Title: Real-World Risk of Recurrent Cardiovascular Events in Atherosclerotic Cardiovascular Disease Patients with LDL-C Above Guideline-Recommended Threshold: A Retrospective Observational Study

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Supplementary Materials

Supplementary Table 1: Study Population Inclusion Criteria (based on FOURIER Trial[1])

Criteria (literature source for algorithm)	Definition	ICD-9-CM/ICD-10-CA codes	Algorithm
Age 40-85, inclusive			
AND at least one of the following three criteria:			
Diagnosis of MI[2]	AMI in the pre-index period	**ICD-10-CA:** I21-22	1 IP (Inpatient) admission, any position (discharge date as event date)
Diagnosis of IS[2,3]	Ischemic stroke in the pre-index period	**ICD-9-CM:** 362.3,430,431, 434.x, 436, 435.x **ICD-10-CA:** I63 (excluding I63.6), H34.1	1 IP (discharge date); OR 2 physician claims, 2 emergency department (ED) visits or 1 physician claim/1 ED visit at least 30 days apart, any position (second date=event date); earliest as event date[a]
Diagnosis of PAD[2]	PAD in the pre-index period	**ICD-9-CM:** 443.9, 440.2 **ICD-10-CA:** I73.9, I70.2, I79.2	1 IP (any position, discharge date); OR 2 physician claims, 2 emergency department (ED) visits or 1 physician claim/1 ED visit at least 30 days apart, any position (second date=event date); earliest as event date[a]
AND any LDL -C test ≥1.8 mmol/L or non-HDL-C ≥2.6 mmol/L prior to index date while on moderate/high intensity statin therapy:			
Moderate intensity statins:	Atorvastatin 10-20mg Rosuvastatin 5-10mg Simvastatin 20-40mg Pravastatin 40-80mg Lovastatin 40, 60mg Fluvastatin XL 80mg Fluvastatin 40mg bid Pitavastatin 2-4mg		1 dispensation of either moderate or high intensity statin; AND A pre-index LDL-C test ≥1.8 mmol/L OR non-HDL-C ≥2.6 mmol/L
High intensity statins:	Atorvastatin 40-80mg Rosuvastatin 20-40mg		
AND most recent fasting triglycerides ≤4.5 mmol/L prior to index date			
AND at least one major risk factor or two minor risk factors as defined below:			
Major Risk Factors			
Diabetes (type 1 or 2)[2]	Diabetes prior to index date	**ICD-9-CM:** 250 **ICD-10-CA:** E10-14	1 IP (discharge date), ED visit or physician claim
Age ≥65 years and ≤85 years at index	--	--	--
If qualifying with MI, history of IS and/or PAD in the pre-index period or MI within 6 months pre-index	IS	**ICD-9-CM:** 362.3,430,431, 434.x, 436, 435.x **ICD-10-CA:** I63 (excluding I63.6), H34.1	1 IP (discharge date); OR 2 physician claims, 2 emergency department (ED) visits or 1 physician claim/1 ED visit at least 30 days apart, any position (second date=event date); earliest as event date[a]
	PAD	**ICD-9-CM:** 443.9, 440.2 **ICD-10-CA:** I73.9, I70.2, I79.2	1 IP (any position, discharge date); OR

			2 physician claims/ED visits 30 days apart (second date=event date); earliest as event date.[a]
If qualifying with IS, history of MI and/or PAD in the pre-index period or IS within 6 months pre-index	AMI	**ICD-10-CA:** I21-22	1 IP (Inpatient) admission, any position (discharge date as event date)
	PAD	**ICD-9-CM:** 443.9, 440.2 **ICD-10-CA:** I73.9, I70.2, I79.2	1 IP (any position, discharge date); OR 2 physician claims/ED visits 30 days apart (second date=event date); earliest as event date.[a]
Minor Risk Factors			
History of non-MI related coronary revascularization[2]	PCI prior to index date	**CCP:** 48.02, 48.03 **CCI:** 1.IJ.50, 1.IJ.57.GQ, 1.IJ.54	1 IP or 1 ED CCP/CCI (Procedure date if available, otherwise discharge date); earliest date as event date
	CABG prior to index date	**CCP:** 48.1 **CCI:** 1.IJ.76	1 IP or 1 ED CCP/CCI code (Procedure date if available, otherwise discharge date); earliest date as event date
CAD[4]	CAD/stenosis prior to index date	**ICD-9-CM:** 433.10 **ICD-10-CA:** I65.2 **CCP:** 51.59 **CCI:** 1.JE.50	1 IP or 1 ED CCP/CCI code (Procedure date if available, otherwise discharge date); earliest date as event date
Metabolic syndrome	Metabolic syndrome prior to index date	**ICD-9-CM:** 277.8 **ICD-10-CA:** E88.80	1 IP (discharge date), ED visit or physician claim
Elevated LDL-C	Most recent LDL-C test >3.4 mmol/L prior to index date	**--**	1 laboratory value
Low HDL-C	Most recent HDL-C test <1.0 mmol/L for men or <1.3 mmol/L for women prior to index date	**--**	1 laboratory value
Elevated non-HDL-C	Most recent Non-HDL-C test >4.1 mmol/L prior to index date	**--**	1 laboratory value

