Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Diagnosis and Procedure Codes for Identification of ASCVD in the Database

Subgroup	Diagnosis/ Procedure	Code Type	Code Value[a]	Code Description
Recent ACS	Acute MI	ICD-9-CM	410.x	Acute MI
	Unstable angina	ICD-9-CM	411.1	Intermediate coronary syndrome
		ICD-9-CM	411.81	Acute coronary occlusion without MI
Other CHD	Acute MI	ICD-9-CM	410.x	Acute MI
	Unstable angina	ICD-9-CM	411.1	Intermediate coronary syndrome
		ICD-9-CM	411.81	Acute coronary occlusion without MI
	Old MI	ICD-9-CM	412	Old MI
	Stable angina	ICD-9-CM	413.x	Angina pectoris
	Other chronic ischemic heart disease	ICD-9-CM	414.x	Other forms of chronic ischemic heart disease
	Coronary revascularization procedures	CPT	33510-529 33531-6	Coronary artery bypass
		HCPCS	S2205-S2209	Minimally invasive direct coronary artery bypass surgery
		ICD-9-CM	36.0x	Removal of coronary artery obstruction and insertion of stent(s)
		ICD-9-CM	36.1x	Bypass anastomosis for heart revascularization
		ICD-9-CM	36.2	Heart revascularization by arterial implant
		ICD-9-CM	36.3x	Other heart revascularization
		CPT	92982 92984	Percutaneous transluminal coronary balloon angioplasty
		CPT	92995 92996	Percutaneous transluminal coronary atherectomy
		CPT	92980 92981	Transcatheter placement of an intracoronary stent(s)
		HCPCS	G0290 G0291	Transcatheter placement of a drug-eluting intracoronary stent(s)
		ICD-9-CM	00.66	Percutaneous transluminal coronary angioplasty or coronary atherectomy
Ischemic cerebrovascular disease	Ischemic stroke	ICD-9-CM	433.x1	Occlusion and stenosis of precerebral arteries – with cerebral infarction
		ICD-9-CM	434.x1	Occlusion of cerebral arteries – with cerebral infarction
	Asymptomatic evidence of cerebrovascular occlusion	ICD-9-CM	433.00	Occlusion and stenosis of basilar artery without cerebral infarction

		ICD-9-CM	433.10	Occlusion and stenosis of carotid artery without cerebral infarction
		ICD-9-CM	433.20	Occlusion and stenosis of vertebral artery without cerebral infarction
		ICD-9-CM	433.30	Occlusion and stenosis of multiple and bilateral precerebral arteries without cerebral infarction
		ICD-9-CM	433.80	Occlusion and stenosis of other specified precerebral artery without cerebral infarction
		ICD-9-CM	433.90	Occlusion and stenosis of unspecified precerebral artery without cerebral infarction
	Carotid artery disease	ICD-9-CM	00.63	Percutaneous insertion of carotid artery stent(s)
		ICD-9-CM	38.13, 38.18	Endarterectomy of upper limb vessels/lower limb arteries
		CPT	37215, 37216	Stenting of carotid artery
		CPT	35301	Endarterectomy
PAD	PVD	ICD-9-CM	443.9	Peripheral vascular disease, unspecified
		ICD-9-CM	00.55	Insertion of drug-eluting peripheral vessel stent(s)
		ICD-9-CM	39.90	Insertion of non-drug-eluting peripheral vessel stent(s)
		ICD-9-CM	00.61	Percutaneous angioplasty or atherectomy of precerebral (extracranial) vessel(s)
		ICD-9-CM	00.64	Percutaneous insertion of other precerebral (extracranial) artery stent(s)
		ICD-9-CM	39.50	Angioplasty or atherectomy of other noncoronary vessel(s)
		ICD-9-CM	39.72	Endovascular repair or occlusion of head and neck vessels
		ICD-9-CM	39.74	Endovascular removal of obstruction from head and neck vessel(s)
		ICD-9-CM	445.0X	Atheroembolism of extremities
		CPT	35450-35459	Transluminal angioplasty: open (excluding venous)
		CPT	35470-35475	Transluminal angioplasty: percutaneous (excluding venous)
		CPT	35480-35485	Transluminal atherectomy: cutdown
		CPT	35490-35495	Transluminal atherectomy: percutaneous
		CPT	35501-35571	Arterial bypass using vein grafts
		CPT	35583-35587	Lower extremity revascularization: in-situ vein bypass
		CPT	35601-35671	Arterial bypass with synthetic grafts
		CPT	37205-37208	Insertion of intravascular stent
		CPT	93668	Rehabilitation services: PAD
		CPT	37220-37235	Endovascular revascularization, lower extremities

