Five-Year Residual Atherosclerotic Cardiovascular Disease Risk Prediction Model for Statin Treated Patients With Known Cardiovascular Disease

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Despite statin therapy, many patients with atherosclerotic cardiovascular disease (ASCVD) still suffer from ASCVD events. Predictors of residual ASCVD risk are not well-delineated. We aimed to develop an ASCVD risk prediction model for patients with previous ASCVD on statin use. We utilized statin-treated patients with ASCVD from the AIM-HIGH trial cohort. A 5-year risk score for subsequent ASCVD events with known ASCVD was developed using Cox regression, including potential risk factors with age, sex, and race forced in the model. Internal discrimination and calibration were evaluated. We included 3,271 patients with ASCVD (85.4% male, mean age 63.6 years, 65% on moderate- and 24% on high-intensity statin) with complete risk factor data and mean follow-up of 4.18 years. Overall, the estimated 5-year ASCVD risk was 21.1%: 10.2% of patients had a 5-year risk of >30%, and 38.8% had risk of between 20% and 30%. In the model, male sex, hemoglobin A1c, alcohol use (inversely), family history of cardiovascular disease, homocysteine, history of carotid artery disease, and lipoprotein(a) best predicted residual ASCVD risk. Niacin treatment status did not enter the model. A C-statistic of 0.59 was obtained, with the Greenwood-Nam-D'Agostino test showing excellent calibration. We developed a risk prediction risk model for predicting 5-year residual ASCVD risk in statin-treated patients with known ASCVD that may help in identifying such persons at the highest risk of recurrent events. Validation in larger samples with patients on high-intensity statin is needed. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;137:7−11)

Clinical trials of statin therapy over the past several decades have been highly effective in reducing atherosclerotic cardiovascular disease (ASCVD) event risk by 30% to 40% in many cases.[1−4] However, many persons, especially those with previous ASCVD, still suffer from high rates of ASCVD events despite statin therapy, a concept termed "residual risk."[5] Major risk factors such as elevated cholesterol levels, blood pressure, and diabetes are long recognized to predict recurrent ASCVD events and mortality.[6] Risk scores have also been developed for persons with ASCVD for the prediction of subsequent events[7,8]; however, their utility is limited in contemporary populations who are on statins and other cardioprotective therapies as the standard of care. Low-density lipoprotein cholesterol (LDL-C) levels are also lower than several decades ago. There is a need for newer algorithms for predicting future ASCVD risk in more contemporary patients who are often on statin therapy. This project aimed to develop a risk score for ASCVD residual risk in persons with ASCVD on statin therapy.

Methods

We studied statin-treated patients with previous ASCVD from the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) clinical trial cohort.[9] In brief, 3,414 participants aged ≥45 years from 92 centers in the United States and Canada with documented ASCVD (coronary artery disease, cerebrovascular or carotid disease, and/or symptomatic peripheral arterial disease) in addition to having atherogenic dyslipidemia defined as: (1) LDL-C of less than or equal to 160 mg/dl; (2) High-density lipoprotein cholesterol (HDL-C) ≤40 mg/dl for men or ≤50 mg/dl for women; (3) triglycerides of 150 to 400 mg/dl were randomly assigned to niacin or matching placebo in a 1:1 ratio in addition to simvastatin. The trial terminated early (mean follow-up of 3 years) due to a lack of efficacy in reducing ASCVD risk. In the present study, 3,271 participants were included who had data on the candidate risk factors considered in the risk prediction algorithm.

The predicted end point was the composite ASCVD primary end point from the AIM-HIGH trial which included nonfatal myocardial infarction, death from coronary heart disease (CHD), ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. After the main trial ended, the cohort was followed up for a maximum of 6 years. Time to event was defined from baseline to the date of the first occurrence of any of the above events, the last day of the extended follow-up, or the date of loss-to follow-up, whichever came first. All end points were reviewed by the AIM-HIGH clinical events committee.

