Premature coronary artery disease, risk factors, clinical presentation, angiography and interventions: Hospital based registry

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1. Introduction

Premature coronary artery disease (CAD) is currently defined as occurrence of first clinical manifestation in women less than 60 years and men less than 55 years. Empirical evidence suggests that it is highly prevalent in India. The Global Burden of Diseases study has reported that among the young, ischemic heart disease (IHD) is one of the important causes of morbidity and mortality, especially in developing countries. The study also reported that in the age-group 20–54 years, IHD led to more annual deaths in India compared to USA, China and countries in Europe and Central Asia. It has been reported that in contrast to many large countries (China and USA) and European region, premature IHD mortality (in absolute numbers as well as rates) are increasing in India.

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Abstract

Background & aims: Premature coronary artery disease (CAD) is endemic in India. We performed a study to identify risk factors, clinical presentation, angiographic findings and interventions in premature CAD. 

Methods: Successive patients who underwent percutaneous intervention (PCI) were enrolled from January 2018 to June 2021. Premature CAD was defined as women 45–59 y and men 40–54 y and very premature as women <45 y and men <40 y. Descriptive statistics are presented. Univariate odds ratio (OR) and 95% confidence intervals (95%CI) were calculated to identify differences in various groups. 

Results: 4672 patients (women 936, men 3736) were enrolled. Premature CAD was in 1238 (26.5%; very premature vs non-premature CAD, OR (95%CI) for high cholesterol ≥200 mg/dl [women 1.52(1.03–2.25) and 1.59(0.79–3.20); men 1.73(1.38–2.17) and 1.92(1.22–3.03)], non-HDL cholesterol ≥130 mg/dl [women 1.84(1.35–2.52) and 1.32(0.72–2.42); men 1.69(1.40–1.92) and 1.67(1.17–2.34)], LDL cholesterol [men 1.10(0.95–1.25) and 1.04(0.77–1.41)], and tobacco [women 1.40(0.84–2.35) and 2.14(0.95–4.82)]; men 1.63(1.34–1.98) and 1.27(0.81–1.97)] were higher while hypertension, diabetes and chronic kidney disease were more in non-premature (p < 0.05). Presentation as STEMI was marginally more in women with premature [1.13(0.85–1.51)] and very premature [1.29(0.75–2.22)] CAD and was significantly higher in men [1.35(1.16–1.56) and 1.79(1.29–2.49)]. Location and extent of CAD were not different. 

Conclusions: In India, a third of CAD patients presenting for coronary intervention have premature disease. Important risk factors are high total and non-HDL cholesterol and tobacco (men) with greater presentation as STEMI. Extent and type of CAD are similar to non-premature CAD indicating severe disease.

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although recent population-based studies in the US suggest increasing incidence of premature CAD.7

Studies from India have reported a significant proportion of patients with premature CAD among hospital admission in both government and non-government hospitals.8–18 Adverse lifestyles among the young with earlier onset of major coronary risk factors are considered important.19,20 Small case–control and registry-based studies have reported that traditional factors (smoking, hypercholesterolemia, low density lipoprotein (LDL) cholesterol, hypertension, unhealthy lifestyles, etc.) as well as emerging risk factors (lipoprotein(a), triglycerides, metabolic syndrome and social determinants) are important.21–23 Studies that have reported type of CAD in young patients are few and it has been reported that there is high prevalence of single vessel disease and that multivessel disease is not highly prevalent.10,13,14,24 Studies of premature CAD among migrant South Asians to USA, UK and elsewhere have reported diffuse multivessel disease in the young.25,27 We used data from ongoing Cath-PCI registry, part of the American College of Cardiology (ACC) National Cardiovascular Disease Registry (NCDR) Centre of Excellence program,26 at our hospital to identify prevalence of premature CAD, risk factors, clinical presentation, type and extent of CAD and coronary interventions. We then compared risk factors, clinical and angiographic parameters and interventions in patients with premature (women <60 y, men <55 y) and very premature (women <45 y, men <40 y) CAD with older non-premature CAD patients.

