Special Article

Coronary Artery Disease Epidemic in Indians: A Cause for Alarm and Call for Action

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Coronary artery disease (CAD) rates in urban areas in India are now 4-fold higher than in the United States (US) although the rates were similar in 1968. Both overseas and resident Indians have the highest rates of CAD, although almost half of them are life-long vegetarians. When compared to Whites, Blacks, Hispanics and other Asians, CAD rates among Indians worldwide are two to four times higher at all ages and five to ten times higher in those < 40 years of age. Although CAD is a fatal disease with no known cure, it is also highly predictable, preventable, and treatable. During the past 30 years, CAD rates halved in the US, Australia, Canada, France, Japan, and Finland. These vast reductions in CAD mortality are attributed to nationwide changes in specific risk factors that were identified through epidemiological research and addressed through population-based interventions, rather than extensive use of expensive technology. Reduction in risk factors explains most of the decline with modest contributions from advances in treatment. Ironically, the CAD rates doubled in India during the same period, primarily due to dietary changes associated with epidemiological transition from a rural sustenance economy to an urban market oriented economy. The impact of such changes appears to be greater in Indians than in other populations due to a genetic predisposition. Significant decline of CAD is readily achievable in India, by adopting a combined population-wide and high–risk primary prevention strategy. This requires concerted action by the medical profession, government, media, and the public.

Key words : Coronary artery disease (CAD), Indians, United States, Asians, Whites, Blacks.

Ethnic differences in CAD rates have now been clearly documented with the world's two largest populations, namely Indians and Chinese, occupying the opposite ends of the CAD spectrum[1]. In this article the term "Indian" denotes people originating from the four Indian subcontinent countries of India, Pakistan, Bangladesh and Sri Lanka. Indians worldwide have the highest rates of CAD, with those settled in the US having a 4-fold higher prevalence (Fig 1)[2,3] than White Americans and a 6-fold higher hospitalisation[2] than Chinese Americans[4] (Fig 2). The excess risk of CAD is seen in both men and women, although tobacco abuse is virtually non-existent among Indian women[5]. Among women, Indians have the highest CAD mortality in UK, South Africa, Canada, and Singapore[5] and also in Fiji, Mauritius, Uganda, and Trinidad. Whereas the CAD rates halved in the West in the past 30 years, the rates doubled in India with no signs of a downturn. This article reviews the potential causes and strategies for arresting and reversing this epidemic of CAD among Indians.

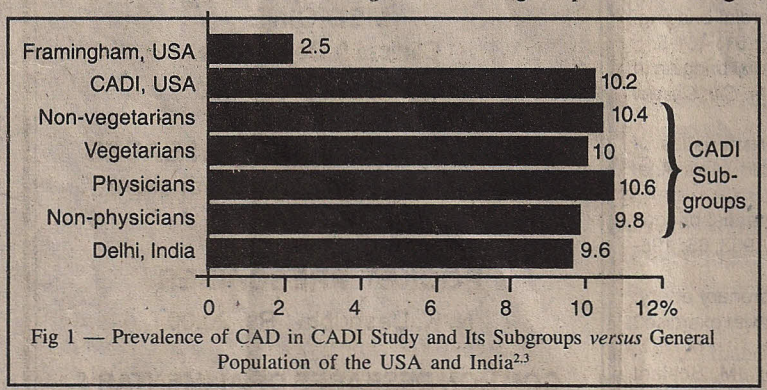

Fig 1 — Prevalence of CAD in CADI Study and Its Subgroups *versus* General Population of the USA and India[2,3]

Magnitude of CAD among Rural and Urban Indians :

CAD in India appears to follow the same pattern that was observed in the US[6], where high rates of CAD first appeared in the affluent and in the urban areas followed by rural villages[7]. The prevalence of CAD in India[8] is depicted in Table 1. One recent cross-sectional survey revealed CAD prevalence rates of 10% in urban Delhi and 5% in rural

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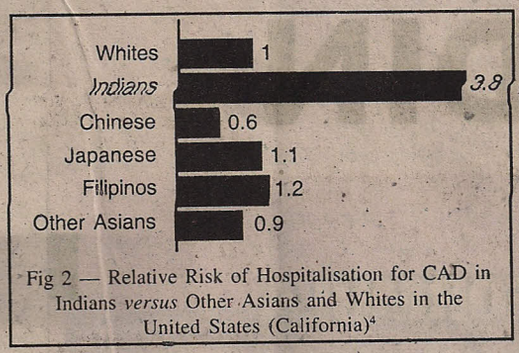

