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Cardiovascular risk and subclinical atherosclerosis in first-degree relatives of patients with premature cardiovascular disease

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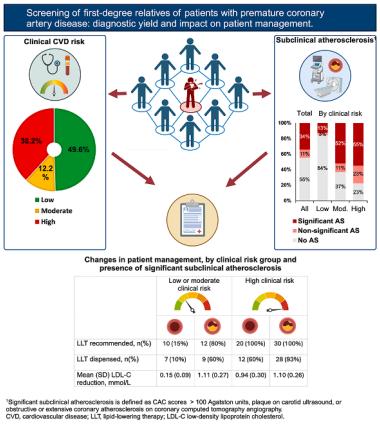
HIGHLIGHTS

- Screening of first-degree relatives of patients with premature CAD has a high diagnostic yield leading to initiation of preventive treatments.
- The prevalence of significant subclinical atherosclerosis is higher among patients with a family history of premature CAD than in the general population.
- Patients with a family history of premature CVD and a low or moderate risk of CVD estimated with conventional algorithms may benefit from screening with non-invasive cardiovascular imaging. In patients with high estimated risk, positive imaging findings may improve the intake of preventive medications.
- The screening program incorporating clinical assessment and non-invasive cardiovascular imaging of patients with a family history of premature CVD was feasible and impacted CVD risk management the year following the assessment. Studies longitudinally evaluating retention of these changes and cardiovascular outcomes are needed to assess risk reduction and the benefits of such programs to public health.

GRAPHICAL ABSTRACT



Abbreviations: CAC, coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CUS, carotid ultrasound; CVD, cardiovascular disease; FDRs, first-degree relatives; LDL-C, low density lipoprotein cholesterol; LLT, lipid-lowering therapy; mFRS, modified Framingham Risk Score; PCE, Pooled Cohort Equations; SIS, segment involvement scores; SA, significant subclinical atherosclerosis.

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ABSTRACT

Background: Screening first-degree relatives (FDRs) of patients with premature coronary artery disease (CAD) is recommended but not routinely performed.
Objectives: To assess the diagnostic yield and impact on clinical management of a clinical and imaging-based screening program of FDRs delivered in the setting of routine clinical care.
Methods: We recruited FDRs of patients with premature CAD with no personal history of CAD and prospectively assessed for: 1) cardiovascular risk and presence of significant subclinical atherosclerosis (SA) defined as plaque on carotid ultrasound, stenosis >50% or extensive atherosclerosis on coronary computed tomography angiography, or coronary artery calcium scores >100 Agatston units or >75% percentile for age and sex; 2) utilization of preventive medications and lipid levels prior enrolment and after completion of the assessment.
Results: We assessed 132 FDRs (60.6% females), mean (SD) age 47(17) years old. Cardiovascular risk was high in 38.2%, moderate in 12.2%, and low in 49.6% of FDRs. SA was present in 34.1% of FDRs, including 12.5% in low, 51.9% in moderate, and 55.0% in high calculated risk groups. After assessment, LLT was initiated in 32.6% of FDRs and intensified in 16.0% leading to mean (SD) LDL-C decrease of 1.07(1.10) mmol/L in patients with high calculated risk or SA. LLT was recommended to all patients with high calculated risk, but those with SA were more likely to receive the medications from pharmacies (93.3% vs 60.0%, $p = 0.006$).
Conclusion: Screening the FDRs of patients with premature CAD is feasible, may have high diagnostic yield and impact risk factor management.

1. Introduction

Despite enormous effort put in screening and prevention of atherosclerotic cardiovascular disease (CVD) it remains the leading cause of death worldwide [1]. Preventive therapy is widely recognised to decrease risk of cardiovascular events and prevent death, loss of lifetime productivity, and lifetime healthcare use, however, numerous studies reported insufficient utilization of preventive medications and poor risk factors control among patients with high cardiovascular risk, especially in the younger age groups [2-7]. CVD has been long recognized to be heritable, especially when it occurs at a young age, and risk of CVD is approximately two-fold higher among first-degree relatives of patients with premature CVD [8-10]. For more than two decades, professional societies and guidelines have recommended targeted screening of family members of patients with premature CVD [11-14]. However, it is rarely undertaken in clinical practice, and prospective studies assessing the feasibility, diagnostic yield, and clinical impact of such screening are lacking [15-17].

Multiple previous studies have shown that conventional approaches to risk calculation provide suboptimal assessment in several subgroups of patients, including younger individuals, females, and those with a family history of premature coronary artery disease (CAD), the most frequent clinical presentation of CVD [3-7]. Multiple emerging risk factors and enhancers were recently proposed for more precise risk assessment, including non-invasive cardiovascular imaging techniques [11-13]. Several non-invasive imaging techniques can detect and quantify atherosclerotic plaque burden and are recommended to guide management decisions in patients with intermediate or uncertain risk. Coronary artery calcium (CAC) scoring using non-contrast computed tomography and assessment of plaque burden with carotid ultrasound (CUS) has shown reliable performance in estimating the atherosclerotic burden and CVD risk prediction and are recommended by major guidelines for screening of asymptomatic individuals at low or moderate risk for whom treatment decisions are uncertain [11–13,18–22]. Evaluation of plaque burden with coronary computed tomography angiography (CCTA) also provides incremental prognostic value over traditional risk stratification approaches [23-28]. Several community-based cohort studies of individuals free of CVD have evaluated the burden of coronary atherosclerosis in the general population [26-28], however, data on its prevalence and characteristics in FDRs of patients with premature CVD as well on impact of the finding on approaches to patients' management are limited [29]. Current guidelines endorse using cardiovascular imaging alongside the traditional clinical assessment tailoring it to individual patient characteristics, however strategies of incorporating this information into risk evaluation and management are not well defined, underscoring the need for further research in this field.

The present study aims to explore: 1) The feasibility and diagnostic yield of a screening program incorporating clinical and radiological testing of FDRs of patients with premature CAD and delivered as part of routine clinical care; 2) The impact of participation in the program on patient management, overall and in different risk groups determined clinically and by imaging findings.

