (<35 mg/dl) (Table 2) (ref. 3). The corresponding percentages among the White Americans were 27%, 31%, 19%, 23%, 11%, and 21% respectively. Contrary to studies in other countries, the serum levels of triglycerides and HDL in Asian Indians were not significantly different from Whites. This finding is attributed to the surprisingly high levels of leisure-time physical activity among these health-conscious physicians.

The relationship of diet, abdominal obesity, and physical activity to plasma lipoprotein levels was studied in a subgroup of 153 Asian Indian male physicians[19]. Their leisure-time physical activity averaged 136 minutes per week, nearly double the level of physical activity recommended by the American Heart Association. Their diet averaged 56% energy from carbohydrates, 32% from total fat, and 8% from saturated fat. Thus, the diet of these physicians appears to be better than the Step 1 diet recommended by the National Cholesterol Education Program (NCEP). High carbohydrate intake (>282 g per day) was associated with high triglycerides level ($P < 0.05$), whereas high total fat intake was associated with high waist-to-hip ratio ($P < 0.01$). Abdominal obesity was the prevalent form of obesity and a waist-to-hip ratio (WHR) of 0.90 appears to be the cut-off point since those with higher WHR had an adverse pattern of lipid profile.

Insulin resistance syndrome

Asian Indians worldwide have higher rates of diabetes. Therefore, insulin resistance syndrome has been invoked as the most plausible explanation for the excess burden of CAD in this population. Diabetes mellitus was found in 8% of the Asian Indians compared with 1% of the White Americans in the CADI Study. Interestingly, all minority populations in the US have higher rates of diabetes than Whites but no higher rates of CAD. Hispanics actually have a lower rate of CAD than Whites (Hispanic paradox). More importantly, the Pima Indians

Table 2. Prevalence of CAD and its risk factors in Asian Indians in comparison with other populations in the United States

	CADI[1] Asian Indians	PHS[2,3] American Physicians	FHS[4] White Americans	SHS[5] Pima Indians
CAD prevalence (%)	10	NA*	2.5	1
Cigarette smoking (%)	3	9	27	30
High blood pressure (%)	14	14	19	32
High serum cholesterol >240 mg/dl (%)	17	Low	23	5
Mean serum cholesterol in mg/dl	200	214	NA	177
Diabetes (%)	8	4	1	65
Obesity (%)	3	Low	31	71
Body mass index	24.7	25	NA	31.1
Sedentary lifestyle (%)	20	33	NA	High
Lp(a) >30 mg/dl (%)	25	NA	NA	Low ?
Daily aspirin use (%)	NA	49	NA	NA
Saturated fat intake (% of calories)	8	NA	NA	NA

[1]Coronary Artery Disease in Indians Study (refs 3, 18, 19, 22).
[2]Physicians' Health Study (ref. 6).
[3]Enas, E. A., (ref. 5).
[4]Framingham Offspring Study (ref. 4).
[5]Strong Heart Study (ref. 20).
*Mortality 15–22% of the general population; NA, not available.

known for the world's highest rates of diabetes (65%), have the lowest rate of CAD among all Americans (American Indian Paradox)[20]. In addition, several contemporary studies in India show a prevalence of diabetes of only 5–10%, whereas the prevalence of CAD is about 10%. These data suggest that even insulin resistance cannot explain the extreme prematurity, severity, morbidity and mortality from CAD in the Asian Indian population[21].

Lipoprotein (a) – the genetic risk factor for premature CAD in Asian Indians

Elevated serum levels of lipoprotein (a) {Lp(a)} were the most common risk factor in Asian Indians in the CADI Study. Lp(a) levels >30 mg/dl, generally considered the threshold for high risk of CAD, were found in 25% of Asian Indians[22]. For comparison, 17% of Whites and 8% of Hispanics have Lp(a) levels >30 mg/dl. Among the Hispanics, those with the greatest Native American admixture have the lowest levels of Lp(a), suggesting low levels of Lp(a) in Native Americans.

Lp(a) is now recognized as the most powerful and most prevalent risk factor for premature CAD in diverse populations. Its levels are largely genetically determined with environmental factors having minimal influence. Thus, Lp(a) is a true genetic risk factor for premature CAD. It is ten times as atherogenic as LDL. In addition, it has significant thrombogenic and antifibrinolytic properties due to its structural homology with plasminogen. Since stable adult levels are reached in infancy, the pathological effects of elevated Lp(a) start about 15 to 20 years earlier than other risk factors; hence its crucial role in premature CAD.

Unlike other lipoproteins, Lp(a) levels are highly correlated with the severity of atherosclerosis in various vascular beds. Lp(a) levels not only modulate the risk of CAD and its clinical events in patients with hypercholesterolemia but also determine the outcome following percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass surgery (CABG)[23]. Lp(a) levels were the dominant determinant of death in the 4S and many other studies. More recently, Lp(a) levels were found to be the dominant determinant of target-organ damage in patients with hypertension[24]. These target organ damages included left ventricular hypertrophy, angina, myocardial infarction, and heart failure.

