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Original Research

Lipid-lowering therapy for primary prevention of premature atherosclerotic coronary artery disease: Eligibility, utilization, target achievement, and predictors of initiation

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ABSTRACT

Objectives: Despite advances in screening and prevention, rates of premature coronary artery disease (CAD) have been stagnant. The goals of this study were to investigate the barriers to early risk detection and preventive treatment in patients with premature CAD. In particular, we: 1) assessed the performance of the latest versions of major international guidelines in detection of risk of premature CAD and eligibility for preventive treatment; and, 2) investigated real-life utilization of primary prevention with lipid-lowering therapies in these patients.

Methods: We included patients in the Study to Avoid cardioVascular Events in British Columbia (SAVE BC), an observational study of patients with premature (males $\leq$ 50 years, females $\leq$ 55 years) angiographically confirmed CAD. Eligibility for primary prevention and treatment received were assessed retrospectively based on information recorded prior to or at the index presentation with CAD.

Results: Of 417 patients (28.1% females) who met the criteria, 94.3% had at least one major cardiovascular risk factor. In the retrospective risk assessment, 41.7%, 61.4%, and 34.3% ($p < 0.001$) of patients met criteria for initiation of statin therapy, and an additional 13.9%, 8.4%, and 46.8% may be considered for treatment using the American College of Cardiology/American Heart Association, Canadian Cardiovascular Society, and European Society of Cardiology guidelines, respectively. Only 17.1% of patients received statins and 11.0% achieved guideline-recommended lipid goals before presentation. Diabetes and elevated plasma lipid levels were positively associated with treatment initiation, while smoking was associated with non-treatment.

Conclusions: The current versions of major guidelines fail to recognize many patients who develop premature CAD as being at risk. The vast majority of these patients, including patients who have guideline-directed indications, do not receive lipid-lowering therapy before presenting with CAD. Our findings highlight the need for more effective screening and prevention strategies for premature CAD.

1. Introduction

The overall incidence of coronary artery disease (CAD) has decreased in many countries over the past two decades due to improvements in screening and treatment [1–3]. However, rates of premature CAD events have remained stagnant [4–6]. Additionally, the prevalence of important cardiovascular risk factors (CVRFs) such as diabetes, hypertension, and obesity are increasing among younger age groups in many populations [1,6–8]. One of the major challenges in the primary prevention of premature CAD is to identify individuals at risk who will derive the greatest

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benefit from lipid-lowering therapy. Previous studies have shown limited performance of major guidelines on cardiovascular risk assessment and primary prevention in recognizing younger patients at high risk [9–11]. Since that time, risk assessment guidelines have been updated, including the addition of new risk factors and enhancers, such as family history, high-risk ethnicity groups, new blood biomarkers, and new thresholds for plasma lipids, in an effort to improve the identification of patients at risk and expand the population eligible for preventive therapies [12–14]. However, the estimation of 10-year cardiovascular risk is still the first step in risk assessment and the main guide for treatment decisions. How well contemporary guidelines work relative to each other and what factors can drive potential differences in performance in this challenging population of younger patients has not been assessed.

Young people are often unaware of their underlying CVRFs, do not perceive themselves as being at high cardiovascular risk, and do not discuss risk modification and prevention strategies with their healthcare providers [1,7,15]. In previous studies describing lipid-lowering prescription patterns in primary care, younger age and absence of established cardiovascular disease were associated with a lower likelihood of receiving statins [16–19]. Younger age was also linked to lower rates of participation in population-based prevention programs [20]. However, what factors are associated with use of statins for primary prevention of CAD in young adults at high cardiovascular risk is unknown.

This study's objectives were to investigate barriers to early risk detection and preventive treatment in patients with premature CAD. In particular: 1) to assess and compare performance of the latest versions of major international guidelines in the detection of elevated cardiovascular risk and eligibility for preventive treatment in patients developing very premature CAD; 2) to investigate real-life utilization of primary prevention with lipid-lowering therapies in these patients by assessing treatment administration and achievement of treatment targets; 3) to explore factors associated with the initiation of preventive treatment.

2. Methods

We assessed patients in the Study to Avoid CardioVascular Events in British Columbia (SAVE BC) [21], an ongoing longitudinal study of patients with premature CAD. We included patients with a first presentation of CAD (referred to hereafter as the index event) at the age of $\leq$50 years old in males and $\leq$55 years old in females. CAD was defined as angiographically-confirmed CAD with stenosis of $\geq$50% in at least one coronary artery in patients presenting with the first STEMI, NSTEMI, unstable or stable angina, or referred electively for angiography.

