Original Article

Premature coronary artery disease in India: coronary artery disease in the young (CADY) registry

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ABSTRACT

Background: Coronary artery disease (CAD) occurs at younger age in India but only a limited number of studies have evaluated risk factors and management status. This is a multisite observational registry to assess risk factors and treatment patterns in young patients presenting with acute coronary syndrome (ACS) and stable ischemic heart disease (IHD).
Methods: We recruited 997 young patients (men <55, women <65 y) presenting with ACS or stable IHD successively at 22 centers across India. Details of baseline risk factors and management status were obtained. Descriptive statistics are reported.
Results: Mean age of participants was 49.1 ± 8y, 72% were men and 68% had ACS. Family history of CAD was in 50%, diabetes 44%, hypertension 49%, history of dyslipidemia 11%, smoking/tobacco use 39%, and sedentary habits in 20%. 1.3% had "possible familial hypercholesterolemia". Metabolic risk factors (high BMI, diabetes and hypertension) were significantly greater in women ($p < 0.01$). Women were older at diagnosis of CAD and presented more often with non-ST elevation ACS. In the study cohort antiplatelet use was in 85%, beta-blockers 38%, statins 63% and ACE inhibitors/ARBs in 41% while in ACS patients it was 80.5%, 54.6%, 80.8% and 40.8%, respectively. 35.9% patients underwent percutaneous coronary intervention while coronary bypass surgery was performed in 10.4%.
Conclusions: Conventional risk factors including family history continue to play a pivotal role in premature CAD in Indians. Women have more of metabolic risk factors, present at a later age and have non-ST elevation ACS more often. There is a need to focus on improving use of evidence-based drug therapies and interventions.

1. Introduction

Cardiovascular diseases (CVD) are the most important causes of mortality and morbidity in India[1]. Global Burden of Diseases (GBD) Study has reported that from year 1990 to 2013, IHD in India increased to become number 1 cause of death[2]. This study also reported that number of patients with IHD increased from less than a million to 2 million. IHD in India is characterized by increasing numbers, regional variations, premature onset, poor management and greater mortality[1,3].

Premature IHD can have devastating consequences for the individual, the family, and the society[4]. INTERHEART study reported that 9 standard risk factors- dyslipidemia (high apolipoprotein B/apolipoprotein A1 ratio), smoking, hypertension, diabetes, high waist-hip ratio, unhealthy diet, low physical activity, irregular alcohol consumption and psychosocial stress- explained more than 90% of the first acute myocardial infarction[5]. Premature IHD in the South Asian region was explained due to premature

Table 1
Socio-demographic characteristics.

	Total	Male	Female
Age, years – Mean (SD)	49.07 (8)	46.67 (7)	55.14 (7)
Psychosocial (n %)			
Excellent	44 (4)	28 (4)	16 (6)
Good/Fair	937 (94)	675 (95)	262 (93)
Poor	11 (1.10)	6 (0.84)	5 (1.76)
Socioeconomic characteristics (n %)			
Upper	87 (9)	74 (10)	13 (5)
Middle	755 (76)	570 (80)	185 (65)
Lower	139 (14)	64 (9)	85 (30)

onset of the same biological risk factors in the INTERHEART study[6]. Smaller case-control studies in India have reported importance of these risk factors[7]. A case-control study highlighted importance of thrombotic (smoking, low fruit/vegetables intake, fibrinogen, homocysteine) as well as atherosclerotic (hypertension, high fat diet, dyslipidemia) risk factors in causing premature IHD[8]. Quality of care of acute coronary syndrome (ACS) patients in India has been reported in large registries. The nationwide CREATE registry (n = 20468) reported that use of evidence based medical drugs (thrombolytics, beta-blockers, antiplatelets, RAAS blockers and statins) as well as revascularization (coronary interventions or surgery) was low[9]. Similar results were reported in Kerala ACS registry (n = 25748)[10] and multicenter DEMAT[11] and SPREAD[12] registries. However, all these studies were focused in all age-groups and not in premature IHD patients. We undertook a multi-centric, prospective, observational study across India to find out possible risk factors associated with CAD among young Indian population. The study included not only patients of ACS but also patients with stable IHD, and analyzed different treatment strategies.