Fig 2 — Relative Risk of Hospitalisation for CAD in Indians *versus* Other Asians and Whites in the United States (California)[4]

Haryana[9]. This latest CAD rate from rural Haryana is 2.5-fold higher than the 2.0% rate reported by Dewan in 1974 from the same village, and 8-fold higher than the 0.6% reported from Tanushimaru, the Japanese cohort of the seven countries study[10]. The prevalence of CAD in urban India (10%) is about double that of rural India (5%) and about 4-fold higher than in the US (2.5%)[9]. The rates appear to be higher in South India, with a major tertiary care centre in Chennai reporting an 8-fold increase in the proportion of CAD patients from 4% to 33% over the past 30 years[11]. The CAD rates appear to be highest in Kerala with Trivandrum having a prevalence of 7% in rural and 13% in urban areas[12].

Table 1 — *Prevalence of CAD in Urban and Rural India*[8]

Author	Year	Age group	Place	Sample size	CHD (%±SD)
Urban population					
Mathur KS	1960	30-70	Agra	1046	1.05 ± 0.3
Padmavathi S	1962	30-70	Delhi	1642	1.04 ± 0.3
Sarvotham SG	1968	30-70	Chandigargh	2030	6.60 ± 0.6
Gupta SP	1975	30-70	Rohtak	1407	3.63 ± 0.5
Chanda SL	1990	25-65	Delhi	13723	9.67 ± 0.3
Gupta R	1995	20-80	Jaipur	2212	7.59 ± 0.6
Singh RB	1995	20-70	Moradabad	152	8.55 ± 2.3
Begom R	1995	20-70	Trivandrum	506	12.65 ±1.5
Rural population					
Dewan BD	1974	30-70	Haryana	1506	2.06 ± 0.4
Jajoo UN	1988	30-70	Vidarbha	2433	1.69 ± 0.3
Kutty VR	1993	25-65	Kerala	1130	7.43 ± 0.8
Wander GS	1994	30-70	Punjab	1100	3.09 ± 0.5
Gupta R	1994	20-80	Kajasthan	3148	3.53 ± 0.3
Singh RB	1995	20-80	Uttar Pradesh	162	3.09 ± 1.4

Important Role of Urbanisation :

The CAD rates in urban India are similar to those among the generally more affluent overseas Indians. The high rates of CAD in urban India compared to rural India, despite lower rates of smoking, suggest important roles for nutritional and environmental factors. There is a significant increase in body mass index (BMI) in urban India compared to rural India (BMI, 24 *versus* 20 in men, 25 *versus* 20 in women). There is also a higher rate of abdominal obesity among the urban population, with urban men having a waist to hip ratio (WHR) of 0.99 compared to 0.95 among rural men. These increases in BMI and WHR result in significant insulin resistance and dyslipidaemia[11]. The cholesterol levels are at least 25 mg/dl higher in urban than in rural areas of India. Though contemporary mortality data from India are unavailable, the totality of the data suggests that an epidemic of CAD is already underway. It appears that this CAD epidemic could explode in parallel with affluence and "urbanisation" of rural villages, unless the gravity and magnitude of the problem is recognised and immediate action taken.

Contrasting CAD Rates between Indians and Other Asians :

The high rates of CAD in Indians are in sharp contrast to very low rates in other Asians. Despite high rates of smoking and hypertension, CAD rates among both Chinese and Japanese are about 4-fold lower than in the US[11]. The Japanese cohort of the seven countries study[10] had the lowest 25-year age-standardised mortality (SMR) for CAD among all 16 cohorts (Japan 3.2%; US 16%; Northern Europe 20.3%). In the WHO MONICA Project, the SMR for CAD per 100,000 were 37 in Japan, 49 in Beijing, and 391 in Glasgow (UK) for men[13]. The corresponding figures were 9, 27, and 133 respectively in women. The mortality rates among Chinese immigrants are 3 to 4-fold lower than Indian immigrants in many countries. The low rate of CAD despite high rates of other risk factors in Chinese is attributed to their highly anti-atherogenic lipid profile. In one study[14], the typical levels in rural China were: Cholesterol 127 mg/dl; low density lipoprotein (LDL) 63 mg/dl; triglycerides 100 mg/dl; high density lipoprotein (HDL) 44 mg/dl and total cholesterol/HDL (TC/HDL) ratio by a factor of 2.9. Others have reported cholesterol level as low as 80 mg/dl in some Chinese communities, where CAD is virtually non-existent[15].