Clinical data including demographics, cardiovascular risk factors and comorbidities, characteristics of the index event, biochemistry profiles, and information about primary preventive treatment for the period up to 5 years prior to the first presentation (baseline period) were obtained through detailed review of electronic medical records, cardiac catheterization laboratory reports, and collected on study visits by physicians and study coordinators. Detailed information about family history was obtained from medical records and patients' pedigrees generated by study coordinators or genetic councillors based on patients' questionnaires.

Dyslipidemia was defined as total cholesterol $\geq$240 mg/dL (6.2 mmol/L), low-density lipoprotein cholesterol (LDL-C) $\geq$ 160 mg/dL4 (4.1 mmol/L), high-density lipoprotein cholesterol (HDL-C) $\leq$ 40 mg/dL (1.0 mmol/L), serum triglycerides (TG) $\geq$ 200 mg/dL (2.3 mmol/L) [22], or treatment of dyslipidemia. For patients who received statins prior to the index event and did not have pre-treatment data available, lipid values were adjusted according to the medication and dose using the method described by Ellis et al. [23]. Hypertension was defined as systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, physician diagnosis, or treatment of hypertension. Diabetes was defined as fasting plasma glucose $\geq$126 mg/dL (7 mmol/L) in at least 2 baseline measurements, hemoglobin A1c $\geq$ 6.5%, physician diagnosis, or treatment of diabetes [24]. Obesity was defined as a body mass index (BMI) $\geq$30 kg/m^2 and was calculated based on measurements obtained at the time of the index event. Smoking was defined as current if present at the time of the index event. Family history of premature cardiovascular disease (CVD) was defined as fatal or non-fatal MI, coronary revascularization, fatal or non-fatal stroke in one or more male first-degree relatives $<$ 55 years old or female first-degree relatives $<$ 65 years old. Dietary patterns and physical activity before index event were assessed from patients' questionnaires. We evaluated proportions of patients who reported regular daily consumption of fruits or vegetables and regular consumption of potentially unhealthy food, defined as at least one of following: 1) daily consumption of salty or fried food; 2) consumption of meat or poultry 2 or more times per day. Physical activity was assessed based on regular performance of moderate (walking, bicycle riding, light gardening) or strenuous exercises (running/jogging, football, vigorous swimming) for 4 h or more per week, as previously defined by Yusuf et al. in the INTERHEART study [25]. Information was self-reported and collected retrospectively.

For each participant, we used American Heart Association Guidelines on the Management of Blood Cholesterol 2018 (ACC/AHA), Canadian Cardiovascular Society Dyslipidemia Guidelines 2016 (CCS), and European Guidelines on Cardiovascular Disease Prevention in Clinical Practice 2019 (ESC/ESC) using the Pooled Cohort Equation (PCE), modified Framingham Risk Score (mFRS), and Systematic Coronary Risk Evaluation (SCORE, low-risk version) equations, respectively, to retrospectively assess cardiovascular risk and eligibility for lipid-lowering therapy. For individuals younger than 40 years at the presentation, the age of 40 was used for assessment with PCE. The specific eligibility criteria for primary prevention according to the three guidelines and definitions of statin-indicated conditions are summarized in Online Table 1. If available, the first baseline laboratory values and blood pressure values were used for risk assessment. For individuals who did not have values estimated in 5 years prior to presentation with CAD, data obtained at the time of index event were used.

The analysis was performed using IBM SPSS Statistics for Macintosh, Version 25.0. Categorical variables were summarized as frequencies and proportions and compared with 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 Student's test or Wilcoxon rank-sum test, as appropriate.

To assesses interobserver variation in retrospective risk assessment, 25% of randomly chosen patients were re-assessed by a blinded independent physician, then Cohen's kappa statistic (κ) was calculated for each of guidelines-based algorithm. We observed excellent interobserver agreement with $\kappa = 0.86$ ($p < 0.0001$), $\kappa = 0.90$ ($p < 0.0001$), and $\kappa = 0.91$ ($p < 0.0001$) for ACC/AHA, CCS, and ESC/EAS, respectively.