2. METHODS

Coronary Artery Disease in the Young (CADY) is a prospective observational study to examine the risk factor profile and management strategies in premature CAD in a cohort of Indian patients. 997 patients were recruited in 22 participating centers between November 2010 and January 2012. The centers are distributed across India, more from South India (Fig. 1). Men less than 55 years of age and women less than 65 years presenting with CAD or those with established CAD on follow up were included in the study. The diagnosis of CAD was made by a positive stress test or a definite imaging technique. Patients who had prior PTCA or CABG were also included in the study. Ethics clearance was obtained from the central coordinating unit and individual sites. Informed consent was obtained from all patients.

The data collection was performed either by the designated staff or trained research coordinators. Demographic data regarding socioeconomic status and age were collected. Medical history of associated risk factors such as hypertension, diabetes, dyslipidemia, stroke and peripheral vascular disease were documented. Data on lifestyle factors such as diet, smoking, non-smoked tobacco use, alcohol consumption, exercise patterns and psychosocial factors were also obtained. Data regarding socioeconomic status was obtained using Kuppuswami classification[13] and for psychosocial stress we used the modified INTERHEART questionnaire[14]. Details of hospitalization including diagnostic tests, medications and laboratory tests were obtained from hospital records. Dutch lipid clinic network (DLCN) criteria was used to identify patients with familial hypercholesterolemia. TIMI score for patients with non-Q ACS[15] were also calculated during hospitalization. Treatment advice at discharge was noted from the hospital records. Although the study was designed to gather follow-up information up to 24 months after enrolment this report is restricted to the data available at discharge.

2.1. Statistical analyses

All the data were computerized and data analysis performed using EpiInfo programme. Descriptive statistics are reported.

The study is registered with Clinical Trials Registry of India at www.ctri.nic.in (CTRI/2012/12/003232).

3. Results

Patient enrolment was performed in different parts of the country to cover various geographical regions. Of the 997 participants, 714 (72%) were men. Mean age of study participants was 49.1 years, 46.7 years in men and 55.1 years in women. Out of 997 patients, 680 (68%) had ACS and 317 (32%) stable IHD. Of the 680 ACS patients, 51% had ST-elevation myocardial infarction (STEMI) and 49% had NSTE-ACS. According to the universal definition of myocardial infarction[16], it was determined that 3 patients had type-2, 2 had type-4b and the rest had type-1 infarctions. Of these, 348 had STEMI and 158 had non-STEMI. 57.6% of patients with NSTE-ACS had a TIMI score of 3 or greater.

Socio-demographic characteristics and associated risk factors are shown in Tables 1 and 2. 75.6% of participants belonged to middle socioeconomic status. Moderate to high psychosocial stress level was reported in 55.9% of the study population. Family history of premature IHD was present in half of the participants (49.6%) and was more in men (72.3%) as compared to women (27.7%). Significant proportion of participants had modifiable risk factors: hypertension 49.3%, diabetes 44.2%, dyslipidemia 11.4%, smoking

Table 2
Associated Risk Factors.

Charactertistics	CAD n (%) 997	Male n (%) 714	Female n (%) 283	P-value
Age	49.1 ± 8	46.67 ± 7	55.1 ± 7	<0.001
Diabetes Mellitus	441 (44.23)	265 (37.11)	176 (62.19)	<0.0001
Hypertension	492 (49.35)	288 (40.34)	204 (72.08)	<0.0001
Dyslipidemia	114 (11.43)	76 (10.64)	38 (13.43)	0.2119
Psychosocial (fair and poor)	559 (56.07)	403 (56.44)	156 (55.12)	0.7050
Physical activity (low)	195 (19.56)	120 (16.80)	75 (26.50)	0.0005
Socioeconomic characteristics (upper)	87 (8.73)	74 (10.36)	13 (4.59)	0.0036
Socioeconomic characteristics (Middle)	755 (75.73)	570 (79.83)	185 (65.37)	<0.0001
Socioeconomic characteristics (Lower)	139 (13.94)	64 (8.96)	85 (30.04)	<0.0001
Family history (Positive)	495 (49.65)	358 (72.32)	137 (27.68)	0.6241
Substance Use (Tobacco)	385 (38.62)	376 (52.66)	9 (3.18)	<0.0001
Waist circumference	362 (36.31)	251 (35.15)	111 (39.22)	0.2301
Body Mass Index (≥23)	562 (56.37)	395 (55.32)	167 (59.01)	0.2891