We included all variables that were found to be associated with cardiovascular disease (CVD) in other studies and were available at baseline as our potential predictors, including age, sex, race, body mass index (BMI), blood pressure, LDL-C, HDL-C, triglycerides, lipoprotein(a), apolipoprotein A1, apolipoprotein B, smoking status, alcohol consumption, family history of CVD, glycated hemoglobin (HbA1c), atrial fibrillation, serum creatine, homocysteine, and specific ASCVD conditions (previous myocardial infarction, stroke, heart failure, carotid, or peripheral arterial disease), antihypertensive, or diabetes drugs, aspirin use, previous use of higher versus lower intensity statins, and treatment assignment. Additional variables allowed to enter were: BMI as a categorical variable, as well as considering non-HDL-C, as well as estimated glomerular filtration rate and pulse pressure. We selected predictors with a p-value <0.15 from the full Cox regression model.

Age, sex, and race were forced in the final model. Absolute 5-year ASCVD risk was calculated from the equation:

$$R = 1 - S_5^{e^{\sum beta*X_{indv} - \sum beta*X_{mean}}},$$

where S_5 is the population mean survival at year 5 in the final Cox model, beta is coefficient of each predictor, X_{indv} is individual's predictor value and X_{mean} is population predictor mean.

The prediction model was internally validated with 10-fold cross validation with the Harrell's c-statistic used to evaluate the discrimination performance and the Greenwood-Nam-D'Agostino (GND) goodness-of-fit test for internal calibration. A calibration plot of predicted versus observed risk was done by categorizing the whole sample into decile groups according to predicted risk. The smaller the difference between the predicted risk and observed risk is, the smaller Chi-square value and the bigger p-value are. The calibration slope and intercept were calculated based on the predicted versus observed risk, with a calibration slope of 1 and intercept 0 in perfect conditions. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). P-values <0.05 were considered as statistically significant. All data (de-identified) were obtained with permission from the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center and our study was exempt from Institutional Review Board review at the University of California, Irvine.

Results

Our cohort included 85.4% men, with a mean age of 63.6 years (ranged 45 to 85 years) and with 65% on moderate-intensity and 24% on high-intensity statin at baseline. Compared with those without any ASCVD during follow-up, those who had recurrent ASCVD events were more likely men, with less alcohol consumption and more family history of CVD (Table 1). During mean follow-up of 4.18 years, 621 (16%) of patients had a first recurrent ASCVD event with 189 having symptomatic driven revascularization, 185 myocardial infarction, 141 other acute coronary syndrome events, 53 CHD deaths and 53 strokes. The rate of first recurrent ASCVD events was 45.4/1000 person-years.

In the final prediction model, male sex, HbA1c, alcohol use (inversely), family history, homocysteine, lipoprotein (a), and previous carotid artery disease were significant predictors of residual ASCVD event risk (Table 2). For instance, a 1 SD greater lipoprotein(a) was associated with