Contrasting CAD Trends between India and the United States :

CAD epidemics are essentially preventable according to existing knowledge. In the majority of developed countries, CAD mortality has fallen by a third or half in the last two decades. In the US, the SMR for

stroke declined by 70% and CAD by 54%, with those <55 years of age experiencing a 65% decline[15]. The rate of decline in CAD was substantially greater among the educated and the affluent, with the physicians experiencing an 87% decline. This is a clear proof that the ravages of CAD can be reduced with appropriate measures. On analysing the responsible factors, Goldman and Cook[16] found that more than half of the early (1968-1976) decline of CAD in the US was due to changes in risk factors, mainly from modification of lifestyle. Reduction in cholesterol level (by 25 mg/dl from 230 to 205 mg/dl) contributed to 30% , reduction in smoking 24%, and treatment of hypertension 9% of the decline. Hunink *et al*[17] analysed the reasons for the accelerated decline in CAD mortality from 1980 – 1990 and found that 25% of the decline was due to primary prevention, 29% due to secondary prevention, and 43% was due to improvements in treatment of patients with CAD.

Cardinal Features of CAD in Indians :

One of the cardinal features of CAD in Indians is the marked prematurity[18]. The excess risk of CAD in Indians appears to be greater at younger ages. For example, compared to Whites in the UK, the relative risk of CAD mortality in Indians is 3.13 between the ages of 20 and 29 *versus* 1.36 in all age groups. In Singapore, the relative risk of CAD mortality in Indians compared to Chinese is 12.5 in men aged 30-39 compared to 3.0 in men aged 60-69. In an angiographic study of CAD in Malaysia, Indians <40 years of age had a15-fold higher rate of CAD compared with Chinese and a10-fold higher rate compared with Malays. In the Calicut Medical College (Kerala) the incidence of myocardial infarction (MI) in those < 40 years of age increased 47-fold and the average age at first MI decreased by 20 years, over a 20-year period[19]. Other cardinal features of CAD in Indians are given in Table 2.

Table 2 — Cardinal Features of CAD among Indians Compared to Other Populations

- Higher rates
  - 2-4-fold higher prevalence, incidence, hospitalisation, mortality
- Greater prematurity
  - 5-10 years earlier onset of first myocardial infarction(MI)
  - 5-10-fold higher rate of MI and death in the young (<40 years of age)
- Greater severity
  - Three vessel disease common even among young premenopausal women
  - Large MI with greater muscle damage
- Higher prevalence of glucose intolerance
  - Insulin resistance syndrome, diabetes, central obesity
- Lower prevalence of conventional risk factors
  - Hypertension, obesity, cigarette smoking
  - Cholesterol levels - similar to Whites but higher than other Asians
- Higher prevalence of emerging (thrombogenic) risk factors
  - High levels of lipoprotein (a), homocysteine, Apo B
  - High levels of triglycerides, fibrinogen, plasminogen activator inhibitor - 1
  - Low levels of HDL
  - Small dense LDL
- Higher rates of clinical events for a given degree of atherosclerosis
  - Double that of Whites
  - 4-fold higher than Chinese
  - Higher proportion of unstable or vulnerable plaques

Combined Toll of Nature and Nurture :

The excess burden of CAD in Indians is due to a combination of nature (genetic predisposition) and nurture (environmental or lifestyle factors)[7]. Whereas the genetics load the gun, the environment pulls the trigger[20]. The genetic predisposition appears to be mediated by elevated levels of lipoprotein(a) or Lp(a), to be discussed shortly. Given this genetic predisposition, the harmful effects of environmental factors are greatly magnified. Adverse lifestyle factors include those associated with affluence, urbanisation, and mechanisation. When people move from a rural to an urban environment, they become sedentary and/or may adopt western lifestyles. Decreased physical activity and increased consumption of calories and saturated fat result in abdominal obesity, insulin resistance, and atherogenic dyslipidaemia. These acquired metabolic abnormalities appear to have a synergistic effect on the development of CAD in genetically predisposed individuals.

