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Asian Indians constitute approximately one fifth of humanity. Eleven million of these Asian Indians live outside India, including about one million in the United States. Of these, 25,000 are physicians and constitute 5% of all physicians practicing in the United States. Coronary artery disease (CAD) incidence and mortality have been reported to be unusually high among Asian Indians.[1-16] Such reports come from Singapore, Uganda, South Africa, Fiji, Trinidad, Mauritius and United Kingdom. Estimates of the excess risk compared to the indigenous population range from 2.5 to 5 for myocardial infarction and 1.5 to 3 for CAD mortality[1,16-18] (Table I). This review is an attempt to familiarize cardiologists with the magnitude and severity of CAD, differences in the prevalence of risk factors, differences in treatment of risk factors, and possible differences in approach to dietary recommendations between Asian Indians and other racial groups in the United States.

Prevalence of coronary artery disease in Indians in the United Kingdom and India: Balarajan[9] analyzed the mortality data for England and Wales for 1970 to 1972 and 1979 to 1983 to determine changes in CAD mortality among various immigrant groups. CAD mortality during the period of 1970 to 1983 generally reflected the rates reported in the country of origin of various migrant groups.[1,9] During this period England and Wales had one of the highest rates of CAD mortality, having experienced only a minimal decline (5% in men and 1% in women) overall. In this study immigrants from the United States showed a 23% decline in CAD mortality in men and 36% decline in women. This is similar to the 28% overall decline in CAD mortality from 1976 to 1986 in the United States.[19] In sharp contrast, those born in the Indian subcontinent, despite having had the highest death rates from CAD in the 1970 to 1972 survey, experienced an increase of 6% in men and 13% in women. This resulted in an excess CAD mortality of 36% in Asian Indian men and 46% in Asian Indian women during 1979 to 1983 compared with the overall rates in England and Wales (Table II).

Although most immigrants tend to be generally healthier than the population they left behind, the CAD mortality in the first generation of immigrants tends to be intermediate between that of their country of origin and the land of adoption. Within 1 or 2 generations, the pattern of mortality tends toward that of the adopted country as shown by the westernized Japanese-Americans.[17,20] However, the CAD mortality among Asian Indian immigrants continues to diverge from their compatriots of other ethnic origin.[8,9,14]

Although the prevalence of CAD in India was reported to be comparable to the United States, in the 1960s,[21] when the United States had the second highest CAD mortality in the world, big geographic differences between different parts of India were present. CAD was 7 times more common in the Southern states of India compared with the Northern states.[22] There are no current population-based data on CAD incidence, prevalence or mortality in India.[1] Although there are numerous anecdotal experiences of increasing incidence, prevalence, prematurity, severity and mortality of CAD in both urban and rural India, there are no reports of a decline in CAD in India, unlike the marked reduction in the incidence of CAD in several Western nations.

Early and extensive atherosclerosis in Asian Indians: CAD among Asian Indians is often premature, severe, extensive and follows a malignant course. The first myocardial infarction is usually massive, resulting in higher rates of permanent disability and evaluation for heart transplant.[4,12,18] Quantitative analyses of coronary angiograms (34 Asian Indians and 68 whites) by Lowry et al[12] have shown more severe disease in Asian Indians than in whites. Lowry et al[12] recommended early investigation of Asian Indians because more of them were found to be unsuitable for coronary artery bypass surgery (59 vs 47%) because of the severity of disease. The need for early intervention was further supported by the fact that 25% of Asian Indians who were refused surgery died within a period of 19 months compared with 6% of the whites.[12] In a prospective comparison of 131 men (77 whites, 54 Asian Indians) admitted to a coronary care unit in the United Kingdom, the rate of a first myocardial infarction was 5 times higher among the Asian Indians than among the native English, after adjusting for the distribution of various ethnic groups in the area.[18] The age at myocardial infarction was lower in Asian Indians (50.2 years) than in white patients (55.5 years). The age-specific rates of myocardial infarction in Asian Indians was particularly marked in younger persons and was almost 10 times the rate observed in whites between the ages of 30 and 39 years. The size of myocardial infarction assessed by peak creatine kinase, or degree of ventricular dysfunction assessed by radionuclide and contrast ventriculography was significantly greater in Asian Indians. Asian Indians had >2 times the frequency of 3-vessel CAD (54 vs 21%) and substantially higher atheroma scores in arteries not associated with myocardial infarction (3.66 vs 1.97).