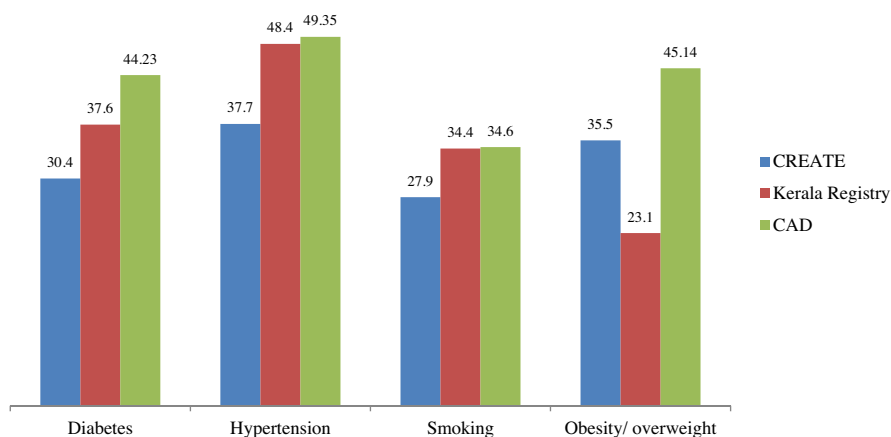*Note:* P < 0.05 implies significant difference between proportions.

Fig. 1. Comparison of Risk factors.

and/or tobacco use 38.6%, overweight/obesity in 56.3% and sedentary habits in 19.5%. 210 (21%) patients had previous coronary interventions (PCI) or coronary bypass surgery, 14 (1.4%) peripheral arterial disease and 11 (1.1%) had stroke. Women, as compared to men, had greater prevalence of diabetes (62.1 vs 37.1%, p < 0.001), hypertension (72.1 vs 40.3%, p < 0.0001) and overweight/obesity (60.1 vs 35.2%, p < 0.0001), whereas men had greater prevalence of smoking/tobacco use (52.7 vs 3.2%, p < 0.0001). "Possible Familial Hypercholesterolemaia" (FH) was diagnosed in 13 (1.3%) patients applying DLCN criteria, mean age being 55.07 years, 08 were male patients and 10 had ACS and others stable IHD.

Details of therapies are provided in Table 4. In the overall group, 834 (83.7%) received antiplatelet drugs (aspirin and/or clopidogrel), 632 (63.5%) statins, 413 (41.4%) ACE inhibitors/ARBs, and 386 (38.7%) beta blockers. Calcium channel blockers were prescribed in 94 (9.43%) patients and nitrates in 149 (14.9%). 358 (35.91%) underwent percutaneous coronary intervention, 261 (36.55%) being male and 97 (34.28%) being female patients. 104 (10.43%) underwent coronary bypass surgery.

In the hospitalized group of 735 patients, 649 had ACS and 86 had stable IHD. 561(86.2%) patients of ACS stayed in the hospital for 1–7 days, 29.3% for less than 48 hours. 42(43.7%); patients of stable IHD were in the hospital for 1–7 days, and 18.6% for less than 48 hours.

4. Discussion

This study shows that prevalence of standard coronary risk factors (smoking, hypertension, diabetes and dyslipidemia) is high in premature CAD in India and is similar to previous case-control studies from the country[4] and registries (Fig. 1) Women with premature CAD have greater prevalence of metabolic risk factors as compared to men. High prevalence of family history, especially in men, is a unique finding and suggests importance of genetic factors[17]. This study also shows a low use of evidence-based therapies in ACS.

CREATE[9], Kerala-ACS[10] DEMAT[11] and SPREAD study[12] registries have provided information on coronary atherosclerotic risk factors, treatment patterns and outcomes in Indian populations. However, these studies included all age groups and only patients of ACS. Kerala ACS study was confined to the Kerala state population. The present study, a multisite, prospective registry included patients with ACS as well as patients with stable IHD from different states of the country, which would give a better overall view of the burden of CAD in the country. Moreover, this study focused on premature CAD, a major concern for patients, practitioners and policy makers