Conventional Risk Factors and Indian Paradox :

The high rates of CAD in Indians worldwide are accompanied by paradoxically low rates of conventional risk factors. Indians, however, have a higher prevalence of emerging thrombotic risk factors, which render the conventional risk factors doubly dangerous[21]. This is particularly true of elevated levels of Lp(a)[22], which render many Indians genetically susceptible to CAD, as early as childhood. In addition, the pathological effects of elevated Lp(a) levels are exponentially increased by a highly atherogenic metabolic

milieu, consisting of small dense LDL, high levels of triglycerides, apolipoprotein B, homocysteine, glucose, plasminogen activator inhibitor-1, fibrinogen, and low levels of HDL (Table 2), frequently seen in Indians. More than a third of the Indians have atherogenic levels of most of these emerging biochemical risk factors and an even higher percentage may have the cardiodysmetabolic syndrome (consisting of abdominal obesity, high triglycerides, low HDL, glucose intolerance, hyperinsulinaemia, and hypertension).

Multiplicative Effects of Emerging and Conventional Risk Factors :

High levels of Lp(a) increase the risk of CAD by a factor of two to four. More importantly, levels of Lp(a) >40 mg/dl increase the risk of CAD associated with hypertension by a factor of 4.6, high TC/HDL ratio, by a factor of 6.9, and high homocysteine by a factor of 9.3 and all four[23] by a factor of 122. Certainly, the presence of diabetes, high triglycerides, or smoking can further double or triple this risk[24]. These multiplicative effects of conventional and emerging risk factors appear to provide a plausible explanation for the excess burden of CAD among Indians, many of whom are lean, non-smoking, vegetarian, yoga guru, and marathon athletes[20]. The excess burden of emerging risk factors in the development of vulnerable plaques and clinical coronary events in Indians has just been reported from a landmark study from Canada[25].

Crucial Role of Cholesterol Level in CAD :

The primary determinant of the >10-fold difference in CAD rates between populations is the ambient average cholesterol level[26]. The cholesterol levels among Indians are similar to Whites but significantly higher than other Asians[27]. However, Indians have low levels of HDL resulting in a high TC/HDL ratio, perhaps the single best predictor of CAD. Moreover, cholesterol level significantly underestimates its atherogenicity among Indians, because of the abnormal concentrations of other lipoproteins and homocysteine. Furthermore, the risk of recurrent coronary events increases markedly at cholesterol levels >200 mg/dl in Indians *versus* 240 mg/dl in the US. At a given level of cholesterol (eg, 200 mg/dl), the absolute risk of CAD compared with Americans is only 20% in Japanese[10] (but may be as high as 200% in Indians). The same is also true of hypertension, with the Japanese having only 33% risk of CAD of Americans at a given blood pressure of 140/90 mm Hg[28]. Thus the conventional risk factors consistently overestimate the CAD risk among Japanese and underestimate the risk among Indians.

The differing risk of CAD among different populations with any given level of risk factor underscores the need for developing appropriately lower cut points for various risk factors to warrant intervention in Indians[29]. Although the most desirable level of cholesterol remains unknown, the average level in middle-aged men is about 120-140 mg/dl in hunter-gatherer societies and rural China, two populations with extremely low rates of CAD. Contrary to the common belief, low cholesterol levels do not lead to excess mortality.

Contrasting Trends in Cholesterol Levels between India and the US :

Cholesterol level decreased by 25 mg/dl in the US (230 to 205 mg/dl)[30] but increased by 25 mg/dl in India (165 to 190 mg/dl) in the last 25 years[31]. Cholesterol level in Kerala (229 mg/dl) is substantially higher than in Delhi (190 mg/dl) and in the US (205 mg/dl). Kerala, renowned for the universal use of fresh coconut, has almost double the rate of adults with high cholesterol (>240 mg/dl) as the US (Kerala 32% *versus* US 18%)[32]. The contrasting trends in cholesterol level closely parallel the contrasting trends of CAD in these countries.

Crucial Role of Saturated Fat Intake in Cholesterol Level :

The major determinant of cholesterol level is the proportion of saturated fat in the diet, with dietary cholesterol having only a small impact. The SMR for CAD in Japan and the UK are at the opposite ends of the spectrum, with a 10-fold difference between them. The 50 mg/dl difference in cholesterol levels between them (Japan 200 mg/dl and the UK 250 mg/dl) is mainly due to the difference in their intake of saturated fat calories (Japan 6% *versus* UK 16%). Indians worldwide should limit the saturated fat intake to < 7% of daily energy (AHA step II diet). A diet high in saturated fat includes not only meat but also whole milk as well as

high-fat dairy products and certain vegetable oils (coconut, palm and, palm kernel oil). Trans-fatty acids formed during hydrogenation of vegetable oils can also raise cholesterol levels[33].