2. Methods

The Cath-PCI Registry at the hospital is part of ACC-NCDR Centre of Excellence program.26 The registry has been approved by the institutional ethics committee (Government of India, CDSCO Registration No. ECR/615/Inst/RJ/2014/RR-20). Informed consent was obtained from each participant included in the registry with specific consent for inclusion of anonymized data.28 Patients: Successive patients undergoing PCI were enrolled over a 42-month period from January 2018 to June 2021. Clinical data were prospectively obtained from admission at the time of coronary intervention and entered into the NCDR database following discharge by research assistants. Details of methodology and list of imputed variables are available at the NCDR website.26 In short, we obtained details regarding age and sex, risk factors-hypertension, diabetes, hypercholesterolemia (total cholesterol >200 mg/dl and >170 mg/dl, non-high-density lipoprotein cholesterol (non-HDL=total cholesterol - HDL cholesterol) >130 mg/dl and >100 mg/dl), directly measured low density lipoprotein (LDL) cholesterol >100 mg/dl and >70 mg/dl), hypertriglyceridemia (>150 mg/dl), smoking or smokeless tobacco use, chronic kidney disease (admission creatinine ≥2.0 mg/dl), symptoms and physical findings, laboratory investigations, echocardiography for left ventricular ejection fraction (EF) and coronary angiography. Details of clinical presentation, ST-segment myocardial infarction (STEMI) or non-STEMI (NSTEMI)/unstable angina were recorded. We have also recorded details of location and extent of coronary artery disease from angiography reports, type of intervention and number of stents deployed. Almost all stents deployed (>95%) are drug-eluting. Details of pre-hospital, in-hospital and post-discharge medications were also recorded. In-hospital follow-up included duration of hospitalization (median days) and deaths. Details of long-term follow up are not yet available.

Statistical analyses: The whole cohort of CAD patients has been divided into three age-groups (A) premature CAD (women 45–60 years; men 40–54 years) (B) very premature CAD (women <45 years, men <40 years); and (C) non-premature CAD, according to existing consensus and guidelines.1,2,25 Data have been downloaded from the ACC-NCDR website and transferred to MS Excel work sheets.28 Data analyses have been performed using SPSS software. Continuous variables are reported as mean ± 1 SD and categorical variables as percent. Inter-group differences have been determined using ANOVA for continuous variables and χ² test using 2 × 3 factorial design for categorical variables. Trends for categorical variables were calculated using Mantel-Haenszel χ² test. To identify magnitude of inter-group difference in significant risk factors, clinical presentation and angiographic data we calculated unadjusted odds ratio (OR) and 95% confidence intervals (CI) using logistic regression. We separately evaluated ORs in women and men with premature and very premature CAD as compared to non-premature CAD patients. Age-adjustment was not performed as it is the variable of interest. P values < 0.05 are considered significant.

