

## Editorial Focus

# Premature coronary artery disease: An inferred cardiovascular variant or a South Asian genetic disorder?

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Coronary artery disease (CAD) is the leading cause of morbidity and mortality in both the developed and developing world, and in particular, people originating from the Indian subcontinent appear to have a particular susceptibility (1–6). Contextually, age standardised rates of death from CAD in India were 127% higher than that in the US during 2002 (7), and deaths from this disease are projected to afflict some 2 million resident Indians by year 2010. Not only is the disease burden on the Indian subcontinent estimated to be the highest worldwide (8, 9) but there also is a markedly earlier progression of disease within the resident population (10). Indeed, the terms ‘pre-mature-’, ‘early onset-’ and ‘young-’ CAD were almost exclu-

sively used by authors between the 1970s to the 1990s to distinguish the impact of CAD on the Indian subcontinent (11–13).

Despite a growing global familiarity of these terms and associated definitions (Table 1), this condition is altogether less frequently looked at in the West (14), which may underline the ominous ancestral relationship between CAD with the Indian subcontinent. Given the wide interest into the underlying pathophysiology of atherogenesis, and more specifically, CAD itself (15–18) relatively little interest has been directed to ethnic predisposition to premature CAD.

However, is there really any pathological or etiological basis to characterise ‘pre-mature’ CAD *per se*? In the May issue

**Table 1: The evolution of premature coronary artery disease (CAD).**

Definition	Upper age limit (years)	Study population, CAD patients	Reference
Young CAD	≤45 men and women	Singapore	26
	≤40 men and women	Nine countries study of patients (Auckland, New Zealand; Melbourne, Australia; Los Angeles/Atlanta, USA; Cape Town, South Africa; Tel Aviv, Israel; Heidelberg, Germany; Edinburgh, UK; Bombay, India, Singapore)	27
	≤45 women	Canada	28
	≤40 men and women	Shinshu, Japan	29
	≤40 men & women	Poland	30
Premature CAD	≤50 men, ≤60 women	Baltimore, US	31
	≤50 men	Australia	32
	≤40 men and women	Singapore	33
	≤45 men, ≤55 women	London, UK	34
	≤45 men	Turkey	35
	≤45 men and women	Lucknow, India	36
	≤49 men	Poznań, Poland	37
	≤45 men and women	Tehran, Iran	38
Early onset CAD	≤45 men and women	Israeli Jewish CAD patients in Tel-Aviv, Israel	39
	≤45 men and women	California	14

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of *Thrombosis and Haemostasis*, Maitra et al. (19) added further fuel to this debate by reporting a genetic susceptibility to CAD that appears to be dependent on the age of CAD onset amongst people living in India. Epidemiologically, one could argue whether one can truly define the age of CAD onset with any real certainty, and whether the presence of an ischemic event can distinguish between CAD and normality amongst asymptomatic individuals with increased cardiovascular risk. Nonetheless, Maitra et al. report an interesting study which highlights an association between gene variants of the promoter region of the interleukin 6 (IL6) gene, circulating levels of inflammatory markers and the presence of premature CAD.

Does this article add weight to the rationale for a pathophysiological difference between CAD and premature CAD? Our classical concept of atherosclerosis has developed beyond disordered lipid metabolism and deposition, and now includes inflammation as the catalytic environment needed for the progression of this disease (17). Inflammatory mechanisms play a key role in all stages of atherosclerosis from the initial recruitment of circulating leucocytes to the arterial wall to the eventual rupture of the unstable plaque. Inflammation may be intimately related via gene polymorphisms. For example, in African Americans, circulating levels of inflammatory markers have also been associated with genetic variations (20). Hence, a genetic susceptibility to the

presence of a pro-inflammatory state, may justify an earlier progression to an advanced form of atherosclerosis. Raised plasma markers of low-level chronic inflammation such as high sensitive C-reactive protein and IL6 have been shown to predict the increased risk of cardiovascular events (21, 22), and higher C-reactive protein levels have been reported in South Asians compared to white Caucasian counterparts (23, 24). However, these 'ethnic differences' in inflammation are best used to describe an inferred relationship, rather than an etiological pathway.

Maitra et al. also illustrate how the technology of genomics can be used to identify the susceptibility to a particular disease modifying gene. However, one can argue whether a true Medelian approach is feasible for the presence of premature CAD. For example, the 'proband' in this study are identified through the presence of a clinical history of premature CAD rather than a defined genetic disorder *per se*. Nonetheless, techniques such as the 'linkage approach' (used here) and 'association strategy' continue to be established approaches for relating variations in genetic sequence to cardiovascular risk (25).

Clearly, renewed interest into the ethnic predisposition to premature CAD is urgently called for. Not only would such research address a clinical problem but understanding why CAD occurs prematurely in some groups rather than others would give us unique insights into the pathophysiology of CAD.

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