2. Methods

2.1. Study population

The Study to Avoid cardioVascular Events in British Columbia (SAVE BC) is an observational, longitudinal study of patients with premature CAD and their FDRs [31]. Patients who presented with CAD with stenosis ≥50% confirmed by angiography or underwent coronary revascularization at the age ≤50 years old for males and ≤55 years old for females were identified in tertiary care hospitals providing cardiac care for residents of the Canadian province of British Columbia and enrolled as Index cases. Eligible FDRs ≥ 19 years of age (Supplemental Figure 1) without a personal history of CVD who provided informed consent underwent structured clinical assessment of cardiovascular risk and cardiovascular imaging [30]. Personal history of CVD was collected from patients and confirmed with electronic medical records (EMRs) and was defined as previous diagnoses of CAD, cerebrovascular disease, or peripheral artery disease, or previous coronary, carotid, or peripheral arterial revascularization procedures [6].

2.2. Data collection and clinical assessment

Clinical assessment performed by study clinicians and nurses as recommended by national guidelines included: 1) Collection of medical, social, family history, and physical examination; 2) Measurement of fasting lipids, glucose, creatinine, complete blood count, C-reactive protein, and thyroid function with all tests performed at clinical laboratories following the pathways of routine clinical care. Laboratory values measured at enrollment were established as baseline (Supplemental Table 4). Additionally, laboratory values available for the period up to one year prior to enrollment were collected from EMRs and followed by prospective collection pools performed every six months by the study personnel; 3) Review of EMRs and province-wide pharmacy network records collecting information on treatment with preventive

medications and historical relevant laboratory results [11,31]. Cardiovascular risk factors and comorbidities were considered present if reported by patient, physician, or recorded in EMRs. Information about prescribed medications was collected from EMRs. Medications were considered received if dispensations were recorded in pharmacy network records. All information was validated by SAVE BC study physicians and coordinators and entered in the SAVE BC study database [31].

Cardiovascular risk was evaluated using the modified Framingham Risk Score calculator (mFRS) with calculated 10-years risk of CVD doubled for family history of premature CVD as recommended by the national guidelines on cardiovascular prevention [11]. Patients with statin-indicated conditions including diabetes, severe dyslipidemia, and chronic kidney disease were classified as the high risk. Definitions for cardiovascular risk factors and statin-indicated conditions are summarized in the Supplemental Methods and described elsewhere [4].

2.3. Radiological assessment

FDRs underwent assessment for subclinical atherosclerosis with either CAC, CUS, or CCTA. The decision on the preferred modality of radiological screening was made by the treating physician taking into consideration age-specific recommendations provided to physicians participating in the study (Supplemental Table 1), logistical considerations, and patient preferences. All tests were performed at local radiological laboratories and reported using standardized criteria [32-35]. For CAC, the proportion of patients with Agatston scores of 0, 1–100, 101–400, and 400% as well as disease burden ≥75th population percentile for sex and age was reported [36,37]. For CCTA, segment involvement scores (SIS) were calculated as the number of segments with any atherosclerosis using a 16-segment model of the coronary arteries [24]. The proportion of patients with coronary stenosis ≥ 50% as well as proportions of patients with no disease, non-extensive non-obstructive, extensive and obstructive disease were reported. Non-obstructive disease was considered extensive in patients with SIS > 75th percentile based on age- and sex-specific nomograms described elsewhere and non-extensive otherwise [24]. For CUS, the proportion of patients with plaques was reported. For this study, we defined significant subclinical atherosclerosis (SA) as CAC > 100 Agatston units, plaque on CUS, or obstructive or extensive non-obstructive coronary atherosclerosis on CCTA.

2.4. Changes in patient management

Results of clinical and radiographic assessment were made available to the patients' study physicians in prevention clinics as well as primary care and specialist physicians, and other healthcare professionals involved in the patients' care. Management decisions were left to the discretion of the treating physicians and as per current clinical practice guidelines. Treatment with lipid-lowering, antihypertensive, antihyperglycemic, anticoagulant and antiplatelet medication was assessed using physician consultation notes and pharmacy dispensation records (Supplemental Table 2) for periods prior to enrollment in the SAVE BC study and up to two years after completion of the study assessment. For the assessment of management by clinical risk group patients were classified based on clinical risk estimation and presence of SA.

2.5. Statistical approach

Analyses were performed using IBM SPSS Statistics v28.0 and R version 3.5.1. Categorical variables were summarized as proportions and compared with the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were summarized as mean with standard deviations or medians with first and third quartile and compared with ANOVA, Student's *t*-test, or Wilcoxon rank sum test, as appropriate. A 2-tailed p-value <0.05 was considered statistically significant. Benjamini–Hochberg method was used for multiple testing corrections.

2.6. Ethics

The study was approved by the Providence Health Care Research Ethics Board, certificate number H20–00758. All participants provided written informed consent.

3. Results

3.1. Clinical assessment

This study included 132 FDRs (60.6% females) who completed screening (Supplemental Fig. 1). The demographics, cardiovascular risk factors, comorbidities, and laboratory values are summarised in Table 1, along with those of the index patients. A detailed description of the cardiovascular risk and laboratory values by sex and age in FDRs compared to the general Canadian population is shown in Supplemental Tables 3 and 4. The most prevalent cardiovascular risk factors among FDRs were dyslipidemia (37.12%), obesity (25.0%), and hypertension (21.97%). When assessed with the mFRS and for presence of station-indicated conditions, 30.30% of FDRs had high, 20.45% had moderate, and 49.24% had low calculated risk. Diabetes was present in 12.21% of the cohort, and 13.64% of patients had LDL-C > 5.0 mmol/L. In total, 38.17% of patients had high, 12.21% had moderate, and 49.61% had low clinical risk. The summary of patients' distribution by clinical risk group, overall, by age, and when assessed with Pooled Cohort Equations (PCE) calculator in addition to mFRS is presented in Table 2.

3.2. Imaging

The results of imaging studies with the distributions by imaging type, clinical risk assessed with mFRS, age, and sex are presented in Fig. 1. The distribution of the findings by clinical risk determined with PCE-based algorithms is presented in Supplemental Figure 2.

CAC scores were measured in 51 participants aged 56.5(12.8) years old (Fig. 1A). Of these, 28.9% had CAC scores >100, including 12.5% of participants with moderate, and 46.6% of those with high clinical risk (Fig. 2). Additionally, 7.1%, 37.5%, and 43.3% of participants with low, moderate, and high risk, respectively, had CAC scores 1–99. Notably, 20.0% of participants <40 years of age had non-zero CAC.

CCTA was performed in 59 patients aged 44.9(12.6) years old (Fig. 1B). Of these, 17.6% had stenosis ≥ 50%. SA (extensive or obstructive) was found in 19.4% of FDRs with low, 50.0% with moderate, and 70.0% with high clinical risk. An additional 3.2% of those with low, 16.7% of those with moderate, and 10.0% of those with high clinical risk had non-obstructive non-extensive lesions. When assessed by age, 23.5% of participants <40 and 46.4% of those ≥40 years old had SA.