3. Results

We enrolled 4672 successive CAD patients (women 936, men 3736) who underwent coronary interventions at this hospital from Jan 2018 to June 2021. Mean age was 60.1 ± 11 years (women 61.5 ± 11, men 59.8 ± 11 years). Almost all the cohort was urban and 46.4% were uninsured. There was high prevalence of hypertension (n = 2560, 55.2%), diabetes (n = 1770, 37.9%) and raised total cholesterol >200 mg/dl (n = 531, 11.4%) and >170 mg/dl (n = 1188, 25.4%), non-HDL cholesterol >130 mg/dl (n = 1184, 25.3%) and >100 mg/dl (n = 2107, 45.1%), LDL cholesterol >100 mg/dl (n = 1956, 41.9%) and >70 mg/dl (n = 3068, 65.7%), triglycerides >150 mg/dl (n = 1648, 35.2%), and current smoking/tobacco use (n = 647, 13.8%). Previous PCI was in 562 (12.0%) and coronary bypass surgery in 151 (3.2%). Clinical presentation was mainly acute coronary syndrome (n = 4446, 95.0%) with more NSTEMI/ unstable angina (n = 2545, 54.5%) compared to STEMI (n = 1895, 40.5%). Mean left ventricular EF at admission was 45.5 ± 10%, half of the patients (n = 2459, 53.1%) had EF 30–45% while low EF <30% was in 202 (4.4%). Coronary angiography revealed that a majority of patients had disease of left anterior descending (LAD) artery (n = 3667, 78.5%). Single vessel disease was in 2060 (44.1%), double vessel disease in 1659 (35.5%) and triple vessel disease in 933 (20.0%) while left main CAD was in 267 (5.7%). Drug-eluting stents were deployed in almost all the patients: one stent in the majority (2924, 62.6%) while 386 (8.2%) had ≥3 stents. Incidence of in-hospital deaths was low (n = 54, 1.0%) and insignificantly different in women and men. Median duration of hospital stay was 4 days (IQR 2–6). At discharge from the hospital more than 95% patients received aspirin, P2Y12 inhibitors (predominantly ticagrelor) and statins apart from other cardiovascular medicines. The overall prevalence of premature CAD was in 1399 (29.9%) and was more in women (n = 309, 33.0%) as compared to men (n = 1090, 29.2%) (p < 0.05). Premature CAD (women 45–59 y, men 40–54 y) was in 1238 (26.5%) and was also more in women (n = 299, 31.9%) than men (n = 939, 25.1%), while very premature CAD was in 212 (4.5%) and slightly more in women (n = 61, 6.5%) than men (n = 151, 4.0%).

Data on risk factors, clinical presentation, angiography and interventions among non-premature, premature and very premature CAD in women and men are in Tables 1 and 2, respectively. In women and men with premature as well as very premature CAD the mean levels of total cholesterol and non-HDL cholesterol were significantly more (p < 0.01). The mean levels of LDL cholesterol and median levels of triglycerides were not dissimilar among various groups in women (Table 1) but were slightly more in men with premature disease (Table 2). The prevalence of raised total cholesterol (>200 mg/dl and >170 mg/dl), raised non-HDL cholesterol (>130 mg/dl and >100 mg/dl) and smoking/tobacco use was more in premature and very premature CAD patients.
(Tables 1 and 2, p < 0.01); while raised LDL cholesterol (≥100 mg/dl) were slightly more in men with premature disease. OR (95% CI) for raised total cholesterol (>200 mg/dl) in premature and very premature CAD vs non-premature CAD patients, respectively were: women 1.52 (1.03–2.25) and 1.59 (0.79–3.20) and men 1.73 (1.38–2.17) and 1.92 (1.22–3.03) and were almost similar for total cholesterol ≥170 mg/dl (Table 3). For non-HDL cholesterol ≥130 mg/dl, OR (95% CI) were for women 1.84 (1.35–2.52) and 1.32 (0.72–2.42) and men 1.69 (1.43–1.90) and 1.67 (1.17–2.34) and were similar for non-HDL cholesterol ≥100 mg/dl. The OR for LDL cholesterol >100 mg/dl as well as >70 mg/dl were of borderline significance in men with premature and very premature CAD (Table 3). No inter-group difference was observed for raised triglycerides. For smoking/tobacco use the OR (95% CI) were slightly higher for women [1.40 (0.84–2.35) and 2.14 (0.95–4.82)] and significantly greater in men [1.63 (1.34–1.98) and 1.27 (0.81–1.97)] (Table 3). In both women and men, the prevalence of hypertension, diabetes, chronic kidney disease and uninsured status were more in non-premature CAD patients as indicated by significant ORs of <1.0 (Tables 1 and 2).

Presentation as STEMI was more in premature and very premature CAD, especially in men (Table 2). In premature and very premature CAD patients, especially in men (Table 2).
premature CAD vs non-premature the OR were signiﬁcant for men (premature 1.35, CI 1.16–1.56; very premature 1.79, CI 1.29–2.49) (p < 0.01) and of borderline signiﬁcance for women (Table 1). There was no difference in mean ejection fraction and coronary angiographic ﬁndings did not reveal signiﬁcant anatomical differences in location and extent of CAD in both women and men with premature CAD (Tables 1 and 2). The number of stents deployed (1, 2 or ≥3) were not signiﬁcantly different (Tables 1 and 2) although ≥2 stents were less deployed in premature and very premature CAD patients [women 0.85 (0.64–1.13) and 0.68 (0.38–1.20); men 0.83 (0.71–0.97) and 0.64 (0.42–0.89)]. The number of the total in-hospital deaths was 54 (1.2%) with insigniﬁcant difference in non-premature, premature and very premature CAD patients (Tables 1 and 2).