Table 1

Baseline characteristics according to occurrence of recurrent ASCVD events

| Variable | ASCVD Event | | p value |
	No (N = 2,650)	Yes (N = 621)	
Age (years)	63.52 ± 8.78	64.12 ± 8.6	0.124
Men	2242 (84.6%)	550 (88.6%)	0.012
White	2448 (92.4%)	573 (92.3%)	0.928
Current smoker	481 (18.2%)	121 (19.5%)	0.625
Alcohol consumer	1380 (52.1%)	285 (45.9%)	0.006
Family history of CVD	1035 (39.1%)	281 (45.3%)	0.005
Diabetes mellitus	1033 (39.0%)	285 (45.9%)	0.002
Systolic blood pressure (mm Hg)	128.17 ± 16.1	128.72 ± 17.27	0.471
Diastolic blood pressure (mm Hg)	74.49 ± 9.81	74.06 ± 9.74	0.328
Body mass index (kg/m²)	31.17 ± 5.27	31.56 ± 5.57	0.096
HDL-C (mg/dl)	34.85 ± 5.64	34.16 ± 5.44	0.006
LDL-C (mg/dl)	73.93 ± 23.14	74.37 ± 22.44	0.664
Lp(a) (nmol/L)	73.44 ± 87.65	89.69 ± 92.64	<0.0001
Triglycerides (mg/dl)	181.72 ± 66.36	185.89 ± 69.39	0.162
ApoA1 (mg/dl)	123.34 ± 16.19	121.52 ± 15.95	0.011
ApoB (mg/dl)	82.59 ± 19.9	84.23 ± 20.35	0.067
HbA1c (%)	5.97 ± 0.79	6.08 ± 0.88	0.005
Serum creatinine (mg/dl)	0.98 ± 0.23	1.02 ± 0.26	0.001
Homocysteine (μmol/L)	11.31 ± 4.74	12.1 ± 8.4	0.024
Atrial fibrillation	187 (7.1%)	53 (8.5%)	0.204
History of myocardial infarction	1,487 (56.1%)	356 (57.3%)	0.590
History of heart failure	179 (6.8%)	59 (9.5%)	0.018
History of stroke	157 (5.9%)	49 (7.9%)	0.070
History of peripheral vascular disease	327 (12.3%)	100 (16.1%)	0.012
History of carotid artery disease	355 (13.4%)	116 (18.7%)	0.0007
Aspirin use	2,585 (97.5%)	611 (98.4%)	0.207
Hypertension medication	2,522 (95.2%)	598 (96.3%)	0.229

ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; HbA1c = glycated hemoglobin; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; Lp(a) = lipoprotein(a).

Table 2
Final Cox regression model for 5-year recurrent ASCVD event risk prediction

Parameter	Beta	Wald Chi-sq	p value	HR (95% CI)*
Age, per 1 SD	0.00212	0.1735	0.677	1.02 (0.93-1.11)
Sex, 1=male,0=female	0.32063	5.9028	0.015	1.38 (1.06-1.79)
Race, 1=White, 0=Non-White	0.02306	0.0226	0.881	1.02 (0.76-1.38)
Alcohol use, 1=Yes, 0=No	0.19119	5.4328	0.020	0.83 (0.70-0.97)
Family history of CVD, 1=Yes, 0=No	0.25629	9.7769	0.002	1.29 (1.10-1.52)
HbA1c per 1SD	0.11435	5.3807	0.020	1.10 (1.01-1.19)
BMI, per 1 SD	0.01358	3.1488	0.076	1.08 (0.99-1.16)
Serum creatinine, per 1 SD	0.3446	3.8394	0.050	1.09 (1.00-1.18)
Homocysteine, per 1 SD	0.01336	8.8025	0.003	1.08 (1.03-1.13)
Lp(a), per 1 SD	0.00174	18.7007	<.0001	1.07 (1.04-1.10)
History of heart failure	0.27109	3.8023	0.051	1.31 (1.00-1.72)
History of carotid artery disease	0.31782	9.1159	0.003	1.37 (1.12-1.69)

Final Risk Score: $R_5 = 1 - 0.7971 e^{\Sigma beta*X - 2.2383}$

Potential risk factor list: age, sex, race, smoking status, alcohol consumption, family history of CVD, diabetes, atrial fibrillation history, body mass index, systolic and diastolic blood pressure, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, lipoprotein (a), Apolipoprotein AI, Apolipoprotein B, serum creatine, homocysteine, and treatment assignment.

* HRs are presented per 1 SD increase of continuous variables; beta coefficients are presented in original units. BMI = body mass index; Lp (a) = lipoprotein(a) 1 SD of age = 8.75 years; 1SD of HbA1c=0.81%; 1SD of BMI =5.33 kg/m2; 1SD of serum creatinine = 0.24 mg/dl; 1 SD of Lp (a) = 37.02 nmol/L; 1SD of Homocysteine = 11.36 umol/L.