CUS was performed in 35 patients aged 37.1(19.2) years old. Of these, carotid plaque was observed in 28.6%, including 8.0% of patients with low, 75.0% with moderate, and 83.3% of those with high calculated risk (Fig. 1C).

Across all three imaging modalities, 34.1% of FDRs had SA, including 12.5% of participants with low, 51.9% with moderate, and 55.0% with high calculated risk. When assessed by age, 9.1% of participants <40 years old and 46.6% of those ≥40 years old had SA (Fig. 1D).

3.3. Patient management

Prior to enrolment in the study, 36.4% of FDRs received at least one medication recommended for management of cardiovascular risk factors, including medications with lipid-lowering, antihypertensive, antihyperglycemic, antiplatelet or anticoagulation activity, and 21.97% were receiving lipid-lowering therapy (LLT) (Table 3, 4). Among

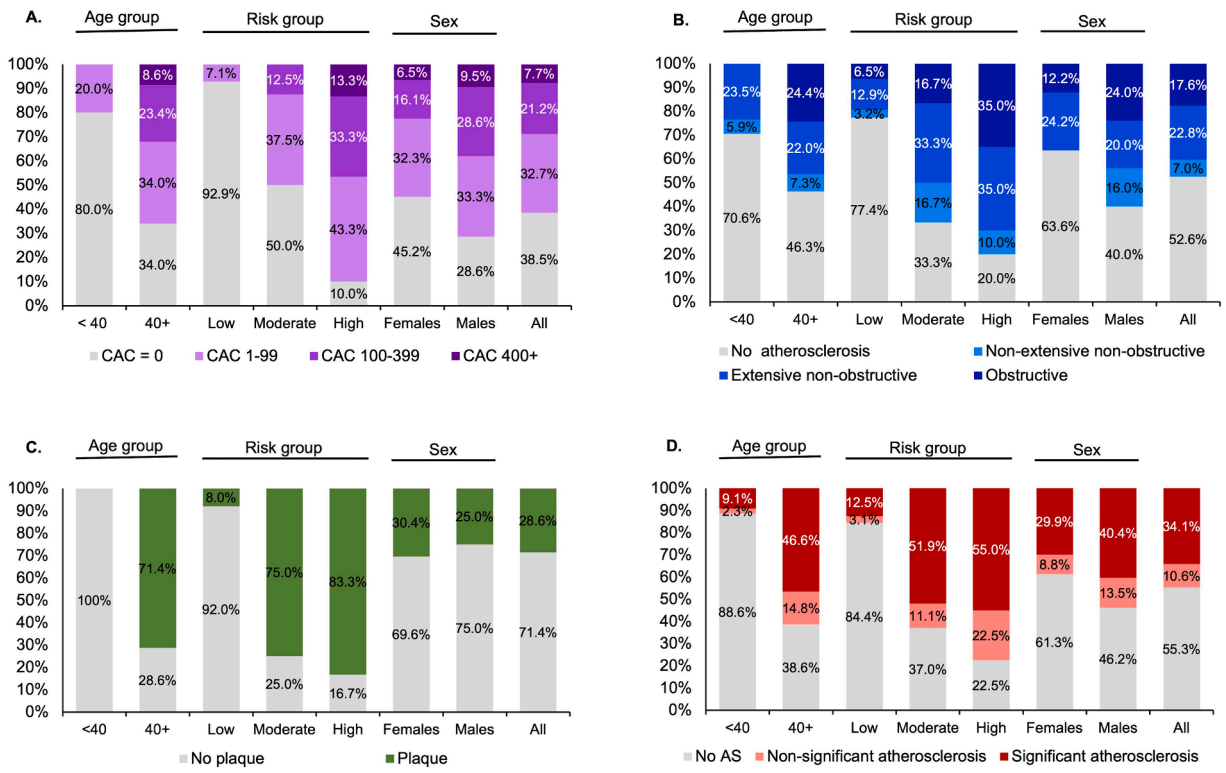


Fig. 1. Burden of subclinical atherosclerosis in FDRs of patients with premature CAD.
Legend: Distribution of atherosclerotic lesions in patients who underwent assessment with coronary artery calcium scoring, $N = 51$ (A), coronary computed tomography angiography, $N = 59$ (B), carotid ultrasound, $N = 35$ (C), and total yield across all imaging techniques (D), overall, by sex, age, and cardiovascular risk group.
CAC, coronary artery calcium scores; AS, atherosclerosis.

patients with high calculated cardiovascular risk, only 52.0% were treated with LLT, and 26.0% achieved lipid targets recommended for their risk level [11]. Of patients with LDL-C $\geq$ 5 mmol/L, 67.7% were receiving LLT prior to enrolment, and 44.5% reached recommended lipid targets. Among patients with diabetes and hypertension, 62.5% and 82.8% were receiving antihyperglycemic and antihypertensive medications, respectively.

In the two years after enrollment, 82 (62.1%) were receiving at least one preventive medication. LLT was initiated in 32.6% of FDRs and intensified in 16.0%. Antihyperglycemic and antihypertensive medications were initiated in 6.2% and 12.1% of participants, respectively. Notably, among participants younger than 40 years of age, 10.3% were started on LLT and 14.6% were started on antihypertensive medications. Tables 3 summarises changes in LLT and lipid levels by calculated cardiovascular risk groups. While all patients with high and 68.8% with moderate calculated risk were recommended to start or continue LLT, only 80.0% and 50.0% of patients in these risk groups received the medications from pharmacies.

Tables 4 summarises changes in LLT and lipid levels by calculated cardiovascular risk and presence of SA. While all patients with high calculated risk received recommendation to start, up-titrate or continue LLT, those without significant burden of the disease on imaging studies less frequently filled these prescriptions (60.0% vs 93.3%, $p = 0.006$). Among all FDRs who received recommendations for LLT, the medication was dispensed in 83.3% of those with SA on imaging versus 45.5% of those without imaging findings of atherosclerosis ($p = 0.09$). The mean (SD) reduction in LDL-C was 1.10 (0.26) mmol/L in patients with high clinical risk and positive imaging findings, 0.94 (0.30) mmol/L in those with high risk and negative or non-significant imaging findings, and 1.79 (0.78) mmol/L in those with low or moderate calculated risk and positive imaging findings, resulting in mean reduction of 1.07 (1.10) mmol/L in these groups. No significant changes were observed in participants with low or moderate calculated risk and negative or non-significant imaging findings.