Abbreviations: AMI: acute myocardial infarction, CABG: coronary artery bypass graft surgery, CAD: coronary artery disease, CCI: Canadian Classification of Health Interventions, CCP: Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures, ED: emergency department, FOURIER: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk, HDL-C: high density lipoprotein cholesterol, ICD 9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-10-CA: International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada, IP: inpatient, IS: ischemic stroke, LDL-C: low density lipoprotein cholesterol, MI: myocardial infarction, PAD: peripheral arterial disease, PCI: percutaneous coronary intervention

[a] The earliest as index/event date meaning, earliest IP or physician claims/ED visits combination as index date if both criteria are met (or criteria are met multiple times within the case ascertainment period).

[1] Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017; 376(18): 1713-22.

[2] Chen G, Farris MS, Cowling T, et al. Prevalence of atherosclerotic cardiovascular disease and subsequent major adverse cardiovascular events in Alberta, Canada: A real-world evidence study. Clinical Cardiology 2021; 44(11): 1613-20.

[3] Hall R, Mondor L, Porter J, Fang J, Kapral MK. Accuracy of Administrative Data for the Coding of Acute Stroke and TIAs. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques 2016; 43(6): 765-73.

[4] Hussain MAMD, Mamdani MPMAMPH, Saposnik GMDM, et al. Validation of Carotid Artery Revascularization Coding in Ontario Health Administrative Databases. Clinical and Investigative Medicine (Online) 2016; 39(2): E73-E8.

Supplementary Table 2: Definitions for subgroups and CV outcomes of interest

Criteria	Definition	ICD-9-CM/ICD-10-CA codes	Algorithm
Clinically evident ASCVD and any of the following:			
High-Risk ASCVD Subgroups of Interest			
Diabetes (type 1 or 2) or metabolic syndrome	Diabetes within one year pre- or post-index date	**ICD-9-CM:** 250 **ICD-10-CA:** E10-14	1 IP (discharge date), ED visit, or physician claim
	Metabolic syndrome within one year pre- or post- index date	**ICD-9-CM:** 277.8 **ICD-10-CA:** E88.80	1 IP (discharge date), ED visit, or physician claim
Recurrent MI	MI within one year pre- or post-index date	**ICD-10-CA:** I21-22	1 IP, any position (discharge date as event date)
MI in the past two years	MI in the two years pre-index date	**ICD-10-CA:** I21-22	1 IP, any position (discharge date as event date)
LDL-C ≥2.6 mmol/L (surrogate for heterozygous FH)	Defined from the most recent LDL-C test prior to index date (surrogate for FH)	N/A	Having the most recent test with LDL-C ≥2.6 mmol/L
Very High-Risk ASCVD Subgroups of Interest			
ACS event, including recent MI or UA	MI within the follow-up period, re-indexing on the ACS event for additional CV outcome rates	**ICD-10-CA:** I21-22	1 IP any position (discharge date as new index date)
	UA within the follow-up period, reindexing on the ACS event for additional CV outcome rates	**ICD-10-CA:** I20.0	1 IP any position (discharge date as new index date)
Individual CV Outcome Definitions			
Non-fatal MI	AMI	**ICD-10-CA:** I21, I22	1 IP (discharge date), any position
Non-fatal Ischemic stroke	Cerebral infarction and central retinal artery occlusion	**ICD-10-CA:** I63 (excluding I63.6), H34.1	1 IP (discharge date), any position
UA	UA	**ICD-10-CA:** I20.0	1 IP (discharge date), any position
Coronary revascularization	PCI or CABG Surgery	**CCI:** 1IJ50, 1IJ57GQ, 1IJ54, 1IJ76	1 IP CCI code (Procedure date if available; otherwise discharge date)
CV death	--	**ICD-10-CA:** I00-I78	Hospitalization, ED death, or vital statistics record with corresponding ICD-10-CA code.