Factors associated with primary preventive treatment received by patients were assessed using multivariable logistic regression. Selection of the predictors was conducted utilizing the forward stepwise regression method. The following covariates were considered for selection: age at index event, BMI, cardiac conditions other than CAD (includes valvular heart disease with/without arrhythmia, non-valvular arrhythmias, non-valvular congenital structural defects), chronic immune-mediated inflammatory disorders, chronic obstructive pulmonary disease or asthma, chronic kidney disease, diabetes, family history of premature CVD, history of malignancy, human immunodeficiency virus infection, hypertension, hypothyroidism, inflammatory bowels disease, liver diseases, LDL-C, major psychiatric disorders and/or depression and/or anxiety, non-inflammatory gastro-intestinal diseases, smoking at index event, sex, TG. Predictors with p-value $\leq$ 0.1 were considered statistically significant and retained in the final model. The final model also included sex and family history of premature CVD regardless of their statistical significance because of its clinical significance in the context of primary prevention.

The study was approved by the University of British Columbia Research Ethics Board, certificate number H17-01110-A017. All participants provided written informed consent.

3. Results

The study included 417 patients (117 (28.1%) females) who met the inclusion criteria. The median age at first presentation with CAD was 50.7 (47.2–53.1) years for females and 45.9 (42.4–48.5) years for males. Demographics and characteristics of patients at index presentation are shown in Table 1.

In total, 385 (94.3%) patients had at least one of six major CVRFs: dyslipidemia (68.6%, including 14.1% of patients with LDL-C ≥ 5 mmol/L), hypertension (47.0%), family history of premature CVD (40.8%), obesity (40.6%), current smoking (26.9%), or diabetes (26.9%). The prevalence of CVRFs and baseline laboratory values summarized by sex are presented in Table 2. In total, 112 patients had diabetes at first presentation with CAD, including 27 (24.1%) who were not aware of the diagnosis. Additionally, 89 (21.3%) patients had impaired fasting glucose or prediabetes, and 12 (3.9%) patients developed diabetes within the subsequent two years. Multiple CVRFs were found in 315 (75.5%) patients, with 26.9% having two, 25.2% having three, 23.5% having four or more CVRFs. A summary of the cumulative burden of CVRFs is presented in Online Table 2.

In addition to the major CVRFs, 78.8% of patients reported regular consumption of potentially unhealthy food. Conversely, 54.0% of patients had high levels of physical activity and 52.0% reported daily consumption of fruits and vegetables. Rates of other risk enhancers and comorbidities present at baseline are summarized in Online Table 3. Of note, 20.4% of participants had physician-diagnosed or treated depression or anxiety. More than 18% of females in the study had a history of gestational diabetes.

We assessed eligibility for statin therapy in these 417 patients at or prior to their presentation with CAD using major international guidelines. We found that 174 (41.7%) qualified for therapy according to ACC/AHA guidelines, 256 (61.4%) according to CCS guidelines, and 143 (34.3%) according to ESC/EAS guidelines (Fig. 1A). An additional 58 (13.9%), 35 (8.4%), could be considered for treatment under ACC/AHA and CCS guidelines, respectively, after additional investigations such as coronary artery calcium scoring, and 195 (46.8%) patients would be considered for treatment by ESC guidelines if initial lifestyle modification would be unsuccessful.

Table 1
Demographics and characteristics of first presentation with coronary artery disease.

	Female (N = 117)	Male (N = 300)	p
Age at first presentation with CAD	50.7 (47.2–53.1)	45.9 (42.4–48.5)	
Ethnicity			0.032
European	42 (35.9%)	102 (34.0%)	
Asian	25 (21.4%)	101 (30.3%)	
Others	50 (42.7%)	97 (29.1%)	
Diagnosis at presentation			0.107
STEMI	22 (18.8%)	63 (21%)	
NSTEMI	36 (30.8%)	121 (40.3%)	
Unstable angina	16 (13.7%)	20 (6.7%)	
Stable angina	31 (26.5%)	74 (24.7%)	
Atypical angina	3 (2.6%)	3 (1%)	
Other	9 (7.7%)	19 (6.3%)	
LVEF ≤50%[a]	21 (17.9%)	61 (22.1%)	0.495
N of vessels with stenosis ≥50%			0.001
1	67 (57.3%)	110 (37.3%)	
2	29 (24.8%)	99 (33.6%)	
3	21 (17.9%)	86 (29.2%)	
Revascularization			0.067
PCI	71 (60.7%)	185 (61.7%)	
CABG	16 (13.7%)	63 (21.0%)	
No revascularization	30 (25.6%)	52 (17.3%)	

Values are presented as median (interquartile range), mean (SD) or n (%).
CABG, coronary artery bypass grafting; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; NSTEMI, non- ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
[a] 27 missing.