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TABLE I Coronary Artery Disease Mortality Among Overseas Asian Indians Compared with the Indigenous Population

	Period of Survey	Standardized Mortality* (no.)	Ref.
Singapore	1954–1957	400	2
South Africa—Women	1955–1957	149	5
Singapore	1957–1978	300	3
South Africa—Men	1968–1977	145	1
Fiji	1971–1980	300	6
Trinidad compared with Africans	1977–1984	260	7
Trinidad compared with mixed descent	1977–1984	820	7
London boroughs	1979–1983	150	13
England and Wales—women	1979–1983	146	9
England and Wales—men	1979–1983	136	9
England and Wales—men (age 20–29 years)	1979–1983	313	9

*Standard mortality in the reference indigenous population is 100.
Ref. = reference.

The relative excess in mortality in the United Kingdom among Asian Indian men, compared with overall rates in England and Wales, was greatest in young persons. For example, mortality from CAD was 2.1 times higher in Asian Indian men compared with Non-Indians between the ages of 30 to 39, and 3.1 times higher between the ages of 20 to 29.[9] These observations suggest that atherogenesis is accelerated in Asian Indians and leads to high rates of premature mortality and morbidity from CAD.[18]

Traditional risk factors: Examination of the 3 major risk factors (high serum total cholesterol, high blood pressure and cigarette smoking) has failed to explain the high incidence of CAD in Asian Indians.[1,7,8,14,23] Smoking is less frequent among Asian Indian men and unusual among Asian Indian women who live outside of India.[7,11,24,25] Blood pressure is generally lower in Asian Indians than in whites.[24,25] The total cholesterol level is also lower.[4,11,24,26] The only known major risk factor for CAD that appears to be more prevalent among Asian Indians is diabetes mellitus,[7,8,27–29] which also develops earlier in life.[8] The excess prevalence of diabetes mellitus varied in these studies and was 3.8 to 4.3 times more common, compared with whites in the United Kingdom.[28,29]

To determine the prevalence of CAD and its risk factors in Asian Indians who migrated to the United States, 1,456 adult Asian Indian physicians and their family members (spouses, children and parents) were recently surveyed as part of the Coronary Artery Disease Among Indians Study.[30] Subjects were drawn from attendees at national conventions. Blood was obtained for analyses of glucose and lipoproteins in 461 of these subjects. The prevalence of angiographically documented CAD (i.e., angina or myocardial infarction followed by coronary arteriography) was 3 times more common in Asian Indian men compared with clinically diagnosed cases among men (i.e., clinical diagnoses of angina or myocardial infarction) from the Framingham Offspring Study.[31] Although the prevalence among women appeared to be the same, the number of female subjects in the 2 groups was too low to make reliable comparisons. Asian Indians had significantly higher prevalence of diabetes mellitus, hypertriglyceridemia and lower serum levels of high-density lipoprotein (HDL), but lower prevalence of cigarette smoking, systemic hypertension, family history of premature CAD and obesity compared with the Framingham Offspring Study. There was no difference in the prevalence of elevated (>240 mg/dl) total cholesterol levels, elevated (>160 mg/dl) low-density lipoproteins (LDL) cholesterol levels, or a history of stroke and peripheral vascular disease between the groups.[30]

This pattern of higher prevalence of diabetes mellitus, low HDL and high triglyceride among Asian Indians in the United States without elevations in LDL or higher prevalence of cigarette smoking or systemic hypertension is consistent with reports from other countries.[1,7,11,26,28,32] Furthermore, this pattern contrasts sharply with the distribution of risk factors in whites, among whom higher levels of LDL, and higher preva-