Shaukat *et al.*[25] have reported a strong correlation between Lp(a) levels and the severity of CAD in Asian Indians. In their study, Asian Indians with CAD as well as their healthy offspring had higher levels of Lp(a) than in White CAD patients and their healthy offspring. More recently Mohan *et al.* (pers. commun.) in Madras have shown Lp(a) levels to be the most powerful determinant of CAD in their patients with non-insulin-dependent-diabetes mellitus (NIDDM). Lp(a) levels were nearly double in NIDDM patients with CAD compared to those without CAD (40.5 mg/dl vs 23.1 mg/dl, $P < 0.001$). Lp(a) levels >30 mg/dl were seen in 57% of NIDDM patients with CAD compared to 36% of NIDDM patients without CAD and 30% of control patients with neither NIDDM nor CAD. These data suggest that the Lp(a) level is a dominant determinant of CAD and its

outcome in patients with NIDDM, hypertension and hypercholesterolemia.

Multiplicative effects of Lp(a) with other lipoproteins

Although Lp(a) is a strong independent risk factor for premature CAD, its pathogenicity is markedly influenced by the serum concentrations of other lipoproteins[26]. For example, the risk of CAD increases 100-fold when a total cholesterol/HDL ratio of >5.85 is accompanied by a Lp(a) level of >55 mg/dl (ref. 27). Lp(a) levels are highest in Blacks, but for them its adverse effects are neutralized by the low serum levels of LDL and triglycerides and high serum levels of HDL, all of which are common among this population. On the other hand, the pathological effects of Lp(a) are exponentially increased by the well-known lipid triad (high triglycerides, high LDL, and low HDL), frequently seen among Asian Indians.

As a population, Asian Indians appear to have a unique pattern of dyslipidemia, a 'deadly lipid tetrad'. This lipid tetrad consists of elevated Lp(a) in combination with the lipid triad. This lipid tetrad is rarely seen in other populations in epidemiological studies. However, this combination is frequently seen in patients with severe CAD and in those who have had poor outcomes from repeated PTCA, CABG or heart transplants. This lipid tetrad appears to explain the malignant atherosclerosis in young Asian Indians and accounts for their high morbidity and mortality from CAD.

A Comprehensive Lipid Tetrad Index[28] has been described as the single best predictor of CAD risks in diverse populations, especially Asian Indians. This index reflects the total burden of dyslipidemia and is derived by multiplying the three lipids directly associated with CAD and dividing the product by HDL, which is inversely associated (total cholesterol × triglycerides × Lp(a)/HDL). This lipid index appears to explain the Asian Indian paradox and the numerous paradoxes mentioned earlier[21].

Combined toll of nature and nurture

The high rate of CAD in Asian Indians is due to a combination of nature (genetic predisposition) and nurture (lifestyle factors). The nature is attributed to elevated levels of Lp(a). Given this genetic predisposition, the harmful effects of lifestyle factors are magnified. These lifestyle factors include those associated with urbanization as well as immigration and acculturation[29]. When people move from rural to urban environments, they become increasingly sedentary or may adopt a Western lifestyle. Decreased physical activity and increased consumption of calories and fat resulting in abdominal obesity, insulin resistance and atherogenic dyslipidemia generally accompany this change. These acquired metabolic abnormalities appear to have a synergistic effect on the development of CAD in genetically susceptible individuals[30].

Prevention of CAD in Asian Indians

The most important aspect of prevention of CAD is to identify at an early age those individuals who are at a high risk of developing CAD[31]. Since Lp(a) is fully expressed in the first year of life, tracking Lp(a) from childhood may be a better option than focusing on other dyslipidemias which are not expressed until later in life[32]. In people with elevated Lp(a) levels, the initial therapeutic and preventive goals consist of diligently searching and drastically reducing all concurrent modifiable risk factors[33].

About one in four Asian Indians has elevated Lp(a) and reduced HDL levels, and one in five has elevated triglyceride levels. These lipid abnormalities make the LDL small, dense and highly toxic. Therefore, serum cholesterol concentrations greatly underestimate the total burden of dyslipidemia in Asian Indians and every effort should be made to prevent serum cholesterol from being elevated in this population[34].

Over a lifetime, the serum levels of LDL and Lp(a) are the critical risk factors for CAD in Asian Indians as in other populations[35]. Patients with CAD have a 5- to 7-fold higher risk of recurrent clinical events. The overall risk of CAD in Asian Indians appears to be similar in magnitude to other populations with CAD.

An overwhelming body of data provides compelling evidence of reduction in cardiac morbidity and mortality by aggressive lipid-lowering therapy (Table 3). The angiographic regression studies have demonstrated that the inexorable progress of atherosclerosis can be slowed, arrested, and in some cases reversed by substantial lowering of LDL[36]. A reduction in serum cholesterol level by 10% will decrease the risk of CAD by 50%, provided the reduction occurs before the age of 40 years and is maintained throughout life[37].

More importantly, substantial lowering of LDL markedly reduces the atherogenicity from persistently elevated Lp(a)[38]. Therefore, substantial lowering of LDL offers a new and effective strategy for treating patients with elevated Lp(a) and this can now be readily achieved with statins. In addition, elevated levels of Lp(a) can be reduced with estrogens in post-menopausal women and with large doses of niacin in both genders.

