Epilogue: Coronary artery disease in Indians – Methodological issues and challenges

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RESEARCHERS from India and abroad have presented in this special section, a wide range of findings to substantiate that both overseas and native Indians have high rates of coronary artery disease. Coronary artery disease (CAD) in Indians is associated with a high morbidity and mortality, tends to be more severe, and affects a younger age group compared to the West. The role of putative coronary risk factors, in explaining these findings has also been elucidated. We examine the critical role of *study design, study sample selection* and *definition of select predictor variables* in making some of the inferences presented in this section.

Data related to the high prevalence of coronary artery disease and elevated coronary mortality and morbidity among Indians are non-controversial. The evidence for describing the relative contributions of potential risk factors to the risk of CAD among Indians is, however, considerably weak.

A majority of currently available investigations of CAD among Indians are cross-sectional surveys or utilize a case-control design. These two epidemiological study designs generate relatively weak evidence in relating exposure (risk factors) to outcome (coronary artery disease) compared to cohort designs or clinical trials. In essence, such studies describe *disease correlates* rather than *risk associations*, and are affected by numerous biases (prevalence-incidence bias, survivor bias, selection bias, recall bias, to name just a few). There are no prospective longitudinal studies wherein a cohort of healthy Indians are followed-up over time and risk factor status at baseline is related to the development of coronary artery disease. Such cohort studies constitute stronger evidence in relating risk factors to coronary artery disease. Additionally, such studies generate vital data on coronary artery disease incidence, which are currently lacking. Randomized controlled clinical trials can provide strong evidence to substantiate that clinical interventions, which lower coronary risk factors to desirable levels, are effective in altering disease outcome. Such trials are also lacking in the Indian context. Before accepting that conventional coronary risk factors do not explain high coronary artery disease rates among Indians, it would be desirable to relate levels of risk factors to disease outcome *prospectively* to identify the levels associated with a disease-free state.

The appropriateness of using cut-off points employed in the West to define risk factor thresholds (such as desirable level of serum cholesterol) among Indians is also debatable. Arguments that a level of LDL-cholesterol less than 100 mg/dl is ideal for Indians or that a lipid tetrad index predicts best the coronary risk among Indians (as proposed by Enas A. Enas) are interesting but should necessarily be construed as hypothesis generating; they must be supported by prospective data relating risk factor levels to health outcomes.

The importance of selecting an appropriate study sample to investigate coronary disease among Indians cannot be over-emphasized. D. Bhatnagar observes that caution should be exercised in interpreting data based on overseas Asians. Given that immigrant Asians are a select upwardly mobile group, are heterogeneous in ethnic origin, and have lifestyles influenced by acculturation, immigration, urbanization and economic changes, the observations in overseas Asians can be generalized to native Indians only to a limited extent. Likewise, we should be very cautious in extrapolating from data on Indian physicians in the United States. Enas underscores that even maximal lifestyle and dietary modification seems to be ineffective in lowering coronary risk in this subgroup and therefore advocates screening for Lp (a) and aggressive lipid-lowering strategies. The validity of these findings in the Indian context merits detailed study before we dismiss the potential role of treating conventional coronary risk factors. Information on the population attributable risks associated with some of the newly-recognized risk factors is required before recommending expensive population-based screening programmes.

The computerized clinical and laboratory records from Vellore represent a gold mine of information from a single tertiary care center, meticulously compiled over three decades. Limited conclusions only can be drawn, however, based on the data presented in this issue by Krishnaswamy. The data principally demonstrate that the prevalence of risk factors among patients with documented CAD, presenting to a tertiary care referral

hospital in south India, have not changed over time. What it suggests is that there may have been no major changes in the pathogenesis of the disease over time in south India. No conclusions can be made based on the data, with regard to secular trends in the prevalence of coronary risk factors in the community. While the prevalence of risk factors in the community may be increasing over time, the risk factor profile in subjects with coronary artery disease may not have changed. In fact, it is logical to infer that the two-to-three fold increase in prevalence of coronary disease in the community from 1960 to 1990 (reported by R. Gupta) is likely to be related to a concomitant increase in prevalence of coronary risk factors in the community over the same period. The data from Vellore on the prevalence of CAD among subjects with coronary risk factors also need to be interpreted with great caution. The study is based on a highly select sample of subjects who presented at a Cardiology Unit of a tertiary care center and underwent angiography for suspected coronary artery disease. The skewed sex ratio of this study sample further corroborates that the sample is quite unrepresentative of the community. While useful from a research perspective, such data should not be used to make suggestions regarding preventative community-based strategies.

The impact of predictor variable definitions on epidemiological inferences also merits comment. The use of race and ethnicity as epidemiological variables is considered problematic given that these are social constructs and represent an aggregate of cultural, linguistic, environmental and lifestyle-related influences, which are not easy to characterize individually. The comparison of urban and rural differences presented by Chadha as well as Guptas, while relevant and insightful, also poses several problems. The association of disease and risk factors with urban or rural environments is confounded by the stage of epidemiologic transitions in these localities. Experiences from developed countries suggest that there is an initial clustering of coronary disease in the urban areas (where there is a preponderance of upper social classes). With the passage of time, this gradient may reverse with the burden of coronary disease shifting to the rural areas, which are often socio-economically backward. Disease trends and associations obtained from cross-sectional surveys reflect in part the stage of epidemiologic transitions in the study sample. Data provided by Chadha also suggest that the rural areas are likely to face a mounting impact of the coronary epidemic in India, given the coronary prone profile (high prevalence of smoking and low levels of HDL-cholesterol). These urban–rural comparisons from Delhi and Rajasthan also demonstrate considerable regional heterogeneity in coronary risk factor prevalence. For example, the serum levels of HDL-cholesterol in men in rural Rajasthan average 44 mg/dl (which does not differ from that of urban men) while that of men from rural Delhi average 52 mg/dl (which is lower from that of urban men).

The authors who have contributed to this section have emphasized the need for strategies to lower coronary risk among Indians. In our opinion, an initial focus on public health policies to lower conventional coronary risk factors (such as a tobacco policy, a healthy food policy, lifestyle-related recommendations, etc.) is appropriate. Concomitantly additional research is required using prospective study designs and a multi-regional community-based study sample to study the role of insulin resistance, Lp (a), homocysteine and other coronary risk factors. The importance of initiating community-based coronary disease surveillance to monitor trends in disease incidence and to study the impact of community-based public health interventions must be recognized by physicians, research scientists, health planners and health administrators. These steps are critical for halting the emerging epidemic of coronary artery disease in the Indian subcontinent.