Abbreviations: ACS: acute coronary syndrome, AMI: acute myocardial infarction, ASCVD: atherosclerotic cardiovascular disease, CABG: coronary artery bypass graft, CCI: Canadian Classification of Health Interventions, CV: cardiovascular, ED: emergency department, FH: familial hypercholesterolemia, ICD 9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-10-CA: International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada; IP: inpatient, LDL-C: low-density lipoprotein-cholesterol, MI: myocardial infarction, PCI: percutaneous coronary intervention, UA: unstable angina.

Supplementary Table 3: **CV outcome rates/100 patient-years (first CV event and total CV events over the follow-up period) for overall cohort**

CV Events	First CV event n (%)	Rate of first CV event per 100 patient-years	Total CV events	Rate of total CV events per 100 patient-years
		IR (95% CI)	N	IR (95% CI)
Primary outcome[a]	5836 (17.7)	5.58 (5.44-5.73)	9666	8.63 (8.46-8.81)
Secondary outcome[b]	5143[c] (15.6)	4.83 (4.69-4.96)	7366	6.58 (6.43-6.73)
MI	2185 (6.6)	2.02 (1.94-2.11)	3134	2.80 (2.70-2.90)
IS	1078 (3.3)	0.98 (0.92-1.04)	1370	1.22 (1.16-1.29)
Hospitalization for unstable angina	681 (2.1)	0.62 (0.57-0.67)	849	0.76 (0.71-0.81)
Coronary revascularization	1325 (4.0)	1.22 (1.15-1.28)	1451	1.30 (1.23-1.36)
CV death	2862 (8.7)	2.56 (2.46-2.65)	2862	2.56 (2.46-2.65)

Abbreviations: CI: confidence interval, CV: cardiovascular, IR: incidence rate, IS: ischemic stroke, MI: myocardial infarction,

[a] Primary outcome was defined as: CV death, MI, IS, hospitalization for unstable angina, or coronary revascularization

[b] Secondary outcome was defined as: CV death, MI, IS.

[c] Mutually exclusive event distribution: 44.8% CV death, 38.2% MI, 17.0% IS.

Supplementary Table 4: Composite and individual CV outcome rates/100 patient-years (first CV event and total CV events over the follow-up period) for very high-risk subgroups as defined by the CCS guidelines[1]

CV Outcomes in High-Risk ASCVD Subgroups[a]	First CV event	Rate of first CV event per 100 patient-years	Total CV events	Rate of total CV events per 100 patient-years
	n (%)	IR (95% CI)	n	IR (95% CI)
ASCVD with comorbid diabetes type 1 or 2, n=13,415				
Primary outcome [b]	2982 (22.2)	7.40 (7.14-7.67)	5196	11.83 (11.51-12.16)
Secondary outcome [c]	2681 (20.0)	6.51 (6.26-6.76)	4017	9.15 (8.87-9.43)
MI	1189 (8.9)	2.83 (2.68-3.00)	1789	4.07 (3.89-4.27)
IS	549 (4.1)	1.27 (1.17-1.39)	681	1.55 (1.44-1.67)
Hospitalization for unstable angina	327 (2.4)	0.76 (0.68-0.84)	416	0.95 (0.86-1.04)
Coronary revascularization	685 (5.1)	1.62 (1.50-1.74)	763	1.74 (1.62-1.86)
CV death	1547 (11.5)	3.52 (3.35-3.70)	1547	3.52 (3.35-3.70)
Recurrent MI, n=9,603				
Primary outcome[b]	2264 (23.6)	6.83 (6.55-7.11)	4256	11.43 (11.09-11.78)
Secondary outcome [c]	1929 (20.1)	5.62 (5.37-5.87)	2998	8.05 (7.77-8.34)
MI	1233 (12.8)	3.56 (3.37-3.76)	1813	4.87 (4.65-5.10)
IS	226 (2.4)	0.61 (0.54-0.70)	292	0.78 (0.70-0.88)
Hospitalization for unstable angina	373 (3.9)	1.03 (0.93-1.14)	474	1.27 (1.16-1.39)
Coronary revascularization	703 (7.3)	1.99 (1.85-2.14)	784	2.11 (1.96-2.26)
CV death	893 (9.3)	2.40 (2.25-2.56)	893	2.40 (2.25-2.56)
MI in the past 2 years, n=14,709				
Primary outcome [b]	2659 (18.1)	5.45 (5.24-5.66)	4691	8.86 (8.61-9.11)
Secondary outcome [c]	2222 (15.1)	4.43 (4.25-4.61)	3260	6.15 (5.95-6.37)
MI	1189 (8.1)	2.35 (2.22-2.48)	1745	3.29 (3.14-3.45)
IS	309 (2.1)	0.59 (0.53-0.66)	397	0.75 (0.68-0.83)
Hospitalization for unstable angina	460 (3.1)	0.89 (0.81-0.97)	577	1.09 (1.00-1.18)
Coronary revascularization	763 (5.2)	1.49 (1.39-1.60)	854	1.61 (1.51-1.72)
CV death	1118 (7.6)	2.11 (1.99-2.24)	1118	2.11 (1.99-2.24)
LDL-C ≥2.6 mmol/L, n=7,780				
Primary outcome[b]	1422 (18.3)	5.79 (5.50-6.10)	2432	9.11 (8.76-9.48)
Secondary outcome[c]	1241 (16.0)	4.94 (4.67-5.22)	1785	6.69 (6.38-7.00)
MI	591 (7.6)	2.31 (2.13-2.51)	843	3.16 (2.95-3.38)
IS	265 (3.4)	1.01 (0.90-1.14)	329	1.23 (1.11-1.37)
Hospitalization for unstable angina	182 (2.3)	0.69 (0.60-0.80)	214	0.80 (0.70-0.92)
Coronary revascularization	395 (5.1)	1.54 (1.39-1.69)	433	1.62 (1.48-1.78)
CV death	613 (7.9)	2.30 (2.12-2.49)	613	2.30 (2.12-2.49)