TABLE II Change in Coronary Artery Disease Mortality in England and Wales Among Persons Aged 20 to 69 Years by Country of Birth from 1970 to 1972 and from 1979 to 1983

	Men			Women		
Country of Birth	1970–72 SMR	1979–83 SMR	% Change in SMR	1970–72 SMR	1979–83 SMR	% Change in SMR
Scotland	124	111	−10	124	119	−4
All Ireland	113	114	+1	122	120	−2
African Commonwealth	116	113	−3	78	97	+24
Old Commonwealth	110	91	−17	94	72	−23
Caribbean Commonwealth	49	45	−8	89	76	−15
West Europe	84	77	−8	87	81	−7
East Europe	111	112	+1	115	110	−4
Republic of South Africa	117	90	−23	115	73	−37
United States	112	86	−23	87	56	−36
India	128	136	+6	129	146	+13
All England and Wales	105	100	−5	101	100	−1

Adapted from Balarajan[9] and reproduced with permission.
SMR = standardized mortality ratios with England/Wales rates for 1979 to 1983 as the standard.

lence of hypertension and cigarette smoking have been implicated in the development of CAD. Obviously, factors other than the cigarettes-cholesterol-hypertension paradigm must be diligently explored in this population.

Low high-density lipoproteins — a powerful risk factor: Numerous epidemiologic studies from North America, Europe and Israel have conclusively demonstrated that an elevated level of HDL protects against CAD, and an abnormally low level of HDL increases the risk of CAD.[33-39] A low level of HDL is a powerful independent risk factor for the future risk of CAD, not only when total cholesterol is high, but also when total cholesterol is not elevated.[33-39] In the Physician's Health Study, myocardial infarction was 3.2 times more common in the subgroup of men with a total cholesterol of <212 mg/dl and HDL of <47 mg/dl compared to those with similar total cholesterol and HDL of >47 mg/dl.[34]

The analysis of the relation between HDL and the development of myocardial infarction in the Framingham Study has also shown similar results. After 12 years of follow-up, men with HDL of <52 mg/dl had a 60 to 70% excess of myocardial infarction compared with men whose HDL levels were higher. The effect of HDL was even stronger in women, in whom a sixfold excess of myocardial infarction was reported, with a decrease of HDL from >66 to <46 mg/dl.[38] Based on the Framingham data, optimal HDL levels should exceed 52 mg/dl for men and 66 mg/dl for women.[38]

Only 14% of the Asian Indian men and 5% of Asian Indian women had the optimal HDL in the Coronary Artery Disease Among Indians Study.[30] Mean HDL in Asian Indian men is on an average 5 mg/dl lower than in white men, and 15 mg/dl lower than in black men and Japanese men. The gap in HDL levels appears to be even wider in Asian Indian women compared with women of other ethnic groups.[30]

Triglycerides, atherogenic lipoprotein and lipoprotein (a): Austin et al[40] recently described an atherogenic lipoprotein phenotype B characterized by moderate hypertriglyceridemia, a high proportion of small dense LDL, a high level of apolipoprotein B, and a low level of apolipoprotein A1 and HDL, especially HDL-2 which can be inherited as a single gene trait. The small, dense LDL particle appears to carry a threefold risk of CAD regardless of the absolute level of LDL. Atherogenic phenotype B can be differentiated from benign phenotype A by simple measurements of triglycerides and HDL. A triglyceride value of 95 mg/dl discriminates the 2 phenotypes in 83% of cases, whereas an HDL value of 39 mg/dl separates the 2 groups in 72% of cases.