4. Discussion

This study shows that one-third of patients in a hospital-based coronary intervention registry in India have premature CAD with slightly greater burden in women. The study has identiﬁed raised total cholesterol, non-HDL cholesterol and LDL cholesterol (men) and smoking/tobacco use (men) as important risk factors in premature as well as very premature CAD. STEMI is more common for men.

Table 2

| Variable | Total men (n = 3736) | Non-premature (n = 2646, 70.8%) | Premature (n = 939, 25.1%) | Very premature (n = 151, 4.0%) | X2 test (P value) |
|----------|---------------------|-------------------------------|--------------------------|-------------------------------|-------------------|

| Risk factors | Hypertension | Diabetes | Total cholesterol (mean ± SD) | Cholesterol ≥ 200 mg/dl | Cholesterol > 170 mg/dl | Non-HDL cholesterol (mean ± SD) | LDL cholesterol (mean ± SD) | LDL cholesterol > 100 mg/dl | LDL cholesterol ≥ 70 mg/dl |
|--------------|--------------|----------|--------------------------|------------------------|--------------------------|---------------------------|--------------------------|--------------------------|--------------------------|
|              | 1985(53.0)   | 1392(37.2) | 149.6 ± 42.9             | 145.8 ± 41.4           | 137(14.6)              | 90.7 ± 57.6              | 102.8 ± 43.2             | 1552(41.5)               | 2432(65.1)               |
|              | 1557(58.8)   | 1046(39.5) | 158.4±Sol 8.0            | 154.6 ± 45.6           | 137(14.6)              | 86.1 ± 55.2              | 101.9 ± 42.6             | 1073(40.5)               | 1722(65.0)               |
|              | 388(41.3)    | 319(34.0)  | 24(14.5)                 | 19(14.5)               | 300(31.9)              | 97.2 ± 62.3              | 104.9 ± 44.2             | 415(44.2)                | 616(65.6)                |
|              | 36(23.8)     | 27(17.9)   | 0.001                    | 0.001                  | 0.001                   | 0.001                    | 0.001                    | 0.001                    | 0.01                     |