4. Discussion

We performed an exploratory study to evaluate the feasibility, diagnostic yield, and impact on patient management of a structured program to screen the FDRs of patients with premature CAD that combined clinical assessment of cardiovascular risk and imaging tests. The main findings of this study are that an imaging-based screening program is feasible when delivered as part of routine patient care and has high diagnostic yield. Clinical risk scoring predicted high cardiovascular risk in 38.2% of participants, whereas 34.1% had SA, including 12.5% of participants with low and more than half of those with moderate calculated risk. Participation in the screening program led to LLT initiation or intensification in 45.5% of FDRs, and was associated with a ~1 mmol/L mean reduction in plasma LDL-C, which would be anticipated to lead to a ~21% relative risk reduction in major adverse cardiovascular events [38]. We also found that while all patients with high calculated risk were advised to take LLT, those with SA on imaging studies were more likely to fill their prescriptions than those with negative imaging findings.

We observed that FDRs of patients with premature CAD had a high prevalence of major cardiovascular risk factors. While lower than in their relatives who presented with premature CAD, the prevalence of these risk factors was higher than in the general Canadian population of the same sex and age. FDRs of both sexes aged 35 to 50 years had a prevalence of diabetes two to four times higher than reported for the general population. Hypertension was also more prevalent in male FDRs $\geq$ 35 years and females $\geq$ 50 years than in the general population. We also found a high prevalence of statin-indicated conditions that corresponds to that previously observed in SAVE BC index patients [4].

Table 1
Demographics, cardiovascular risk factors, comorbidities, and laboratory parameters in FDRs participants at enrollment to the SAVE BC study and in Index participants at presentation with premature CAD.

	FDRs participants, $N = 132$	Index patients, $N = 476$
Demographics		
Age	47.17 (16.94)	46.36 (5.21)
Females	60.61% (51.10–68.60)	27.30% (23.31–31.31)
Ethnicity[a]		
Aboriginal	0.83% (0–2.5%)	3.37% (1.41–5.33)
Black	0	0
East Asian	13.33% (7.25–19.42)	11.04% (7.64–14.45)
European	50.83% (41.89–59.78)	49.36% (43.96–54.81)
South/West Asian	20.83% (13.57–28.10)	24.54% (19.87–29.21)
Mixed or other	14.17% (7.92–20.41)	11.66% (8.17–15.14)
Education[a]		
College or Diploma	20.17% (12.96–27.38)	18.40% (14.20–22.61)
High School Certificate	28.57% (20.45–36.69)	20.86 (16.45–25.27)
Less than high school	6.72% (2.22–11.22)	5.21% (2.80–7.63)
Trades certificate	5.04% (1.11–8.97)	3.07% (1.20–4.94)
University	39.50% (30.71–48.28)	52.45% (47.03–57.88)
Cardiovascular risk factors		
Diabetes	12.21% (7.40–18.60)	27.07% (23.16–31.28)
Impaired fasting glucose	13.64% (8.59–20.26)	23.05% (18.70–27.89)
Dyslipidemia	37.12% (29.23–45.57)	76.09% (72.03–79.81)
Hypertension	21.97% (15.56–29.59)	45.65% (41.14–50.22%)
Obesity (BMI>30)	25.00% (18.21–32.87)	40.87% (36.22–45.64)
Smoking		
Never	60.31% (51.80–68.40)	53.07% (48.49–57.65)
Current	11.45% (6.80–17.70)	25.66% (21.65–29.67)
Former	28.24% (21.10–36.40)	21.27% (17.52–25.03)
Chronic kidney disease	1.52% (0.32–4.77)	2.42% (1.15–4.51)
Comorbidities		
Chronic inflammation	10.61% (6.21–16.70)	10.71% (8.17–13.73)
Malignancy	6.82% (3.43–12.07)	4.20% (2.67–6.29)
NAFLD	3.79% (1.46–8.10)	8.52% (5.82–11.97)
Cardiac arrhythmias	3.79% (1.46–8.10)	5.97% (3.76–8.99)
Chronic heart failure	0.76% (0.08–3.49)	2.12% (0.95–4.12)
Obstructive sleep apnea	9.85% (5.63–15.80)	22.83% (18.43–27.73)
COPD	3.03% (1.03–7.04)	3.02% (1.56–5.29%)
Gestational hypertension[b]	10.45% (4.80–19.40)	15.38% (8.69–24.59)
gestational diabetes[b]	7.35% (2.90–15.40)	25.32% (16.73–36.67)
preeclampsia[b]	8.82% (3.80–17.30)	5.06% (1.73–11.59)

[a] 147 missing for Index, 13 for FDRs.
[b] N=130 for Index, 80 for FDRs
[c]162 missing for Index, 22 for FDRs
[d]221 missing for Index, 23 for FDRs
Values are presented as median (interquartile range), mean (SD) or% (95% CI).

FDRs, first-degree relatives; CAD, coronary artery disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; COPD, chronic obstructive pulmonary disease.

Table 2
Clinical risk groups and prevalence of statin-indicated conditions and cardiovascular risk enhancers in FDRs of patients with premature CAD.

	All patients, $N = 132$	< 40 years old $N = 41$	≥ 40 years old $N = 91$
Clinical risk group[1], mFRS			
low	65 (49.62%)	40 (97.56%)	26 (28.57%)
moderate	16 (12.21%)	0	16 (17.58%)
high	50 (38.17%)	1 (2.5%)	49 (53.84%)
Clinical risk groups[2], PCE			
Low	75 (56.8%)	42 (95.5%)	33 (37.5%)
Borderline	12 (9.1%)	1 (2.3%)	11 (12.5%)
Moderate	11 (8.3%)	0	11 (12.5%)
High	34 (25.8%)	1 (2.3%)	33 (37.5%)
LDL-C ≥ 5.0 mmol/L	18 (13.6%)	1 (2.4%)	17 (18.68%)
Diabetes	16 (12.2%)	0	16 (17.58%)
CKD	2 (1.52%)	0	2 (2.20%)
Lipoprotein(a)3			
<300 mg/L	79 (72.5%)	29 (80.6%)	50 (68.5%)
300–499 mg/L	5 (4.55%)	2 (5.6%)	3 (4.1%)
500–699 mg/L	5 (4.55%)	1 (2.8%)	4 (5.5%)
≥700 mg/L	20 (18.18%)	4 (11.1%)	16 (21.9%)