in India. In the present study, of the 997 patients, 68% had ACS and 32% had stable IHD. Prevalence of premature stable IHD is an underestimate. On the basis of studies in US, it was estimated that there are 30 patients of stable IHD for every patient with ACS[18]. The situation is likely to be no different in our country and that gives an idea of the magnitude of the burden of premature IHD. Of the 680 ACS patients, 51% had STEMI and 49% had NSTE-ACS. In the CREATE registry STEMI was in 61% and the gap between numbers of STEMI and NSTE ACS has narrowed in the present study. Secular trends in awareness and treatment of risk factors and better management of stable IHD in India may have contributed to this "evolution" in CAD epidemiology. On the other hand, in the Kerala-ACS registry, STEMI rates were lower (37%) as compared to NSTE-ACS (63%). Kerala state which has the highest literacy rate in the country has probably marched much ahead in terms of epidemiological evolution.

Almost half of the study participants have history of premature CAD in the family. Parental history of premature CAD has been shown to be an important, independent, consistent and global determinant of future MI risk[17]. This association was not affected after adjustment for age-, sex-, region, and the 9 INTERHEART risk factors. High prevalence of family history, especially in men, points to presence of genetic factors in premature CAD in India. Although there are no large association studies of genetic factors with coronary atherosclerosis or ACS in India, studies among emigrant South Asians have reported that a few genetic markers are important. The markers with significant associations include 9p21 genotypes and a few single nucleotide polymorphisms. Large studies for identification of genetic markers are required among premature IHD patients. Meanwhile, clinicians caring for CAD patients should screen the close relatives of the patient for family history of premature CAD. Other risk factors included diabetes in 44%, hypertension in 49%, history of dyslipidemia in 11%, smoking/tobacco use in 39%, low physical activity in 20%, high BMI ≥ 23 kg/m^2 in 56% and high waist circumference in 42%. These rates are similar to previous case-control studies although the INTERHEART study reported that dyslipidemia was the most important risk factor.

FH is underdiagnosed and undertreated, as the awareness is poor amongst medical and nonmedical communities. FH is a common genetic disorder, with global prevalence being 1 in 200, and is a common cause for premature CAD. From various criteria that are available for diagnosis of FH – MEDPED criteria, Dutch Lipid Clinic Network(DLCN) criteria, Simon Broom criteria, and Japanese criteria – DLCN criteria[18] was applied to identify FH in this patient population. This takes into consideration family history, clinical history and findings, serum LDL-C levels and genetic testing. No genetic tests were carried out in our patients.
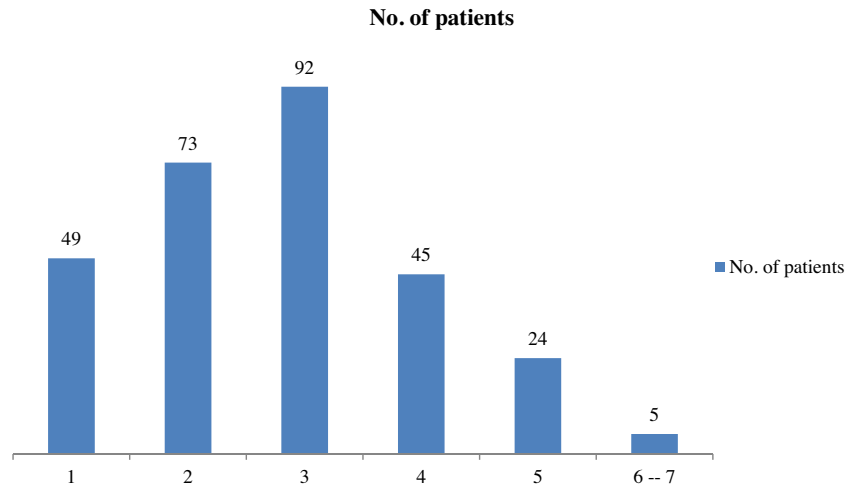
No. of patients

Fig. 2. Timi score for NSTE-ACS patients.

Diagnostic yield of sequencing genes for LDL-receptors, apo-B and PCSK-9 is generally poor. In a study[19] where genes were sequenced in 1,26,025 participants, it was seen that FH was detected in <2% of participants who had a serum LDL-C level of >190 mg%. Importantly, at any level of LDL-C, the CV risk is higher in subjects with mutation.