Figure 1. AIM-HIGH risk score predicted versus observed risk of subsequent ASCVD events.

based on the equation: $R_5 = 1 - 0.7971 e^{\Sigma beta*X - 2.2383}$, where beta is coefficient of each predictor in Table 2, and X is the value of each respective predictor.

In internal validation using 10-fold cross validation, our prediction model had a Harrell's C-statistic of 0.59. The GND test showed good consistency between predicted risk and observed risk at year 5, with Chi-square = 19.69 and p-value of 0.02 (df = 9). The calibration plot (Figure 1) shows a slope of 1.04 with intercept of −0.008, indicating excellent calibration.

a 7% increase in recurrent event risk. Family history was associated with a 29% higher risk. The mean predicted 5-year recurrent ASCVD event risk was 21.1% (range 7.7% to 79.7%). 10.2% of patients had a 5-year risk of >30%.

We additionally tested a number of alternative predictors to improve our model: (1) systolic and diastolic blood pressure was replaced with pulse pressure; (2) HbA1c was replaced with diabetes mellitus (DM); (3) BMI was examined in categories of obesity and overweight; (4) serum creatinine was replaced with estimated glomerular filtration rate; and (5) LDL-C and HDL-C was replaced with non-HDL-C. In the above substitute predictors, none except for DM were selected with p <0.15. But since DM was weaker than HbA1c the latter was used in our model. Also, even when lipoprotein(a) was excluded from the potential predictor list, LDL-C did not enter the model as a predictor.

As an example of applying our risk score, in a 60-year old white female patient with history of carotid artery disease but no history of heart failure and on statin treatment with no alcohol use or a family history of CVD and with the following risk profile: HbA1c = 7.8%, BMI = 30 mg/m², lipoprotein(a) = 110 mmol/L, serum creatinine = 0.7 mg/dl, homocysteine = 20 mg/dl. Based on our calculator, the risk of recurrent ASCVD events within 5 years was 18.7%
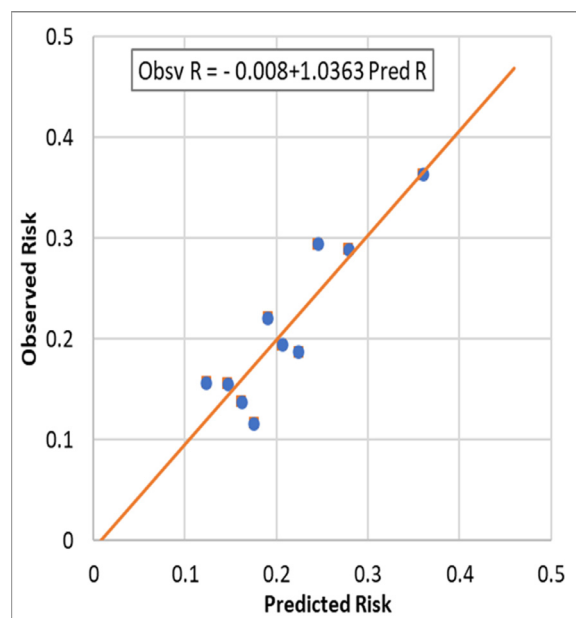
Discussion

Our risk prediction model derived from patients with known ASCVD on statin therapy estimated a mean 5-year ASCVD recurrent event risk of 21.1%, with 16% of patients actually experiencing a recurrent event over the 4.2-year follow-up. Male sex, HbA1c, alcohol use (inversely), family history of CVD, homocysteine, history of carotid artery disease, and lipoprotein(a) were significant predictors of this residual risk. Body mass index, serum creatinine, and history of heart failure were also included in our final model. Internal validation showed excellent calibration. We developed a simple and clinically applicable scoring algorithm incorporating inputs of each of these factors. Since most patients with ASCVD are on statin therapy, our algorithm for predicting the risk of subsequent events is particularly relevant. Our results suggest that more aggressive management of diabetes, obesity, maintaining normal creatinine (e.g., from earlier treatment of chronic kidney disease), prevention of heart failure, and potentially the lowering of lipoprotein(a) if borne out by the results of ongoing outcomes studies, could possibly reduce this residual risk. Although we also show homocysteine to also predict CVD risk, clinical trials to lower homocysteine have

had mixed results showing a benefit primarily for stroke and in those without CVD at baseline CVD risk.[10]