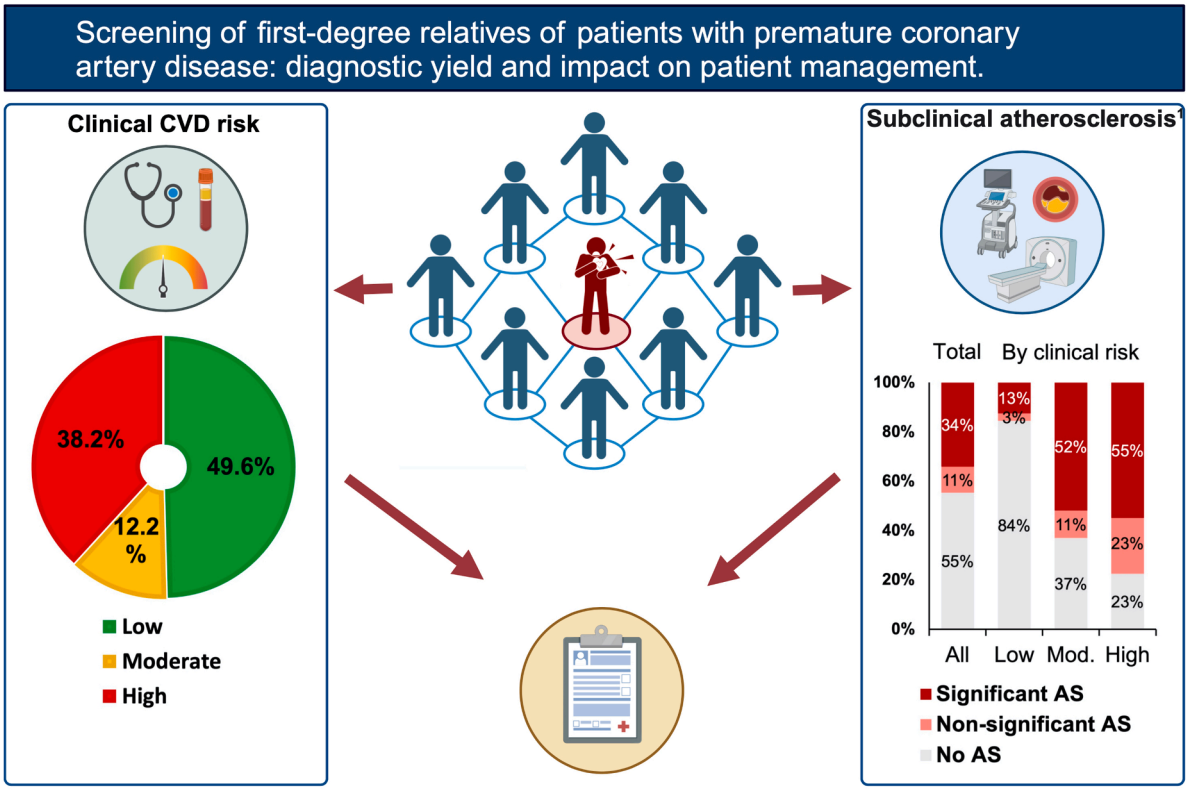
[1] Estimated using Framingham Risk Score calculator and Canadian Cardiovascular Society Guidelines 2016 and 2021;.
[2] Estimated using Pooled Cohort Equations calculator and recommendations of the AHA/ACC Guidelines 2018;
[3]23 missing. Values are presented as n (%).

Despite this, when assessed for risk of cardiovascular disease using conventional clinical risk tools, more than half of all FDRs, and nearly all FDRs younger than 40 years had a low calculated risk of CVD events in the next 10 years. This aligns with previous data showing underperformance of conventional risk assessment algorithms in patients of younger age and highlights the importance of alternative approaches [3-7].

The prevalence of significant subclinical atherosclerosis, which we defined as CAC > 100, plaque on CUS, or obstructive or extensive non-obstructive coronary atherosclerosis on CCTA was 34.1%, and the prevalence of any atherosclerosis was 44.7%. This suggests that ultrasound and radiographic screening of FDRs of patients with premature CAD is likely to have a very high yield. Several community-based cohort studies of individuals free of CVD have evaluated the burden of atherosclerosis in the general population [26-28,36,37,39]. Similar to these studies, we observed increasing plaque burden with age and higher clinical risk group. Notably, the frequency of findings was higher in FDRs than in the general populations of comparable age or risk groups for all methods we studied[26-28,36,37,39]. Only 38.5% of FDRs assessed with CAC were free from atherosclerosis compared to 60–70% previously described for the general populations of comparable age, and the proportion of FDRs with CAC >100 was nearly twice that observed in the general population [26,27,37]. The disease burden was also more severe than was observed for low-risk MESA study participants with a mean age of 48 years who had family history of heart disease in relatives of any age, where the prevalence of CAC = 0 was 68.4% for females and 51.3% for males, and just 11% of participants had CAC > 100 [40]. Similarly, among those assessed with CCTA, the prevalence of obstructive disease was 2–4 times higher than in population cohorts of comparable age and even a cohort 15 years older [26-28]. Finally, the frequency of plaques on CUS was higher in FDRs than in general populations of comparable or higher age [27]. These differences highlight the early development of atherosclerosis in FDRs and underscore the importance of early preventive interventions. Notably, we detected atherosclerotic changes in many patients with low or moderate calculated risk determined with mFRS-based algorithm or those with low, borderline or moderate risk determined with PCE-based algorithm, as well as in FDRs <40 years of age. This suggests potential benefits of imaging assessment in patients with a family history of premature CVD with low calculated risk. However, studies with larger numbers of participants are needed to confirm these observations.

Multiple previous studies have shown that the absence of CAC does not exclude the presence of noncalcified coronary plaque, identifiable with CCTA or CUS, that may also have prognostic implications, especially in younger individuals with a high-risk factor burden [26,27,49]. To account for the possibility of not detecting non-calcified plaque and to allow participation in the program of females of childbearing age, SAVE BC recommended that participating physicians follow age-specific recommendations (Supplemental Table 1) taking into account logistical considerations and patient preferences. This approach has the advantage of providing information on feasibility and yield of the program in a real-world clinical setting. However, different performance characteristics of these imaging tests could lead to biases, such as underestimation of disease burden in younger patients, females, or patients residing in remote rural areas with better access to CUS compared with other imaging modalities.