	Abdominal aortic aneurysm	ICD-9-CM	441.3 441.4	Abdominal aortic aneurysm
		CPT	34800-34805	Endovascular repair of infrarenal abdominal aortic aneurysm
		CPT	35081-35103	Open repair of abdominal aortic aneurysm

[a]Codes 410.x, 411.1, and 411.81 for recent ACS were utilized together with additional criteria defining an ACS event ≤12 months from index. If the criteria for recent ACS were not met, these codes were utilized for the other CHD category.

ACS, acute coronary syndrome; CHD, coronary heart disease; CPT, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; MI, myocardial infarction; PAD, peripheral arterial disease; PVD, peripheral vascular disease.

eTable 2. Mean and SD of Percentage Reduction in LDL-C Levels From Statins and Ezetimibe

LLT Type	Dose	Mean (Reference)[a]	SD (Reference)[b]
Atorvastatin	10 mg	35.5%[3]	10.6%[4,c]
	20 mg	41.4%[3]	13.5%[4,c]
	40 mg	46.2%[3]	12.5%[4,c]
	80 mg	50.2%[3]	13.8%[4,c]
Fluvastatin	20 mg	17.0%[4]	8.0%[4]
	40 mg	23.0%[4]	10.0%[4]
	80 mg	26.0%[4]	9.0%[4]
Lovastatin	10 mg	21.0%[5]	10.1% (Estimated)[d]
	20 mg	24.0%[6]	11.0%[6]
	40 mg	30.0%[6]	11.0%[6]
	60 mg	34.5% (Estimated)[e]	11.7% (Estimated)[f]
Pravastatin	10 mg	20.0%[4]	11.0%[4]
	20 mg	24.0%[4]	11.0% [4]
	40 mg	30.0%[4]	13.0%[4]
	80 mg	33.0%[5]	11.2% (Estimated)[d]
Rosuvastatin	5 mg	38.8%[3]	13.2% (Estimated)[d]
	10 mg	44.1%[3]	12.5%[4,c]
	20 mg	49.5%[3]	13.3%[4,c]
	40 mg	54.7%[3]	12.9%[4,c]
Simvastatin	5 mg	23.0%[5]	11.0%[4,d]
	10 mg	27.4%[3]	13.7%[4,c]
	20 mg	33.0%[3]	10.4%[4,c]
	40 mg	38.9%[3]	14.0%[4,c]
	80 mg	45.0%[3]	11.7%[4,c]

Ezetimibe[f]	10 mg	22.7%[7]	16.5%[8]

[a]Mean of % reduction in LDL-C compared with placebo. [b]SD of % reduction in LDL-C compared with placebo. [c]SD estimated as the product of mean from Nicholls 2010 and coefficient of variation from Ward 2007. [d]SD values were not available in literature and were estimated based on the average coefficient of variation of available data. SD values for approximately 6.6% of patients on a statin (3.6% of the overall cohort) were estimated in this manner. [e]Estimated based on a log-linear fit to available lovastatin data for other doses. [f]Represents ezetimibe's incremental LDL-C-lowering efficacy as an add-on to statins.

LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; SD, standard deviation.

eTable 3. List of Comorbidities for Scenarios Modeling the American College of Cardiology Expert Consensus Decision Pathway Recommendations

#	**Comorbidity**
1	Diabetes mellitus
2	ASCVD event <3 months from index[a]
3	ASCVD event while on statin therapy[b]
4	Baseline LDL-C ≥190 mg/dL[c]
5	Hypertension
6	CKD stage III-V or dialysis

[a]Defined as: myocardial infarction, unstable angina with hospitalization, coronary revascularization, ischemic stroke, and CV death.
[b]Evidence of ASCVD event while on statin therapy limited to the 2-year baseline period before index. Concurrency of ASCVD event and statin treatment defined in a manner analogous to the methodology in eFigure 1, with the index date being replaced by the ASCVD event date. [c]Baseline LDL-C was back-calculated based on the sampled % LDL-C-lowering efficacy for an individual patient from the PDF as described in the methods section.

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; PDF, probability density function.

eTable 4. Comparison of Baseline Characteristics for the Simulation Cohort With ASCVD Populations From the NHANES Database and PINNACLE Registry

	NHANES 2011–2012[9] (N=488)	PINNACLE 2008–2012[10] (N=1,029,633)	Simulation Cohort (N=1,000,000)
Age, mean, years	64.9	65.7	66.4
Male, %	55.0	56.0	54.8
Diabetes, %	25.2	25.3	36.2
Hypertension, %	74.8	77.5	82.8
Heart failure, %	23.3	18.9	18.9
Baseline LDL-C, mean, mg/dL	103	N/A	94

LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey.

eTable 5. Estimated 95% CIs for the Proportion of ASCVD Patients Receiving Add-on PCSK9 Inhibitors in the Simulation for the Base Case

ASCVD Population Size	Lower Bound of 95% CI	Median	Upper Bound of 95% CI
50	6.0%	14.0%	24.0%
100	8.0%	14.0%	22.0%
500	11.0%	14.0%	17.0%
1,000	11.9%	14.0%	16.2%
5,000	13.1%	14.0%	15.0%
10,000	13.4%	14.0%	14.7%

The above estimates are based on a bootstrap methodology, where the entire simulation model was run repeatedly 1,000 times for a given ASCVD population size.

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

eTable 6. Distribution of LDL-C Levels Before and After Treatment Intensification in Base-Case Scenario A

Treatment	LDL-C Level, mg/dL*					
	<10	**10-25**	**25-40**	**40-55**	**55-70**	**>70**
Before Treatment Intensification						
No statin	<0.1	0.1	0.5	1.8	4.2	40.2
Statin only	<0.1	0.2	1.3	5.2	11.1	33.6
Statin + ezetimibe	<0.1	<0.1	0.1	0.2	0.5	0.9
Statin + alirocumab	NA	NA	NA	NA	NA	NA
All	0.1	0.3	1.8	7.3	15.7	74.8
After Treatment Intensification						
No statin	NA	NA	NA	NA	NA	NA
Statin only	0.1	1.9	8.5	19.7	37.0	NA
Statin + ezetimibe	<0.1	0.3	1.9	5.5	10.9	NA
Statin + alirocumab	0.1	3.1	3.7	3.3	3.1	0.7
All	0.2	5.3	14.1	28.7	51.0	0.7

Abbreviations: LDL-C, low-density lipoprotein cholesterol; NA, not applicable.
*Data in the table are expressed as percentage of patients.

eTable 7. Use of LLT With Full Treatment Intensification Across All Scenarios

Treatment	Pretreatment, % of Patients	Scenario, % of Patients*						
		B3	C	B1	A	D	B2	B4
Statin only	51.5	78.7	67.3	69.7	67.3	67.3	48.4	39.4
Statin + ezetimibe	1.7	15.2	25.0	17.4	18.7	18.8	30.7	32.9
Statin + alirocumab	NA	5.9	NA	11.6	NA	12.6	19.6	25.4
Statin + ezetimibe + alirocumab	NA	0.3	7.7	1.3	14.0	1.4	1.3	2.3

Abbreviation: LLT, lipid level–lowering treatment.