Abbreviations: ASCVD: atherosclerotic cardiovascular disease, CCS: Canadian Cardiovascular Society, CI: confidence interval, CV: cardiovascular, IR: incidence rate, IS: ischemic stroke, LDL-C: low-density lipoprotein cholesterol, MI: myocardial infarction.

[a] Subgroups are not mutually exclusive (i.e., a patient fulfilling two risk factors will be selected into both subgroups).

[b] Primary outcome was defined as: CV death, MI, IS, hospitalization for unstable angina, or coronary revascularization

[c] Secondary outcome was defined as: CV death, MI, IS.

[1] 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 Adults. *Canadian Journal of Cardiology* 2021; **37**(8): 1129-50.

Supplementary Table 5: Composite and individual additional CV outcome rates/100 patient-years (first additional CV event and total additional CV event following re-indexing) for very high-risk subgroups as defined by the CCS guidelines: ACS and recent MI

CV Outcomes in Very High-Risk ASCVD Subgroups	First additional CV event	Rate of additional CV events per 100 patient-years	Total additional CV events	Rate of total additional CV events per 100 patient-years
	n (%)	IR (95% CI)	n	IR (95% CI)
ACS, n=2,691				
Primary outcome [a]	1328 (49.4)	38.41 (36.40-40.53)	2436	47.62 (45.77-49.55)
Secondary outcome [b]	1196[d] (44.4)	31.01 (29.30-32.81)	1797	35.13 (33.54-36.79)
MI	721 (26.8)	18.44 (17.14-19.83)	1029	20.12 (18.92-21.38)
IS	88 (3.3)	1.75 (1.42-2.15)	106	2.07 (1.71-2.51)
Hospitalization for unstable angina	179 (6.7)	3.80 (3.29-4.40)	249	4.87 (4.30-5.51)
Coronary revascularization	350 (13.0)	7.97 (7.18-8.85)	390	7.62 (6.90-8.42)
CV death	662 (24.6)	12.94 (11.99-13.97)	662	12.94 (11.99-13.97)
Recent MI[c], n=2,185				
Primary outcome [a]	1179 (54.0)	47.73 (45.08-50.53)	2201	56.90 (54.57-59.33)
Secondary outcome [b]	1135 (52.0)	43.27 (40.82-45.86)	1731	44.75 (42.69-46.91)
MI	721 (33.0)	27.07 (25.16-29.12)	1029	26.60 (25.02-28.28)
IS	82 (3.8)	2.16 (1.74-2.68)	96	2.48 (2.03-3.03)
Hospitalization for unstable angina	97 (4.4)	2.66 (2.18-3.24)	140	3.62 (3.07-4.27)
Coronary revascularization	296 (13.6)	9.06 (8.08-10.15)	330	8.53 (7.66-9.50)
CV death	606 (27.7)	15.67 (14.47-16.96)	606	15.67 (14.47-16.96)

Abbreviations: ACS: acute coronary syndrome, ASCVD: atherosclerotic cardiovascular disease, CCS: Canadian Cardiovascular Society, CI: confidence interval, CV: cardiovascular, IR: incidence rate, IS: ischemic stroke, MI: myocardial infarction.

[a] Primary outcome was defined as: CV death, MI, IS, hospitalization for unstable angina, or coronary revascularization

[b] Secondary outcome was defined as: CV death, MI, IS.

[c] Recent MI is a subgroup of ACS (composed of recent MI and recent hospitalization for unstable angina).

[d] Mutually exclusive event distribution: 41.2% CV death, 55.0% MI, 3.8% IS.