Crucial Role of Statins in the Prevention and Treatment of CAD :

The likelihood of an MI is five to seven times higher in patients with CAD, which increases to 25 times higher if the patient also has elevated levels of cholesterol[34]. The presence of other conventional and/or emerging risk factors can further increase the risk to >100-fold. In the overwhelming majority of patients with CAD, dietary therapy alone is inadequate to lower cholesterol levels sufficiently[35] to attain the National Cholesterol Education Programme (NCEP) LDL goal of <100 mg/dl[36]. Five landmark clinical trials have conclusively demonstrated that lowering LDL, especially with statins (HMG CoA reductase inhibitors)[37], can dramatically reduce cardiovascular morbidity and mortality in patients with and without CAD[38]. The AFCAPS/ TexCAPS have demonstrated that the risk of a first MI can be reduced by about a third by aggressive lowering of LDL to 110 mg/dl, among individuals with average cholesterol and low HDL levels, even in the absence of any other risk factor[39]. This level of LDL corresponds to a total cholesterol level of 160 mg/dl, seen in rural India.

Regression of Coronary Atherosclerosis :

One of the most fascinating developments of the past ten years is the increasing evidence that the inexorable progress of atherosclerosis can be slowed, arrested, and even reversed by aggressive lipid-lowering therapy[40]. In a meta-analysis of eight statin trials, Thompson[41] found that a >40% reduction of LDL is required to arrest atherosclerosis. Others have found that LDL <100 mg/dl is necessary to produce regression of atherosclerosis, but large-scale regression is not necessary to dramatically reduce the risk of major acute coronary events.

Paradigm Change from Palliative to Preventive Cardiology :

According to the old paradigm, coronary angiography has been the gold standard for the diagnosis of CAD and revascularisation its mainstay of treatment [38]. However, according to the new paradigm[42] "coronary angiography does not identify, and consequently revascularisation procedures do not treat, the lesions that lead to myocardial infarction". This conclusion is based on the increasing realisation that "small lipid-rich vulnerable plaques, that are angiographically unimpressive and hemodynamically insignificant, are responsible for most cases of fatal and non-fatal MI, whereas large stable plaques that produce angiographically severe stenoses generally result in stable angina, but rarely result in MI"[42]. The majority of acute MI occur due to sudden total occlusion at sites with mild to moderate stenosis (with an average pre-infarct stenosis of <50% on a previous coronary angiogram). Moreover, >75% of MIs result from the rupture of a vulnerable plaque with <75% stenosis prior to the rupture. Lesions that cause <75% stenosis are effectively stabilised by lipid-lowering therapy[43].

Arresting and Reversing the Epidemic of CAD in Indians :

The major risk factors responsible for the CAD epidemic in India are smoking, high blood pressure, high cholesterol, high saturated fat diet and lack of physical activity. These factors should remain the focus of action in arresting and reversing this epidemic. Since adverse effects of these factors are greater in Indians, the benefits of modifying them are also correspondingly greater. The role of lifestyle modification in the prevention and treatment of CAD in Indians has been reviewed recently[44].

Individual-based Prevention of CAD :

The preventive strategy may be individual-based, population-based, or combined[15]. The first approach aims at identifying individuals with markedly elevated risk factors and targeting them for interventions. Such interventions include low saturated fat diet, regular exercise, tobacco abstinence, and maintenance of ideal body weight and waist circumference. Drug therapy is used when these measures fail to produce optimum results. Although both physicians and patients are generally well motivated to act in high-risk

patients, the success in modification of the lifestyle is low, if the remainder of the population continue to indulge in unhealthy habits. In the Framingham Heart Study, more than twice as many people developed CAD with a cholesterol level <200 mg/dl, as did those with cholesterol levels >300 mg/dl[45]. Since the number of persons with high risk is proportionately much smaller than those in the moderate risk group, the overall benefit to the society from treating high-risk individuals is also small.

Population-based Strategy of Prevention :

The proportion of high-risk cases in a population is directly dependent on the average level and distribution of risk factors[15]. Since the risk associated with most risk factors is a continuum, more people making small changes result in large benefit to the society, as opposed to large changes in a small number of high-risk patients. Although the benefit to the society is large, the benefit to individual member of the society is small. This irony in preventive medicine is termed "Prevention paradox" [46].