Table 2
Cardiovascular risk factors and baseline[a] laboratory values.

	Female (N = 117)	Male (N = 300)	p
Hypertension	59 (50.4%)	137 (45.7%)	0.382
Dyslipidemia	67 (57.3%)	219 (73.0%)	0.003
Diabetes	35 (29.9%)	77 (25.7%)	0.449
Obesity	47 (40.2%)	122 (40.8%)	0.994
Current smoking	38 (32.5%)	74 (24.7%)	0.135
Family history of premature CVD	58 (49.6%)	112 (37.3%)	0.03
Moderate/high physical activity[b]	33 (41.3)	128 (58.7%)	0.011
Daily consumptions of fruit/vegetables[b]	48 (59.3%)	105 (49.3)	0.162
Unfavourable dietary patterns[b, c]	53 (66.3%)	174 (83.7%)	0.002
Total cholesterol, mg/dL	232 (58)	240 (66)	0.3
Non-HDL cholesterol, mg/dL	191 (62)	194 (62)	0.7
LDL cholesterol, mg/dL	143 (50)	147 (50)	0.4
HDL cholesterol, mg/dL	43 (16)	38 (12)	0.7
Triglycerides, mg/dL	196 (142–310)	230 (151–328)	0.5
Lipoprotein (a), mg/L[d]	235 (99–800)	195 (99–700)	0.9
Fasting glucose, mg/dL	106 (95–148)	106 (97–133)	0.3
Hemoglobin A1C, %	5.95 (5.5–7.5)	5.9 (5.5–6.9)	0.1
eGFR, ml/min/1.73 m[d]	84 (24)	85 (23)	0.8
hs-CRP, mg/L[e]	2.3 (1–4.9)	1.3 (0.5–3.6)	0.9

Values are presented as median (interquartile range), mean (SD) or n (%).
CRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a] The period up to 5 years prior to the first presentation.
[b] 119 missing.
[c] Defined as daily consumption of salty and/or fried food or snacks and/or consumption of meat or poultry 2 or more times per day.
[d] 140 missing.
[e] 114 missing.

In 155 (37.2%) patients, statin-indicated conditions were present: 43 (10.3%) patients had an LDL-C ≥ 190 mg/dL (5.0 mmol/L), 96 (23.0%) patients had diabetes meeting criteria for statin indication (Online Table 1), and 16 (3.9%) patients had both. After excluding patients with diabetes, we observed fewer patients eligible for treatment under all guidelines: 21.6% (11.0% in females vs 25.6% in males, p = 0.016) for ACC/AHA, 48.5% (41.5% in females vs 51.1% in males, p = 0.3) for CCS, and 11.8% (6.1% in females vs 13.9% in males, p = 0.09) for ESC/EAS guidelines (Fig. 1B). Cardiovascular risk scores and treatment recommendations for patients without diabetes are summarized in Online Table 4. We observed mean (SD) PCE scores of 4.4 (4.2) points (3.0 (1.9) in females vs 4.9 (4.7) in males, p = 0.001). Mean (SD) 10-year CVD risk calculated by mFRS was 13.1% (8.2) (11.1% (6.5) in females vs 13.9% (8.7) in males, p = 0.003). FRS scores calculated without modification for family history are provided in Online Table 4. When applying the SCORE criteria, 38.4% of patients had scores less than one point (low-risk category) and 61.6% had scores between one and five (medium-risk category).

In total, 53 (12.7%) patients were not eligible for treatment by any of the guidelines. These patients were less likely to have CVRFs and had lower cumulative burdens of risk factors (Online Table 5, Online Fig. 1). These patients had low calculated risk score, with mean (SD) mFRS of 5.7 (2.4), mean (SD) PCE of 1.9 (1.3), and 73.6% had SCORE <1. However, they presented with CAD at a younger age (44.6 (41.5–48.6) vs 47.2 (43.9–49.9), p = 0.015) and were not significantly different from the rest of the patients in clinical presentation and severity of stenosis.