"Possible FH" was identified in 13(1.3%) patients. It is probably an underestimation for various reasons. Firstly, it was not prospectively and actively sought for. Only on a sound suggestion from a reviewer, this was done. Some of these patients were already on statins, altering the serum LDL-C values. Markers like xanthomas could have been missed. Genetic tests were not carried out. Clinical criteria may not be sufficient to assess prevalence of FH[20]. "Possible FH" have mutation in 20–30% of subjects. Since premature CAD is a major problem in our country and FH is probably one of the reasons, it is necessary to look for FH in our population.

There is clearly a need to improve the utilization of evidence based drug therapy in patients with CAD, especially premature CAD in India. Availability of generic drugs and combination pills in the market are likely to enhance evidence based practice and adherence to therapy. We have observed that 46.1% of patients underwent PCI or CABG. Appropriateness of the procedures has not been analyzed. However, when we look at the NSTE-ACS patients, 57.6% had a TIMI score of 3 or more, making them eligible for intervention (Fig. 2). Once the diagnosis of CAD is established, appropriate treatment has to be instituted. Use of all the drug classes is suboptimal (Table 4) but is similar to CREATE and Kerala-ACS. Prospective Urban Rural Epidemiology (PURE)[21] as well as Andhra Pradesh Rural Health Initiative (APRHI)[22] studies have reported that treatment levels for secondary prevention in urban and rural areas in India are disappointing. In APRHI study use of aspirin, beta-blockers, ACE inhibitors/ARBs, and statins was severely underutilized. Of the patients with ischemic heart disease, fewer than 16%, 25%, 10%, and 6% were using aspirin, β-blockers, ACE inhibitors, and statins respectively.

Dual antiplatelet therapy (DAPT) was received by 473 patients (all 358 patients undergoing PCI receiving DAPT), and 361 were on single antiplatelet.

The hospitalization period does appear longer than expected – only 29.3% of ACs patients and 18.6% of stable IHD patients staying in the hospital for less than 48 hours. The study did not look into the factors leading to prolonged hospitalization of these patients. The lack of health insurance coverage in the majority of patients, referral from and to other disciplines in the hospital for cardiac and non-cardiac evaluation and complications following interventions are possible explanations for a prolonged hospital stay.

4.1. Any thing new?

Though this study confirms the findings of the previous studies as regards CAD risk factors, there are two aspects which we feel should be communicated to the medical and non-medical community with renewed emphasis.

Table 3
Distribution of patients falling in each characteristics by disease status.

Characteristics – n (%)	Total 997	ACS 680 (68.20)	Stable IHD 317 (31.80)	P- Value
Diabetes Mellitus	441 (44.23)	280 (41.18)	161 (50.79)	0.0044
Hypertension	492 (49.35)	320 (47.06)	172 (54.26)	0.0340
Dyslipidemia	114 (11.43)	135 (19.85)	61 (19.24)	0.8181
Psychosocial (fair and poor)	559 (56.07)	360 (52.94)	199 (62.78)	0.0036
Physical activity (low)	195 (19.56)	148 (21.76)	47 (14.83)	0.0102
Substance Use (Tobacco)	385 (38.62)	271 (39.85)	114 (35.96)	0.2380
Waist circumference ((Females ≥80 cm and males ≥90 cm))	421 (42.23)	326 (47.94)	95 (29.97)	<0.0001
Body Mass Index (≥23)	562 (56.37)	394 (57.94)	168 (53)	0.1416
Family history (positive)	495 (49.65)	337 (49.56)	158 (49.84)	0.9362
Socioeconomic characteristics				
Upper I	87 (8.73)	65 (9.56)	22 (6.94)	0.1738
Upper Middle II	454 (45.54)	299 (43.97)	155 (48.9)	0.1471
Lower Middle III	301 (30.19)	215 (31.62)	86 (27.13)	0.1499
Upper Lower IV	138 (13.84)	87 (12.79)	51 (16.09)	0.1615
Lower	11 (1.1)	9 (1.32)	2 (0.63)	0.3320

Table 4
Drug therapies in acute coronary syndrome and stable IHD groups.