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Numbers ± indicate 1 SD. Numbers in parenthesis are percent. CAD coronary artery disease; CKD chronic kidney disease; HDL high density lipoprotein; LDL low density lipoprotein; LMCA left main coronary artery; NSTEMI non ST segment elevation myocardial infarction; RCA right coronary artery; STEMI ST segment elevation myocardial infarction.
income countries while it is increasing in many developing countries including India. In India, the annual mortality among age group 20—54 years in the year 2000 was 191,053 (women 53,442 men 137,612) and has increased in 2019 to 286,055 (women 86,823, men 199,232) (absolute increase 49.7%, +2.5% per year). In earlier studies from developed countries, CAD risk factors found important were smoking, saturated fats, physical inactivity, high blood pressure and raised total cholesterol. Subsequent epidemiological and clinical studies, mainly in developed countries, have identified more coronary risk factors in premature CAD including other hyperlipidemias (LDL cholesterol, triglycerides, non-HDL cholesterol, lipoprotein(a), remnant lipoproteins, etc., dietary factors (saturated and trans-fats, refined sugars, etc.) and genetic factors, apart from the upstream social determinants. Recent reviews on premature CAD from India have continued to focus on smoking and tobacco use and unhealthy lifestyles as being of prime importance. The case—control INTERHEART study and the Prospective Urban Rural epidemiology (PURE) studies have identified that 9—10 common risk factors explain more than 90% of CAD in high-, middle as well as low-income countries. In the South Asian cohort of the PURE study CAD risk factors identified as important are raised non-HDL cholesterol, hypertension, diabetes and ambient and household air pollution, each having about 10—11% population attributable fraction. Our study shows that raised non-HDL cholesterol (combination of LDL and VLDL lipoproteins) is an important risk factor for premature CAD in India while raised LDL cholesterol is partially significant in men. Identification of non-HDL cholesterol is important in context of emergence of South and South East Asian region as the global epicenter of raised non-HDL cholesterol. Prevention guidelines from USA and Europe have highlighted importance of lipid factors in premature CAD, and suggested management of raised LDL and non-HDL cholesterol from an earlier age. Recent studies have reported importance of genetic factors (monogenic lipid disorders, familial hypercholesterolemia, polygenic risks). We do not have data on unhealthy diet, physical activity, body-mass index, other lipids factors (lipoprotein(a), remnant lipoproteins, etc.) and monogenic or polygenic factors and cannot comment on their importance. In a case—control study from India, importance of polygenic risk scores in premature CAD has been reported. Presence of severe and widespread coronary involvement in premature and very premature CAD is another important finding in the present study. Some previous studies from India have reported high prevalence of single vessel disease in premature CAD patients. In our study, less than 20% patients with premature CAD had single vessel disease and a much larger proportion had multivessel disease. This is similar to studies from USA and UK where South Asians with premature CAD are known to have premature onset multivessel disease. This has been attributed to higher prevalence of impaired glucose tolerance and diabetes among emigrant South Asians to these countries. Our study has highlighted the importance of lipid abnormalities—especially raised non-HDL cholesterol, as important. Multivessel CAD could be due to this sinister dyslipidemia, however, more prospective studies are required to confirm this finding. The number of coronary stents deployed were almost similar in groups with premature and non-premature CAD, although single stents were slightly more common in very premature CAD patients. This study has strengths and multiple limitations. This is one of the larger studies from India and we have evaluated important coronary risk factors among premature CAD patients. We have highlighted greater burden of premature CAD in women, who are very often neglected in cardiovascular medicine. We also identified raised total, LDL and non-HDL cholesterol as important in premature CAD. However, as noted in Tables 1 and 2, a significant proportion of patients were on statins. It is, therefore, likely that we have underestimated the importance of total, non-HDL and LDL cholesterol in our study cohort and to overcome this limitation we used two levels for total cholesterol (≥200 and ≥170 mg/dl), non-HDL cholesterol (≥130 and ≥100 mg/dl) and LDL cholesterol (≥100 mg/dl and ≥70 mg/dl). We could not correct the cholesterol and non-HDL cholesterol levels for statin treatment. This strategy has been used for LDL cholesterol (mathematical formula are available depending on dose of a particular statin) and not for total or non-HDL cholesterol. We did not have exact dose of statins (atorvastatin or rosuvastatin) in our patients and could not use this formula. Moreover, there was only minimal difference in use of

![Table 3](https://example.com/table3.jpg)

Univariate odds ratios (95% confidence intervals) for selected risk factors, clinical presentation, angiographic findings and outcomes in women and men with premature and very premature CAD as compared to non-premature CAD. Univariate ORs < 1.00 indicate that these variables are more important in non-premature CAD while > 1.00 indicate that these are more important in premature CAD.