We also observed underutilization of preventive LLT in FDRs with



Changes in patient management, by clinical risk group and presence of significant subclinical atherosclerosis

	Low or moderate clinical risk		High clinical risk	
LLT recommended, n(%)	10 (15%)	12 (80%)	20 (100%)	30 (100%)
LLT dispensed, n(%)	7 (10%)	9 (60%)	12 (60%)	28 (93%)
Mean (SD) LDL-C reduction, mmol/L	0.15 (0.09)	1.11 (0.27)	0.94 (0.30)	1.10 (0.26)

[1]Significant subclinical atherosclerosis is defined as CAC scores > 100 Agatston units, plaque on carotid ultrasound, or obstructive or extensive coronary atherosclerosis on coronary computed tomography angiography.
CVD, cardiovascular disease; LLT, lipid-lowering therapy; LDL-C low-density lipoprotein cholesterol.

Fig. 2. Graphical Abstract: Screening of FDRs of patients with premature CAD
Legend: Clinical and imaging screening of FDRs of patients with premature CAD has high diagnostic yield, with 51% of patients having moderate or high calculated cardiovascular risk and 34% having significant subclinical atherosclerosis. The program led to improvement in risk factors management with mean decrease in LDL-C of 1.07(1.10) mmol/L in patients with high calculated risk or significant subclinical atherosclerosis.
[1]Significant subclinical atherosclerosis is defined as CAC scores > 100 Agatston units, plaque on carotid ultrasound, or obstructive or extensive coronary atherosclerosis on coronary computed tomography angiography.
AS, atherosclerosis; CVD, cardiovascular disease; LLT, lipid-lowering therapy; LDL-C low-density lipoprotein cholesterol.

clinically measurable high CVD risk prior to enrolment that agrees with multiple studies reporting that the therapy use remains low in primary CVD prevention [2-7,41-44]. After assessment, all patients with high risk and those with moderate or low risk but SA on imaging studies received recommendations for LLT, resulting in average decrease in LDL-C by approximately 1 mmol/L in the next year. We also found that among those with high clinical risk, patients with no SA were significantly less likely to receive LLT from pharmacies than those with detected SA. This finding corresponds to the previously reported positive relationships between cardiovascular imaging and intensification of risk factor management in asymptomatic and symptomatic cohorts with different levels of clinical risk, that, in some studies, was found to be proportional to the degree of abnormal test findings [45-48]. Studies with larger number of participants and longer follow-up will be needed to confirm retention of these positive changes in patient management and to evaluate their impact on cardiovascular outcomes. Also, it should be noted that in this study, we determined cardiovascular risk with mFRS doubled for a family history of premature CVD. While the

Table 3
Utilization of lipid-lowering therapy and lipid management by risk group established using national guidelines (CCS 2021).

	Calculated cardiovascular risk group		
	Low, *N* = 66	Moderate, *N* = 16	High, *N* = 50
Prior to enrolment to the study			
Received LLT before enrolment, N (%)	2 (3%)	1 (6.3%)	26 (52.0%)
At lipid target before enrolment, N (%)	52 (80.0%)	1 (6.3%)	13 (26.0%)
LDL-C, mmol/L	2.91 (0.67)	3.23 (0.92)	2.93 (1.16)
After enrolment to the study			
LLT, physicians' recommendations			
LLT initiation recommended	9 (13.6%)	10 (62.5%)	24 (48.0%)
LLT intensification recommended	0	1 (6.3%)	19 (38.0%)
LLT continued at the same doses	2 (3.0%)	0	7 (14.0%)
LLT, pharmacy dispensations recorded	8 (12.1)	8 (50.0%)	40 (80.0%)
LDL-C, mmol/L	2.78 (0.78)	2.0 (0.94)	1.93 (0.86)
LDL-C reduction, mmol/L	0.13 (0.69)	1.23 (0.79)	1.07 (1.19)

Values are presented as n (%) or mean (SD).
LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

Table 4
Utilization of lipid-lowering therapy and lipid management by risk group established using national guidelines (CCS 2021) and presence of significant subclinical atherosclerosis (SSAS).

	Low or moderate clinical risk		High clinical risk	
	SSAS (-), *N* = 67	SSAS (+), *N* = 15	SSAS (-), *N* = 20	SSAS (+), *N* = 30
LLT, physicians' recommendations				
Initiation	9 (13.4%)	10 (66.7%)	12 (60.0%)	12 (40.0%)
Intensification	0	1 (6.7%)	5 (25.0%)	14 (46.7%)
Continuation	1 (1.5%)	1 (6.7%)	3 (15.0%)	4 (13.3%)
LLT, pharmacy dispensations recorded	7 (10.4%)	9 (60.0%)	12 (60.0%)	28 (93.3%)
LDL-C at enrolment, mmol/L	2.99 (0.75)	2.90 (0.68)	2.95 (0.99)	2.98 (1.26)
LDL-C at follow-up, mmol/L	2.83 (0.76)	1.79 (0.78)	2.01 (1.06)	1.86 (0.73)
LDL-C reduction, mmol/L	0.15 (0.09)	1.1 (0.27)	0.94 (0.30)	1.10 (0.26)

Values are presented as n (%) or mean (SD).
SSAS, significant subclinical atherosclerosis defined as CAC > 100, plaque on CUS, or obstructive or extensive non-obstructive coronary atherosclerosis on CCTA; LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein cholesterol.

Canadian Cardiovascular Society recommends this approach, other tools are also widely used in clinical practice. Practitioners' preferences introduce subjectivity to initial risk assessment and interpretation of imaging results, making evaluation of the actual trends in treatment in relation to clinically and radiologically identifiable risk difficult and limiting generalization of our findings to real-life practice.

5. Limitations

Our study has several important limitations. Our method of data collection required physician assessment and imaging of each patient, thereby limiting sample size and preventing participation of FDRs residing in other provinces of Canada or other countries. All imaging tests were performed at local hospital-based radiology departments and reported using standardized provincial criteria. While this allowed us to assess the feasibility and potential yield of a screening program designed to be executed in the community, it did not allow us to assess more precise characteristics of atherosclerosis or to assess intra- and inter-observer variability of these investigations. In particular, centres performing CUS do not always measure and report carotid intima-media thickness if protuberant plaque is detected. This led to variability in the information available in the CUS study reports. To harmonize information for all participants who underwent the study, we used only the presence of plaque, limiting our ability to assess other manifestations of subclinical atherosclerosis in these patients. In addition, the majority of participants underwent only one imaging test. Also, as the prevalence of several cardiovascular risk factors was higher in the FDR population than in the general Canadian population, the study's findings represent those in a high-risk population based on family history and cannot be generalized to the whole population. Finally, there is a potential healthy user bias present in those FDRs who agreed to screening, as these individuals may have been more pro-active about health promotion in general compared to FDRs that declined to participate. This implies that the clinical risk and burden of subclinical atherosclerosis may be even greater among FDRs who did not participate in screening.