In total, 272 (65.2%) of patients had lipid profiles performed within 5 years prior to the index event. Only 71 (17.1%) patients received lipid-lowering therapy in this period compared to the 174 (41.7%) patients who qualified under the ACC/AHA guidelines (Table 3). More than half of treated patients received moderate- or low-intensity statins, and in 14 (19.7%) of them therapy was initiated but subsequently discontinued at

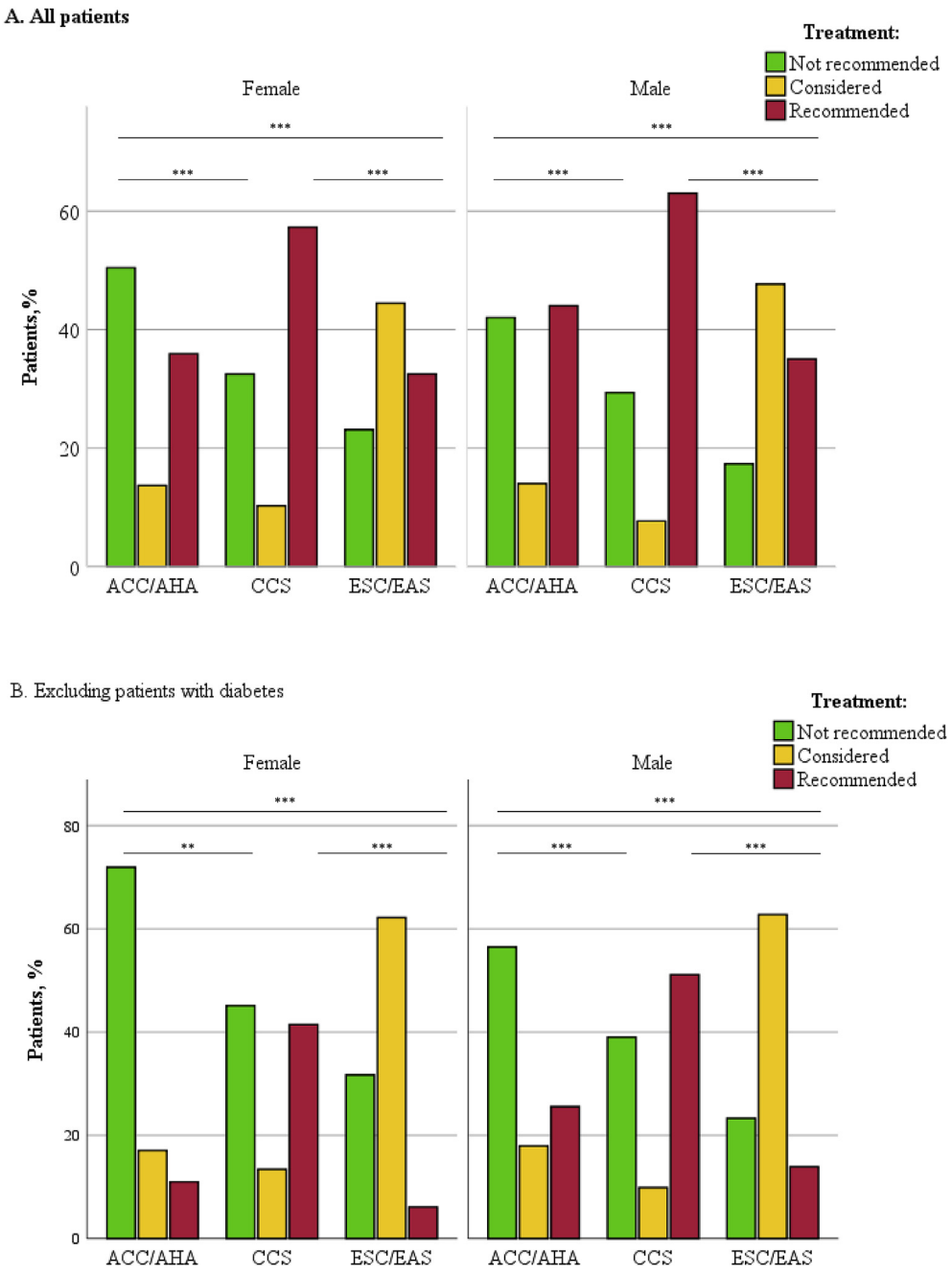

Fig. 1. Statin eligibility by sex for all patients (A) and for patients without diabetes (B). The proportions of all patients (N = 417, Panel A) and patients without diabetes (N = 305, Panel B) who were eligible, considered, or not eligible for primary prevention treatment with lipid-lowering medications according to ACC/AHA, CCS, and ESC/EAS guidelines are shown, stratified by sex.
ACC/AHA, American Heart Association Guidelines on the Management of Blood Cholesterol 2018; CCS, Canadian Cardiovascular Society Dyslipidemia Guidelines 2016; ESC/ESC, European Guidelines on Cardiovascular Disease Prevention in Clinical Practice 2019.

least 6 months prior to the index event. Only 11.0% of all patients reached the target LDL-C of ≤77 mg/dL (2 mmol/L) or non-HDL of ≤100 mg/dL (2.6 mmol/L), as recommended by the CCS guidelines. Importantly, only 31.3% of patients with diabetes and 28.8% of patients with LDL-C ≥ 190 mg/dL (5.0 mmol/L) received lipid-lowering therapy before presenting with CAD, and only 14.3% and 3.4% of them reached lipid targets, respectively.