The prevalence of this atherogenic phenotype is 25% in whites. When a triglyceride level of >95 mg/dl was used, 75% of Asian Indian men in the Coronary Artery Disease Among Indians Study demonstrated this phenotype.[30] Although the role of high triglycerides as an independent factor in the development of CAD remains controversial,[37,41] the data from several prospective studies suggest that triglycerides are probably an important risk factor.[42,43] Hypertriglyceridemia is often associated with increased plasminogen activator inhibitor levels and impaired fibrinolysis.[44] It is possible that elevated triglyceride and low HDL may be very important risk factors among Asian Indians and perhaps as important as LDL in whites and hypertension among blacks.

Recent studies indicate that elevated lipoprotein (a) levels are strong predictors of CAD.[45,46] Lipoprotein (a) levels may be related to both atherogenesis and thrombogenesis and may be a key link between lipids and thrombosis, because its sugar-rich portion competes with plasminogen and the modified apolipoprotein B moeity is actively taken up by the foam cells. The levels of lipoprotein (a) were found to be 3 times higher in Asian Indians than in Chinese in Singapore.[45] This parallels the threefold excess mortality reported among Indians in Singapore compared with the Chinese.[1,3,45] The Coronary Artery Disease Among Indians Study has also demonstrated higher levels of lipoprotein (a) among Asian Indians in United States than among whites.[30]

Diabetes mellitus, hyperinsulinemia and abdominal obesity: McKeigue et al[28] studied the relation between anthropometric measurements and biochemical abnormalities in 1,515 Asian Indian men and 291 Asian Indian women and compared these data with a similar number of European and Afro-Caribbean men and women in the United Kingdom. Although there was no difference in body mass index between the groups, the Asian Indians showed a pronounced tendency for abdominal obesity evident by a higher waist-to-hip ratio. A 0.04 unit increase in waist-to-hip ratio in Asian Indian men (0.98 Asian vs 0.94 European) was associated with a fourfold increase in diabetes mellitus (20% among Asians vs 5% among Europeans) and twofold higher postglucose insulin levels (41 mU/ml in Asian Indians vs 19 mU/ml in Europeans) along with significantly high triglycerides and low HDL. In sharp contrast, Afro-Caribbeans who are known to have low CAD rates in the United Kingdom did not have abdominal obesity (waist-to-hip ratio 0.94 Afro-Caribbeans vs 0.94 Europeans) or hyperinsulinemia (22 mU/ml in Afro-Caribbeans vs 19 mU/ml in Europeans) despite a higher prevalence of diabetes mellitus similar to that in Asian Indians (15% in Afro-Caribbeans vs 20% in Asians).

These findings suggest that the etiology and consequences of non-insulin-dependent diabetes mellitus is different in blacks compared with Asian Indians. It is likely that high HDL levels in blacks may explain their lower CAD mortality compared with the Indians, despite a high prevalence of both diabetes and hypertension.[28]

Indian origin, insulin resistance and syndrome X: Hyperinsulinemia resulting from insulin resistance has been found to be a distinguishing feature and an independent predictor of CAD in men, both within and between populations in many prospective studies.[42,43,47,48] Higher levels of insulin after a glucose load have been reported in Asian Indians with increasing frequency.[24,26,28,47-51] Hyperinsulinemia is a marker of atherogenic pattern of risk factors and lipid profiles that is associated with the high rate of CAD in men in affluent

societies. This has been called syndrome X by Reaven[52] or the deadly quartet by Kaplan.[53] It is often a precursor to diabetes and has been documented to antedate non-insulin-dependent diabetes mellitus by ≥8 years.[54] High triglyceride, low HDL, android obesity, glucose intolerance and predisposition to diabetes seen consistently among overseas Asian Indians constitute the hallmarks of this syndrome.[7,8,28]

Thus, a higher prevalence of insulin resistance syndrome appears to be the most plausible pathogenetic mechanism responsible for the metabolic and lipoprotein abnormalities resulting in high morbidity and mortality from CAD among Asian Indians.[7,8,9,16,24,28,55]