6. Conclusions

A screening program incorporating clinical and radiological testing of FDRs of patients with premature CAD is feasible. Based on the high diagnostic yield and significant impact on risk factor management observed in our study, family-based screening of FDRs of patients with premature CAD may be a promising strategy for the earlier identification of patients at risk to reduce the burden of premature CAD.

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CRediT authorship contribution statement

Diana N. Vikulova: Writing – review & editing, Writing – original draft, Visualization, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Danielle Pinheiro-Muller:** Writing – review & editing, Resources, Project administration, Data curation. **Gordon Francis:** Writing – review & editing, Supervision, Conceptualization. **Frank Halperin:** Writing – review & editing, Supervision, Data

curation. **Tara Sedlak:** Writing – review & editing, Supervision. **Keith Walley:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Christopher Fordyce:** Writing – review & editing, Supervision, Methodology. **GB John Mancini:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization. **Simon N. Pimstone:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Data curation, Conceptualization. **Liam R. Brunham:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Liam Brunham reports financial support was provided by Canadian Institutes of Health Research. Liam Brunham reports financial support was provided by Genome British Columbia. Liam Brunham reports a relationship with Amgen Canada Inc that includes: board membership. Liam Brunham reports a relationship with Ultragenyx Pharmaceutical Inc that includes: board membership. Liam Brunham reports a relationship with Novartis that includes: board membership. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100704.

References

[1] WHO Fact Sheets. Cardiovascular diseases. 2021. Available from, https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed on 16.03.2023.

[2] Leifheit-Limson EC, Spertus JA, Reid KJ, et al. Prevalence of traditional cardiac risk factors and secondary prevention among patients hospitalized for acute myocardial infarction (AMI): variation by age, sex, and race. J Women's Heal 2013;22(8):659–66.

[3] Singh A, Collins BL, Gupta A, et al. Cardiovascular risk and statin eligibility of young adults after an MI: partners YOUNG-MI registry. J Am Coll Cardiol 2018;71(3):292–302.

[4] Vikulova DN, Skorniakov IS, Bitoiu B, et al. Lipid-lowering therapy for primary prevention of premature atherosclerotic coronary artery disease: eligibility, utilization, target achievement, and predictors of initiation. Am J Prev Cardiol 2020;2:100036.

[5] Leifheit-Limson EC, D'Onofrio G, Daneshvar M, et al. Sex differences in cardiac risk factors, perceived risk, and health care provider discussion of risk and risk modification among young patients with acute myocardial infarction: the VIRGO study. J Am Coll Cardiol 2015;66(18):1949–57.

[6] Tsao C, Aday A, Almarzooq Z, et al. Heart Disease and stroke statistics—2022 update: a report from the american heart association', circulation. Am Heart Assoc, 2022;145(8):e153–639. https://doi.org/10.1161/CIR.0000000000001052.

[7] Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the national cholesterol education panel iii guidelines perform? J Am Coll Cardiol 2003;41(9):1475–9.

[8] Sesso HD, Lee IM, Gaziano JM, Rexrode KM, Glynn RJ, Buring JE. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. Circulation 2001;104:393–8.

[9] Marenberg ME, Risch N, Berkman LF, Floderus B, de Faire U. Genetic susceptibility to death from coronary heart disease in a study of twins. N Engl J Med 1994;330:1041–6. Clinical Utility of Using Genomic Data to Assess Cardiovascular Risk and Guide Lipid-lowering Therapy in Patients with High Risk of Premature Cardiovascular Disease Data Access, Integration and Analysis Program, Application form, June 28, 2022 – FINAL 22.

[10] Zdravkovic S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, De Faire U. Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins. J Intern Med 2002;252:247–54.

[11] Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2021. https://doi.org/10.1016/j.cjca.2021.03.016. April.

[12] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;139(25):e1082–143. https://doi.org/10.1161/CIR.0000000000000625.

[13] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J 2019. https://doi.org/10.1093/eurheartj/ehz455. August.

[14] De Backer G, Ambrosioni E, Borch-Johnsen K, et al. european guidelines on cardiovascular disease prevention in clinical practice. Third joint task force of European and other societies on cardiovascular disease prevention in clinical practice. Eur Heart J 2003;24:1601–10.

[15] Hengstenberg C, Holmer SR, Mayer B, et al. Siblings of myocardial infarction patients are overlooked in primary prevention of cardiovascular disease. Eur Heart J 2001;22:926–33.

[16] Swanson JR, Pearson TA. Screening family members at high risk for coronary disease. Why isn't it done? Am J Prev Med 2001;20:50–5.

[17] De Sutter J, De Bacquer D, Kotseva K, Sans S, Pyorala K, Wood D, et al. Screening of family members of patients with premature coronary heart disease; results from the EUROASPIRE II family survey. Eur Heart J 2003;24:249–57.

[18] Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). Eur Heart J 2018;39:2401–8.

[19] Nasir K, Cainzos-Achirica M. Role of coronary artery calcium score in the primary prevention of cardiovascular disease. BMJ 2021;373:n776.

[20] Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, Garcia MJ, Gregson J, Pocock S, Falk E, Fuster V. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. J Am Coll Cardiol 2015;65:1065"1074.

[21] Sillesen H, Sartori S, Sandholt B, Baber U, Mehran R, Fuster V. Carotid plaque thickness and carotid plaque burden predict future cardiovascular events in asymptomatic adult Americans. Eur Heart J Cardiovasc Imaging 2018;19:1042"1050.

[22] Mehta A, Rigdon J, Tattersall MC, et al. Association of carotid artery plaque with cardiovascular events and incident coronary artery calcium in individuals with absent coronary calcification. Circ Cardiovasc Imag 2021;14(4):e011701.

[23] Cho I, Al'Aref SJ, Berger A, et al. Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international confirm study. Eur Heart J 2018;39(11):934–41. https://doi.org/10.1093/eurheartj/ehx774.