We next examined what patient characteristics predicted the use of lipid-lowering medications in patients who were found to be eligible or considered eligible by at least one guideline. In multivariate analysis, diabetes, plasma levels of LDL-C and triglycerides were significantly associated with treatment, whereas smoking was inversely associated with treatment (Fig. 2). Sex and family history of premature CVD were not independently associated with treatment in this cohort but included in the model due to their clinical significance in the context of primary prevention. The other CVRFs and comorbidities were assessed but did not display significant association.

4. Discussion

We assessed the performance of the current ACC/AHA, CCS, and ESC/EAS guidelines in detection of elevated cardiovascular risk and eligibility for preventive treatment and investigated real-life utilization of primary prevention therapy in a population of patients with angiography confirmed premature CAD. The major findings of this study are: 1) that even the most updated version of these guidelines using risk enhancers fail to recognize ~40% of patients who develop premature CAD; 2) that statin therapy is vastly underutilized among individuals with a guideline recommended indication for statins for primary prevention; and 3) that diabetes and hypercholesterolemia are the factors most strongly associated with statin therapy in this population, while other important cardiovascular risk factors, such as hypertension, obesity, smoking, and family

Table 3
Characteristics of primary preventive treatment with lipid-lowering therapy in patients with premature cardiovascular disease.

Parameter	N(%)
Lipid profiles assessed <5 years before presentation with CAD	272 (65.2%)
Lipid-lowering treatment received	
All patients (N=417)	71 (17.1%)
Patients with diabetes (N=112)	35 (31.3%)
Patients with LDL cholesterol ≥ 190 mg/dL *(N=59)*	17 (28.8%)
Therapy continued until first presentation with CAD	57 (13.7%)
High intensity	21 (5.1)
Moderate intensity	29 (7.0%)
Low intensity	7 (1.7%)
Discontinued[a]	14 (3.4%)
Target of LDL-C of ≤77 mg/dL or non-HDL of ≤100 mg/dL reached[b]	
All patients	46 (11.0%)
Patients with diabetes (N=112)	16 (14.3%)
Patients with LDL cholesterol ≥ 190 mg/dL *(N=59)*	2 (3.4%)
All treated patients (N=71)	15 (21.1%)

Values are presented as n (%).
CAD, coronary artery disease; CVD, cardiovascular disease; LDL, low-density lipoprotein.
[a] Treatment discontinued 6 months prior to the first presentation with cardiovascular disease or earlier.
[b] As recommended by the current national guidelines.

history, are not associated or negatively associated with treatment. These findings point to major gaps in both our ability to identify young adults who go on to develop CAD as being at risk, and in the implementation of guideline recommended treatments in this population.

One interesting finding from our study is the variable performance of the major guidelines for identifying risk in young adults who develop CAD. We found that the CCS guidelines identified the highest percentage of patients (61.4%) as eligible for primary prevention. One of the possible reasons for this difference across guidelines is that the CCS guidelines utilize the mFRS for risk assessment, which doubles the calculated 10-year risk for patients with a family history of premature CVD that was frequently reported by patients in this cohort. In support of this hypothesis, we note that using the traditional FRS instead of mFRS would have identified 66 (15.8%) fewer patients as 'eligible' and 19 (4.5%) fewer patients as 'considered' for preventive treatment.

The ACC/AHA guidelines identified 56.0% of all patients and 39.3% of patients without diabetes as eligible or considered for treatment, with a significantly lower percentage of females. Previously, Singh et al. [9] assessed statin eligibility of young patients who experienced myocardial infarction using the previous edition of the ACC/AHA guidelines and found that 34.7% of females and 51.1% of males met criteria for eligibility/consideration for statins. Since then, the new edition of the guidelines [13] were introduced which includes the addition of new risk enhancing factors and increases the proportion of patients in the intermediate-risk group who may qualify for pharmacotherapy. In our study, we applied the new version of ACC/AHA guidelines and identified 49.6% of females and 58.0% of males as eligible/considered for statins. Our data suggest that the guidelines continue to fail to identify many young adults who go on to develop premature CAD as being at increased risk and eligible for primary prevention, highlighting the need to improve risk prediction in this group.