Lipid lowering produces dramatic beneficial effects in both primary[39] and secondary prevention[40] (Table 3) and it does not increase non-coronary deaths. In the 4S and West of Scotland Studies (WOSCOPS), the outcomes in terms of beneficial effects were virtually identical, de-

Table 3. Landmark lipid-lowering clinical trials, reduction in mortality, clinical events, PTCA, and CABG

Landmark trial	4S[1]	CARE[2]	WOSCOP[3]	POSCH[4]
Number of subjects	4,444	4,159	6,595	838
Mode of therapy	Zocor	Pravachol	Pravachol	Ileal Bypass
Duration of study	5.4 years	5 years	5 years	14.7 years
Baseline mean cholesterol (mg/dl)	270	209	272	>220
LDL reduction (%)	35	28	26	38
Coronary event reduction* (%)	34 ($P = 0.00001$)	24 ($P = 0.003$)	31 ($P = 0.001$)	18 ($P = < 0.00001$)
PTCA/CABG reduction (%)	37 ($P = 0.00001$)	27 ($P = 0.001$)	37 ($P = 0.009$)	47 ($P = <0.00001$)
Stroke reduction (%)	30 ($P = 0.05$)	31 ($P = 0.03$)	11 ($P = NS$)	5 ($P = NS$)
Coronary death reduction (%)	42 ($P = 0.00001$)	20 ($P = 0.10$)	33 ($P = 0.042$)	30 ($P = 0NS$)
Total mortality reduction (%)	30 ($P = 0.0003$)	9 ($P = NS$)	22 ($P = 0.051$)	21 ($P = 0.048$)

*Includes MI, resuscitated cardiac arrest, coronary death; NS, not significant.
[1]Scandinavian Simvastatin Survival Study (ref. 40).
[2]Cholesterol and Recurrent Events Study (ref. 45).
[3]West of Scotland Coronary Prevention Study (ref. 39).
[4]Program of Surgical Control of Hyperlipidemia (ref. 18).

spite the fact that the 4S study was a secondary-prevention study, and the West of Scotland Study evaluated primary prevention in high-risk patients who had not had a coronary event. This suggests the distinction between secondary prevention and primary prevention in high-risk populations is not particularly useful and may be, to some extent, misleading.

Today, the statins are the most powerful and consistent means available for lowering total cholesterol and have no major adverse effects. The approximate 30–60% reduction in LDL achieved by statins is a dimension never previously seen with diet modification or any other treatment[41]. The cost-effectiveness of statin therapy in secondary prevention appears to be more favourable than PTCA, CABG, stents[42] or the treatment of hypertension and diabetes. Although the statins are expensive in the short run, the cost is balanced out over a few short years by the great benefits derived, especially from the reduction in the need for PTCA and CABG[43].

Although cigarette smoking, diabetes, high blood pressure, and high cholesterol could not explain the excess CAD in Asian Indians, these time-honoured risk factors should not be ignored under any circumstances. These risk factors are clearly associated with CAD in all populations studied, and Asian Indians are no exception. It appears that about half of all CAD in Indians can be attributed to these conventional risk factors.

Conclusion

The Asian Indians have the highest rates of CAD and the overall risk in this population is comparable to the 5-fold higher risk of recurrent events in patients with known CAD. Conventional risk factors have consistently failed to fully explain this excess burden. Therefore conventional approaches to prevention and treatment may not be sufficient to reduce the excess burden of CAD in this population. Since the lipid tetrad offers the best plausible explanation, an aggressive approach to treatment of dyslipidemia seems not only justified but warranted in Asian Indians[44]. The reduction in cardiac morbidity and mortality with lipid-lowering therapy has now been firmly established in patients with and without CAD[45].

It seems unrealistic to expect any greater degree of modification of lifestyle than what was observed in the CADI Study. These physicians not only had the best knowledge but also the know-how and the resources to make maximum changes in their lifestyle. Therefore, pharmacological intervention to lower cholesterol similar to that in secondary prevention of CAD (LDL <100 mg/dl) seems justified as primary prevention in high-risk Asian Indians[46]. Specific guidelines for Asian Indians that allow pharmacological treatment to be started at a lower LDL concentration and at a younger age are urgently needed.

The results of the WOSCOP Study provide strong evidence that the incidence of a first MI can be reduced by about one-third in those with moderately elevated cholesterol and multiple risk factors. It is my opinion that those with multiple risk factors without manifest CAD would benefit from reduction in LDL to less than 100 mg/dl and preferably 70–80 mg/dl, though the data supporting this recommendation are lacking at this time. Those who wait for susceptible individuals to develop

symptoms before deciding to treat should not forget the fact that often the first symptom could be the last – a sudden death. The best strategy to prevent CAD was elegantly articulated by William Roberts[30]: 'If the serum cholesterol can be prevented from rising above 150 mg/dl, plaques are not laid down; if elevated levels are lowered to 150 mg/dl, further plaques do not form, and parts of those present may vanish'. This strategy may be far more cost-effective than waiting and eventually paying for 'tertiary prevention', such as PTCA and CABG.

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