The population-based strategy aims to lower the risk factors in the entire population through modification of lifestyle. The population-based strategy can create a new generation in which low-risk is the rule and high-risk the exception. Most importantly, this ensures that children adopt healthy eating habits, slowing the rise in cholesterol level with age, creating a new generation with lower risk factor levels. The experiences in the US and Finland have clearly demonstrated that lowering the mean population serum cholesterol level has far greater impact than treatment of all those with high levels of cholesterol[15].

A population-based strategy of prevention is needed to complement the high-risk approach in Indians. In order for such a strategy to be successful four elements are necessary: An enlightened public health policy custom tailored for different parts of the nation, an educated medical profession, an empowered public, and a supportive media[9]. Indian Medical Association should join hand with other medical societies to make reduction in CAD rates in India a lasting reality rather than an elusive dream.

High-risk Primary Prevention for Indians :

Indians at high risk of developing premature CAD may be identified by early determination of emerging and conventional risk factors. Individuals so identified to be at high risk should be targeted for maximum lifestyle changes as early as possible (preferably in childhood). Important modifications include adopting a daily exercise regimen, avoiding cigarette smoking and watching not only the weight and cholesterol level but also the waist and caloric intake[47]. The cholesterol levels should be reduced to <200 mg/dl in individuals without risk factors and <160 mg/dl in those with CAD or risk factors. Pharmacologic treatment of dyslipidaemia similar to that of secondary prevention of CAD (LDL <100 mg/dl or cholesterol <160 mg/dl) seems justified in high-risk Indians without CAD, especially if they have suboptimal levels of HDL (<50 mg/dl) or Lp(a) (>20 mg/dl). The results of the AFCAPS/Tex CAPS seem to support this recommendation[39].

Aggressive Secondary Prevention of Dyslipidaemia :

All patients with CAD or vascular disease should maintain an LDL level of <100 mg/dl. Safe and effective medications are now available to correct even the worst lipid profile and metabolic milieu, in those who are unable or unwilling to achieve these goals with maximum modification of lifestyle. Aggressive medical treatment is also far more cost effective than the extensive use of expensive and technology driven mechanical interventions. The AVERT[48] has demonstrated that in patients with CAD, aggressive lowering of LDL to <80 mg/dl is at least as good as moderate lowering of LDL to <120 mg/dl combined with coronary angioplasty (with or without stent).This trial has also established the safety of aggressive lowering of LDL to <80 mg/dl. In the 4S, those with elevated Lp(a) benefited the least from lowering the cholesterol level to <200 mg/dl (LDL <122 mg/dl) with statins[49]. Since a 25-50 % Indians have high levels of Lp(a), aggressive LDL lowering to <80 mg/dl (rather than <100 mg/dl) may be desirable in Indians with CAD.

Treatment of Other Risk Factors :

Because of the significant synergistic adverse effects of emerging risk factors, raising the low levels of HDL and lowering the elevated levels of homocysteine and Lp(a) should also be considered, although randomised clinical trials demonstrating the benefits of such interventions (other than raising HDL) are yet

to be reported. Niacin can substantially raise HDL and lower triglycerides and Lp(a) levels. Vitamin preparations containing an adequate dose of folic acid, B_{12}, and B_6, can substantially reduce elevated homocysteine levels. Daily exercise, avoidance of tobacco, and reduced intake of saturated fat could reduce both the need and the dose of medications, and the importance of these measures cannot be overstated. Similarly aggressive detection and treatment of hypertension and diabetes using both lifestyle modification and medications should be pursued.

Conclusion :

CAD has become by far the most preventable of all chronic diseases with the possible exception of lung cancer prevention through smoking cessation. Since CAD is a multifactorial disease involving both genetic and environmental factors, a multi-pronged approach for prevention and treatment is warranted. Since sudden death or a silent MI is the first manifestation of CAD in about half of all patients and two-thirds of CAD deaths occur before reaching the hospital, these people can be helped only through preventive strategies directed at reduction of risk factors. Efforts directed at the classic heart attack patient admitted to the hospital have only a small impact on CAD morbidity and mortality in the population. Since atherosclerosis has its origin in childhood, particularly in Indians, preventive strategies should also begin in childhood, though it is probably never too late. The experiences of successful prevention programmes in the developed countries should be exploited to the fullest to reduce the ravages of CAD in the Indian subcontinent. Since Indians have at least double the risk of CAD, adjusted for the conventional risk factors, every effort should be made to maintain a lower level for every risk factor. This appears to be particularly true of cholesterol level. The optimum cholesterol level appears to be <160 mg/dl, the level typically seen in rural India.

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