The ESC/EAS guidelines identified the lowest percentage of patients for whom statin therapy was indicated (34.3%), but the highest percentage of patients in whom statin therapy could be 'considered' (46.8%), after unsuccessful implementation of lifestyle interventions, increasing the overall number of patients potentially eligible for treatment to 81.1%. However, all patients in whom statin therapy would be 'considered' had SCORE values lower than five points, corresponding to low or medium risk categories. In these categories, statin therapy is 'considered' if the LDL-C level is higher than 100 mg/dL (2.6 mmol/L) for the intermediate-risk category or 116 mg/dL (3 mmol/L) for the low-risk category. As these LDL-C levels approximate the 40%–50% percentiles in the contemporary general Canadian population of adults under 59 years

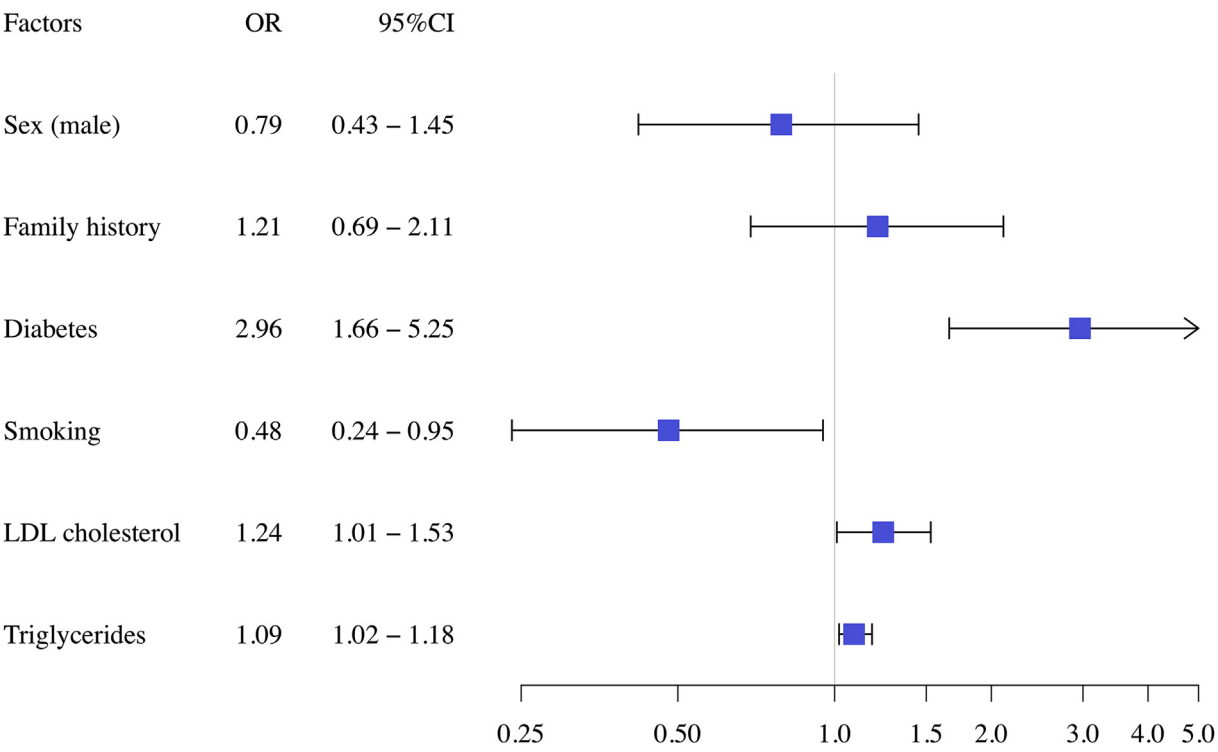

Fig. 2. Factors associated with initiation of primary prevention. Factors associated with receiving primary preventive treatment based on multivariate logistic regression analysis in patients found to be eligible or considered for treatment by at least one guideline studied (N = 364). Data are displayed as odds ratios and 95% confidence interval. CI, confidence interval; LDL, low-density lipoprotein; OR, odds ratio.

old [26], one would expect similar proportions of people considered for treatment in the general population as we observed in this population of young CAD patients.