| Variable                       | Women          | Men            |
|--------------------------------|----------------|----------------|
|                               | Premature      | Very premature | Premature     | Very premature |
| Hypertension                   | 0.67 (0.50—0.90)* | 0.27 (0.16—0.47)** | 0.49 (0.42—0.57)** | 0.22 (0.15—0.32)** |
| Diabetes                       | 1.07 (0.81—1.42) | 0.51 (0.28—0.93)* | 0.78 (0.67—0.92)** | 0.33 (0.22—0.51)** |
| Cholesterol ≥200 mg/dl         | 1.52 (1.03—2.25)* | 1.59 (0.79—3.20) | 1.73 (1.38—2.17)** | 1.92 (1.22—3.03)** |
| Cholesterol ≥170 mg/dl         | 1.53 (1.13—2.07)** | 1.25 (0.79—2.24) | 1.67 (1.42—1.98)** | 1.61 (1.13—2.30)** |
| Non-HDL cholesterol ≥130 mg/dl | 1.84 (1.35—2.52)** | 1.32 (0.72—2.42) | 1.69 (1.43—1.90)** | 1.67 (1.17—2.34)** |
| Non-HDL cholesterol ≥100 mg/dl | 1.59 (1.21—2.11)** | 2.26 (1.31—3.90)** | 1.48 (1.27—1.72)** | 1.92 (1.38—2.67)** |
| LDL cholesterol ≥100 mg/dl     | 0.94 (0.73—1.22) | 1.13 (0.71—1.79) | 1.10 (0.95—1.25) | 1.04 (0.77—1.41) |
| LDL cholesterol ≥70 mg/dl      | 1.07 (0.86—1.33) | 0.96 (0.63—1.46) | 1.01 (0.89—1.13) | 0.96 (0.73—1.24) |
| Triglycerides ≥150 mg/dl       | 1.01 (0.77—1.31) | 0.98 (0.59—1.64) | 1.03 (0.89—1.19) | 0.94 (0.68—1.31) |
| Smoking/tobacco                | 1.40 (0.84—2.35) | 2.14 (0.95—4.82) | 1.63 (1.34—1.98) | 1.27 (0.81—1.97) |
| CKD, creatinine ≥2 mg/dl       | 0.38 (0.08—0.75) | –               | 0.52 (0.30—0.95)* | 1.01 (0.36—2.82) |
| Uninsured status               | 0.81 (0.61—1.08) | 0.43 (0.25—0.74)** | 0.83 (0.72—0.97)* | 0.59 (0.42—0.82)** |
| STEMI/Unstable angina          | 1.13 (0.85—1.51) | 1.29 (0.75—2.22) | 1.35 (1.16—1.56) | 1.79 (1.29—2.49) |
| NSTEMI/Unstable angina         | 0.87 (0.66—1.15) | 0.91 (0.53—1.56) | 0.76 (0.65—0.88) | 0.57 (0.41—0.79) |
| IF <45                         | 0.67 (0.49—0.90)* | 1.0 (0.58—1.72) | 1.08 (0.93—1.26) | 1.07 (0.77—1.50) |
| Single vessel disease          | 1.11 (0.84—1.48) | 0.99 (0.58—1.70) | 1.09 (0.94—1.26) | 0.95 (0.69—1.33) |
| Triple vessel disease          | 0.77 (0.54—1.09) | 0.75 (0.38—1.48) | 0.90 (0.74—1.08) | 1.03 (0.68—1.54) |
| Stents ≥2 deployed             | 0.85 (0.64—1.13) | 0.68 (0.38—1.20) | 0.83 (0.71—0.97)* | 0.64 (0.42—0.89)* |
| In-hospital deaths             | 0.59 (0.11—2.65) | 1.22 (0.63—2.36) | 1.17 (0.28—4.94) (1) |

CKD chronic kidney disease; HDL high density lipoprotein; LDL low-density lipoprotein; NSTEMI non-ST segment elevation myocardial infarction; STEMI ST segment elevation myocardial infarction; *p < 0.05, **p < 0.01, ***p < 0.001.
mortality rates were reported. The ICMR-MACE registry also recon

social contexts in patients with premature CAD. We also note that familial hypercholesterolemia and other hyperlipidemias as well as studies are required to evaluate importance of genetic factors, factors and biological, genetic and social determinants. More proximate risk factors (lifestyle and dietary factors, other lipid interventions are needed to promote healthy living for primary prevention of CAD, especially in the young. Focus on early identification and management of coronary risk factors for pr

In conclusion, this hospital registry-based study shows that premature CAD is an important disease phenotype in India. We have also identified that raised non-HDL cholesterol and total cholesterol in both women and men and raised LDL cholesterol and any tobacco use in men are important risk factors. Presence of microvascular disease in premature CAD and deployment of similar number of stents are important observations. Public health interventions are needed to promote healthy living for primary prevention of CAD, especially in the young. Focus on early identification and management of coronary risk factors for pr

Disclosure statement and conflict of interest
All the authors have nothing to disclose.

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