Evidence based drugs	Total 997 n (%)	Acute coronary syndrome 680 n (%)	Stable IHD 317 n (%)	p value
Antiplatelet drugs	835 (83.7)	544(80.5)	291(91.8)	<0.0001
ACE inhibitors/ARBs	413 (41.4)	244(35.9)	169 (53.3)	<0.0001
Beta blockers	386 (38.7)	371(54.6)	15(4.7)	<0.0001
Statins	637 (63.5)	549(80.8)	88(27.7)	<0.0001

4.1.1. CAD in women

Various aspects of CAD, including epidemiology and clinical manifestations differ between men and women, and these differences are explained by biological factors like hormonal influence, and socio-cultural processes, like gender bias[23]. Women have clinical CAD presenting about 10 years later than it does in men. That means women have an additional period of 10 years to practise preventive measures to effectively counter CAD. The INTERHEART study (5) showed hypertension and diabetes were more important risk factors in young Indian women than men. And this study showed women to have more comorbidities like hypertension, diabetes, dyslipidemia and obesity, which are amenable to corrective preventive measures. Smoking amongst female population, is less prevalent, a characteristic feature which they would do well to retain and improve further. Women have a wider window of opportunities for prevention of premature CAD.

GUSTO IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes), TIMI IIIB (Thrombolysis In Myocardial Infarction), and the Euro Heart Survey studies showed that women present more frequently with unstable angina and non–ST-elevation myocardial infarction (NSTEMI), whereas men have ACS with ST elevation (STEMI).[24–26] It has been shown that women are less likely to undergo reperfusion therapy after ACS.[27,28] In our study, women had NSTE-ACS more often than men (42% vs 29.8%), though not adjusted for age, and there was no gender bias in interventional treatment.

4.1.2. ACS vs Stable IHD

In case of secondary prevention of CAD, it is worth emphasizing another step – "Prevent stable IHD progressing to ACS". The conventional risk factors for CAD account for 90% of acute cardiovascular events.[5] The conventional risk factors for the development of CAD – hypertension, hypercholesterolaemia, diabetes, sedentary life-style, obesity, smoking and a family history have an adverse influence on prognosis in those with established disease, since they influence the progression of atherosclerotic disease process. Appropriate intervention, if instituted can reduce the risk. Once the primary prevention fails, and the patient develops stable IHD, we should strive to prevent its progression to ACS, which would reduce mortality, morbidity and associated economic and psycho-social burden. The message is "If you fail to prevent the development of an atheromatous plaque, then preserve the stability of the atheromatous plaque". Prevention of progression of the atheromatous plaque or even regression of the atheromatous plaque is a reality now, with effective secondary preventive measures.

Comparison between patients of ACS and stable IHD (Table 3) showed that low physical activity and increased waist circumference were significantly more common in patients with ACS, while diabetes, hypertension and lower psycho-social class were more frequent with stable IHD. Inflammatory markers (like hsCRP) were not assessed in the study, and the study is not equipped to explain these points. However, it is not inappropriate to surmise that physical activity and central obesity probably received less attention, while patients with diabetes and hypertension were adequately managed.

Framingham study[29] has shown that aggressive life style measures reduce events in stable IHD. What we know from clinical studies is that aspirin, beta blockers, statins, ACE inhibitors and therapeutic life style changes reduce mortality in stable IHD and so do the appropriately instituted revascularization procedures. Before these measures were widely applied, the annual mortality rate in patients with stable IHD was 4.5%, and now it is 1–3%.[30]

The usage of drugs was suboptimal, as mentioned earlier. Antiplatelets and ACE-I/ARB's were more frequently used in stable IHD patients than in ACS patients, while the use of BB and statins were more frequent in patients with ACS than in patients with stable IHD (Table 4), clearly indicating the urgent need to improve the awareness and practice of evidence based therapy.

Limitations of the study include the inherent limitations of registries such as biases because of regionality, gender-representation, and risk factor assessments as reported above. The follow up was also not adequate to comment on outcomes and adherence to therapy. On the other hand, this multi-centric observational registry of premature CAD in Indians indicates that the conventional risk factors are important and there is an urgent need to focus on these risk factors in primary and secondary prevention.

5. Conclusion

This multi-centric observational registry of premature CAD in Indians indicates that the conventional risk factors continue to be the major cause of CAD in the young. There is an urgent need to focus on these risk factors in primary and secondary prevention. It should not be difficult to correct underuse of life style modification and drugs. Effective secondary prevention would ensure stability of stable IHD. There is a greater scope for preventive practice in the female population, given the delayed onset of CAD and higher rate of comorbidities, offering more time and more opportunities.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ihj.2016.09.009.

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