Scoring algorithms such as what we have developed can be helpful in identifying those ASCVD patients at the highest risk. The 27th Bethesda Conference of the American College of Cardiology noted >20 years ago that the intensity of treatment should match a person's risk.[8] Also, the most recent 2018 American College of Cardiology / American Heart Association / Multisociety cholesterol management guideline has provided a clear definition to define ASCVD patients who are at "very high risk" versus those who are not[11] based on the number of major ASCVD events and high-risk conditions. The more quantitative approach as we have proposed may provide for more precise risk estimation.[12]

More than 30 years ago, we showed age, sex, diabetes, total cholesterol, and systolic blood pressure to be significant predictors of recurrent CHD events in post-myocardial infarction subjects from the Framingham Heart Study.[6] D'Agostino et al[7] subsequently developed a risk prediction algorithm for those with known CHD showing age, blood lipid levels (total and HDL cholesterol), and DM to be significant predictors of subsequent CHD events for men and women, with systolic blood pressure and cigarette smoking being additional predictors in women. In a much larger cohort of adults with CHD from the Euroaspire I, II, and III surveys, where there was a CVD mortality risk of 12.3 per 1,000 person-years in men and 10.2 per 1,000 person-years in women. In multivariate analysis, fasting glucose, total cholesterol, and smoking emerged as the strongest independent modifiable predictors of cardiovascular mortality.[13] Califf et al[8] noted other factors such as type of chest pain present and accompanying co-morbidities should also be considered in the determination of prognosis in persons with CHD. Also, in 4,184 outpatients with CHD, predictors of recurrent CVD events were age, previous hospitalization for decompensated heart failure, left ventricular ejection fraction, previous aortic or peripheral intervention, and estimated glomerular filtration rate.[14] These earlier risk prediction algorithms were based on cohorts with limited post-CHD recommended therapy and were not developed in cohorts with universal statin use, in particular given that statin therapy that has been a key recommendation for such patients now for nearly 2 decades.

Of note, the present study identifies lipoprotein(a) as a predictor of residual ASCVD event risk in patients with pre-existing ASCVD on statin therapy. A recent meta-analysis[15] from a wide range of statin studies (but not AIM-HIGH) recently showed the relation of lipoprotein(a) to ASCVD events; however, many of the studies were primary prevention.

There are important strengths and limitations of our analysis. AIM-HIGH had standardized assessment of laboratory and clinical measures, as well as centralized adjudication of clinical outcomes. Although AIM-HIGH had broad geographic representation across the United States and Canada, the self-selection and inclusion criteria typical for clinical trial populations results in a cohort that may not be representative of all patients with ASCVD. Although the requirement of statin use in AIM-HIGH makes it an ideal cohort for studying residual risk beyond statin therapy, the selection of persons with lower HDL-C and higher

triglycerides may have resulted in a selectively higher risk cohort. Also, with a target LDL-C at randomization of between 40 and 80 mg/dl, there was limited variability in LDL-C levels; thus, it is not surprising LDL-C did not enter the model. Although such criteria arguably are not representative of a real-world clinical practice setting, many patients with ASCVD are on statins with on-treatment LDL-C levels in this range. In addition, half of subjects were randomized to niacin therapy; however, this was not found to enter the predictive model (and of course did not impact on ASCVD outcomes from the original AIM-HIGH trial [9]). Finally, the AIM-HIGH cohort being over 75% white and mainly men also limits the generalizability of our findings.

Disclosures

Author Contribution

Dr. Nathan Wong designed the study and wrote the manuscript. Dr. Yanglu Zhao conducted the analysis and provided critical review and revision. Drs. Coll, Xiang, and Lopez provided critical review and revision.

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