[24] Christopher N, BD S, Amir A, et al. predictive value of age- and sex-specific nomograms of global plaque burden on coronary computed tomography angiography for major cardiac events. Circ Cardiovasc Imag 2017;10(3):e004896. https://doi.org/10.1161/CIRCIMAGING.116.004896.

[25] van Rosendael AR, Bax AM, Smit JM, et al. Clinical risk factors and atherosclerotic plaque extent to define risk for major events in patients without obstructive coronary artery disease: the long-term coronary computed tomography angiography CONFIRM registry. Eur Hear J - Cardiovasc Imaging 2020;21(5):479–88. https://doi.org/10.1093/ehjci/jez322.

[26] Khurram N, Miguel C-A, Javier V-E, et al. Coronary atherosclerosis in an asymptomatic U.S. population. JACC Cardiovasc Imaging. 2022;15(9):1604–18. https://doi.org/10.1016/j.jcmg.2022.03.010.

[27] Östgren CJ, Söderberg S, Festin K, et al. Systematic Coronary Risk Evaluation estimated risk and prevalent subclinical atherosclerosis in coronary and carotid arteries: a population-based cohort analysis from the Swedish Cardiopulmonary Bioimage Study. Eur J Prev Cardiol 2021;28(3):250–9. https://doi.org/10.1177/2047487320909300.

[28] Fuchs A, Kühl JT, Sigvardsen PE, et al. Subclinical coronary atherosclerosis and risk for myocardial infarction in a danish cohort. Ann Intern Med 2023;176(4):433–42. https://doi.org/10.7326/M22-3027.

[29] Mulders TA, Taraboanta C, Franken LC, et al. Coronary artery calcification score as tool for risk assessment among families with premature coronary artery disease. Atherosclerosis 2016;245:155–60. https://doi.org/10.1016/j.atherosclerosis.2015.12.008.

[30] Brunham LR, Lynch K, English A, et al. The design and rationale of save bc: the Study to Avoid CardioVascular Events in British Columbia. Clin Cardiol 2018;41(7):888–95. https://doi.org/10.1002/clc.22959.

[31] About PharmaNet. 2024. Available from: https://www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents/pharmanet Accessed September 28, 2023.

[32] Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the society of cardiovascular computed tomography guidelines commit- tee. J Cardiovasc Comput Tomogr 2014;8:342–58.

[33] Johri AM, Nambi V, Naqvi TZ, et al. Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk: from the American society of echocardiography. J Am Soc Echocardiogr 2020;33(8):917–33. https://doi.org/10.1016/j.echo.2020.04.021.].

[34] Society for Vascular Ultrasound. Professional Performance Guidelines. 2019. Available from: https://www.svu.org/practice-resources/professional-performance-guidelines/ Accessed September 28, 2023.

[35] Hecht HS, Blaha MJ, Kazerooni EA, et al. CAC-DRS: coronary artery calcium data and reporting system. an expert consensus document of the society of cardiovascular computed tomography (SCCT). J Cardiovasc Comput Tomogr 2018;12(3):185–91. https://doi.org/10.1016/j.jcct.2018.03.008.

[36] McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age. Circulation 2006;113(1):30–7. https://doi.org/10.1161/CIRCULATIONAHA.105.580696.
[37] McClelland RL, Jorgensen NW, Budoff M, et al. 10-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (multi-ethnic study of atherosclerosis) with validation in the HNR (heinz nixdorf recall) study and the DHS (dallas heart study). J Am Coll Cardiol 2015;66(15):1643–53. https://doi.org/10.1016/j.jacc.2015.08.035.
[38] Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–81.
[39] Tota-Maharaj R, Blaha MJ, Blankstein R, et al. Association of coronary artery calcium and coronary heart disease events in young and elderly participants in the multi-ethnic study of atherosclerosis: a secondary analysis of a prospective, population-based Cohort. Mayo Clin Proc 2014;89(10):1350–9. https://doi.org/10.1016/j.mayocp.2014.05.017.
[40] Dudum R, Dzaye O, Mirbolouk M, et al. Coronary artery calcium scoring in low risk patients with family history of coronary heart disease: validation of the SCCT guideline approach in the coronary artery calcium consortium. J Cardiovasc Comput Tomogr 2019;13:21–5.
[41] Kotseva K, De Bacquer D, De Backer G, et al. Lifestyle and risk factor management in people at high risk of cardiovascular disease. A report from the European society of cardiology European action on secondary and primary prevention by intervention to reduce events (EUROASPIRE) IV cross-sectional su. Eur J Prev Cardiol 2016;23:2007–18.
[42] Homer K, Boomla K, Hull S, et al. Statin prescribing for primary prevention of cardiovascular disease: a cross-sectional, observational study. Br J Gen Pract 2015;65:e538–44.
[43] Halcox JP, Banegas JR, Roy C, et al. Prevalence and treatment of atherogenic dyslipidemia in the primary prevention of cardiovascular disease in Europe: EURIKA, a cross-sectional observational study. BMC Cardiovasc Disord 2017;17:160.
[44] Saeed A, Zhu J, Thoma F, et al. Cardiovascular disease risk-based statin utilization and associated outcomes in a primary prevention cohort: insights from a large health care network. Circ Cardiovasc Qual Outcomes 2021;14:e007485.
[45] Cheezum MK, Hulten EA, Smith RM, et al. Changes in preventive medical therapies and CV risk factors after CT angiography. JACC Cardiovasc Imaging 2013;6:574–81.
[46] McEvoy JW, Blaha MJ, Nasir K, et al. Impact of coronary computed tomographic angiography results on patient and physician behavior in a low-risk population. Arch Intern Med 2011;171:1260–8.
[47] LaBounty TM, Devereux RB, Lin FY, et al. Impact of coronary computed tomographic angiography findings on the medical treatment and control of coronary artery disease and its risk factors. Am J Cardiol 2009;104:873–7.
[48] Orakzai RH, Nasir K, Orakzai SH, et al. Effect of patient visualization of coronary calcium by electron beam computed tomography on changes in beneficial lifestyle behaviors. Am J Cardiol 2008;101:999–1002.
[49] Mortensen MB, Caínzos-Achirica M, Steffensen FH, Bøtker HE, Jensen JM, Sand NPR, et al. Association of coronary plaque with low-density lipoprotein cholesterol levels and rates of cardiovascular disease events among symptomatic adults. JAMA Netw Open 2022;5(2):e2148139. –e2148139.