Dietary patterns among Asian Indians: There is considerable variation in the diet among Indians living inside or outside India, making it impossible to categorize the average Indian diet as high or low in fat. Even a vegetarian diet in India can be rich in saturated fats. Roberts[56] has called this "contaminated vegetarianism." Many vegetarian dishes are often cooked in clarified butter (ghee) and served with large amounts of cream. Furthermore, coconut oil (92% saturated fat) and palm kernel oil (86% saturated fat) are commonly used in cooking vegetables and other foods in certain regions in India. The average Indian diet in the United Kingdom and probably in the United States and India is high in carbohydrate, vegetable fiber and polyunsaturated fat, and low in cholesterol, saturated fat and omega-3 fatty acids of marine origin. Alcohol consumption is also low.[1,11,26] The low HDL and high triglyceride seen so frequently among Asian Indians[1,8,28,32] is surprisingly not associated with general obesity[1,26,28,30] and is also consistent with the reportedly low fat, high carbohydrate diet among them.[26,57]

A similar observation was made in the Coronary Artery Disease Among Indians Study, which indicated that the Asian Indians in the survey consumed a diet very similar to the step 1 diet of the American Heart Association. There were no significant differences in the serum levels of total cholesterol, triglyceride, LDL, HDL, apolipoprotein A1, apolipoprotein B and CAD between vegetarian and nonvegetarian Asian Indians.[30] This interesting phenomenon is probably due to smaller servings and infrequent consumption of meat by the nonvegetarians.[30]

Relevance of National Cholesterol Education Program Guidelines to Asian Indians: The current National Cholesterol Education Program guidelines focus primarily on the use of total cholesterol measurements as a means of identifying high-risk persons. They focus on reducing the LDL levels and recommend lipoprotein analysis only when total cholesterol is >240 mg/dl or when total cholesterol is between 200 and 239 mg/dl among persons with CAD or 2 other risk factors.[58] Bush and Riedel[59] recently reported that 66% of persons who are at high risk because of low HDL (<35 mg/dl) will not be identified by applying the National Cholesterol Education Program algorithm to the subjects in the Lipid Research Clinic Prevalence Study. An even higher percentage of Asian Indians who may be at high risk because of low HDL will not be identified using the National Cholesterol Education Program guidelines.[30] Thus, it seems likely that strict adherence to the algorithms proposed by National Cholesterol Education Program would miss the overwhelming majority of high-risk Indians. Therefore, screening lipid tests in Asian Indians should routinely include measurement of lipoproteins.[55]

Conclusions and implications: Asian Indians have one of the highest rates of CAD of any ethnic group. This excess is not chiefly due to a high fat diet or high serum cholesterol levels but probably due to abnormalities of glucose and triglyceride metabolism, insulin resistance and low HDL. The role of genetic factors mediated through apolipoprotein A1, apolipoprotein B, lipoprotein (a) and plasminogen activator inhibitor deserves further scrutiny. Given the difference in risk factors, the approach to the prevention of CAD in Asian Indians may also differ from that used in whites and blacks.

Measurements to lower LDL by a low-fat, high carbohydrate diet are unlikely to benefit such a population which traditionally consumes a high carbohydrate diet and whose major metabolic abnormality is low HDL with high triglycerides. Unfortunately, a low-fat, high carbohydrate diet may accentuate the metabolic abnormalities in this population.[60,61] In such persons preventive strategies should focus less on reduction of dietary cholesterol and saturated fats, and more on reducing triglycerides and raising HDL by a combination of regular exercise, weight reduction and decreased caloric and carbohydrate consumption. These recommendations, however, are logical, but not a proven fact.

Since there are no unique diets or medications that can raise HDL, the best dietary approach would be to improve the total cholesterol or LDL cholesterol to HDL ratio by partial substitution of monounsaturated fats for carbohydrates.[60–63] If lipid-lowering drugs are to be used, agents that increase HDL and decrease triglycerides should be considered. Future research should be focused on further elucidating the precise nature and etiology of the disturbances in glucose and lipid metabolism in this population.

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