Due to the low calculated risk scores and the absence of statin-indicated conditions, 12.7% of patients were not eligible for treatment by any of the guidelines. The majority of these patients had only 1 or 2 major cardiovascular risk factors, with the most frequent being dyslipidemia, hypertension, and family history of premature CVD. Additionally, 41 (77.4%) of these patients had a BMI $>$ 25, among whom 17 had obesity. These observations suggest that greater focus on family history and BMI or waist circumstance in risk calculators may improve risk detection and management in such patients.

Despite the finding that statin therapy was recommended by major guidelines in 34.3–61.4% of patients in this study, only a small proportion (17.1%) of patients received primary prevention with lipid-lowering therapy prior to their index event. Moreover, less than half of the patients who received treatment achieved a guideline-recommended lipid target. The low percentage of treated patients reaching target lipid levels may in part reflect the high rate of treatment discontinuation (19.7% of all treated patients), and the low utilization of high-intensity statins (less than 30% of treated patients). Of particular note, less than one-third of patients with statin-indicated conditions such as diabetes or severe hypercholesterolemia (LDL-C $\geq$ 190 mg/dL) received treatment prior to the onset of clinical CAD. Collectively, these findings indicate major shortcomings in both risk prediction and implementation of guideline-recommended treatment in high-risk patients developing very premature CAD.

One possible contributor to the significant undertreatment we observed could be the low awareness of CVRFs among younger CAD patients, as has been previously described [1,7,9]. For instance, while diabetes and elevated lipid levels were the factors were the only factors positively associated with treatment initiation, 24.1% of patients with diabetes in our study were unaware of the diagnosis of diabetes before presenting with CAD, and 34.8% had not undergone lipid screening in 5 years before the presentation.

Finally, we observed that diabetes and dyslipidemia were positively associated with the initiation of lipid-lowering therapy. Smoking showed a significant negative association with preventive treatment, which is consistent with prior data suggesting that smokers are less likely to undergo routine health screening [27], receive vaccinations [28], and to be adherent to treatment for chronic conditions [29]. Other factors studied, despite being major CVRFs or risk enhancers, were not significantly associated with treatment initiation in the cohort.

Our study has several important limitations. Inclusion in the study was based on angiographically documented disease. While this approach improves the specificity of the disease definition, it also limits the generalizability of the results to other patients who may have less severe disease and who undergo non-invasive management. Additionally, young women with CAD are less likely to undergo angiography [8] and are more likely to present with ischemia with non-obstructive coronary arteries [30], and therefore could be underrepresented in our study. Secondly, our method of data collection required physician assessment of each patient. While this provides detailed clinical and lifestyle information, it necessarily results in smaller sample sizes than could be achieved by studies of administrative databases or medical records. Due to the limited sample size, we were not able to evaluate several important socio-demographic factors possibly associated with the initiation of lipid-lowering therapy. A third limitation is that risk calculators may perform differently in different ethnic groups. Our population was ethnically mixed but lacked sufficient power to perform analysis by subgroups. However, our population is likely to be representative of the ethnic diversity of Canada. For some patients, we used lipid levels measured at the time of presentation with CAD. It was previously demonstrated, that in patients presenting with acute coronary syndrome LDL-C levels may temporarily decrease within 24 h after presentation [31]. However, it was also shown, that these changes were not clinically meaningful and did not affect risk assessment [9,31]. Treatment goal for lipids in our study was defined only as LDL-C of $\leq$77 mg/dL (2 mmol/L) or non-HDL of $\leq$100 mg/dL (2.6 mmol/L). As many of the patients had only one pre-presentation lipid panel available, it was not possible to assess percentage of reduction for all patients. Finally, to perform risk estimation with PCE calculator under ACC/AHA guidelines we used age of 40 years for patients who were younger at the time of the first presentation with CAD (11.5% of the study population), that could result into an overestimation of risk in these patients.

5. Conclusions

A significant number of patients who develop premature CAD do not qualify for primary preventive therapy and the vast majority of patients do not receive lipid-lowering medications prior to their presentation with the disease. Our findings indicate the need for improved methods of identifying young adults at risk for premature CAD, and for greater implementation of primary prevention therapy when indicated.

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Author contributions

Diana Vikulova: conceptualization, methodology, formal analysis, investigation, resources, data curation, visualization, writing - original draft, writing - review and editing;

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Chad Brown: provision of study materials, project administration, writing - review & editing;

Emilie Theberge: project administration, writing - review & editing;

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Disclosures

Authors have reported that they have no relationships relevant to the content of this study to disclose.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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