*Scenarios are ordered by increasing use of proprotein convertase subtilisin/kexin type 9 inhibitor therapy, and are described in the methods section.

eTable 8. Achieved LDL-C Levels for the Base Case Compared With Scenarios Representing Treatment With Only Alirocumab, 150 mg, or Evolocumab

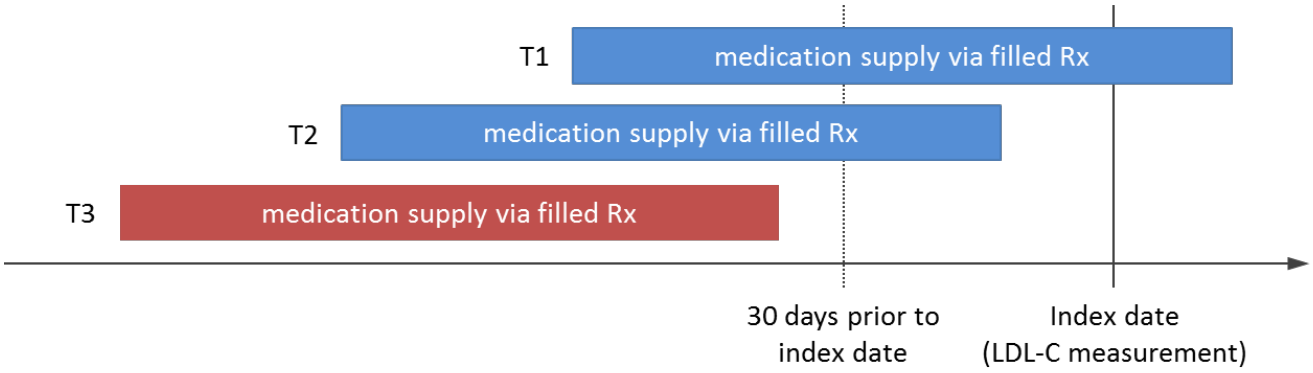
	Alirocumab Uptitration*	Alirocumab 150 mg Only†	Alirocumab 150 mg Only (LTS)‡	Evolocumab (FOURIER)§
≥70 mg/dL	5.4%	5.4%	6.1%	9.7%
<70 to 25 mg/dL	72.0%	47.9%	52.2%	49.9%
<25 to 10 mg /dL	21.8%	33.1%	31.4%	28.1%
<10 mg/dL	0.8%	13.6%	10.2%	12.2%

The above table is a comparison of achieved LDL-C levels in those receiving add-on PCSK9i (not achieving LDL-C <70 mg/dL with statins ± ezetimibe only) in the simulation, under scenarios explained in further detail below.

*Patients initiated on alirocumab 75 mg, with uptitration to alirocumab 150 mg, with efficacies based on on-treatment analyses from pooled ODYSSEY data (mean percent LDL-C reduction of 48.6% and 64.4%, respectively); †All patients initiated on alirocumab 150 mg with efficacy based on on-treatment analysis from pooled ODYSSEY data (mean percent LDL-C reduction of 64.4%), ‡All patients initiated on alirocumab 150 mg with efficacy based on ODYSSEY LONG TERM Study (LTS; Robinson et al. N Engl J Med. 2015;[11] mean percent LDL-C reduction of 61.9%), §All patients initiated on evolocumab with efficacy based on FOURIER study (Sabatine et al. N Engl J Med. 2017;[12] mean percent LDL-C reduction of 59%). The distribution of efficacy was estimated from reported summary measures for placebo and achieved LDL-C in the FOURIER trial.

LDL-C, low-density lipoprotein cholesterol.

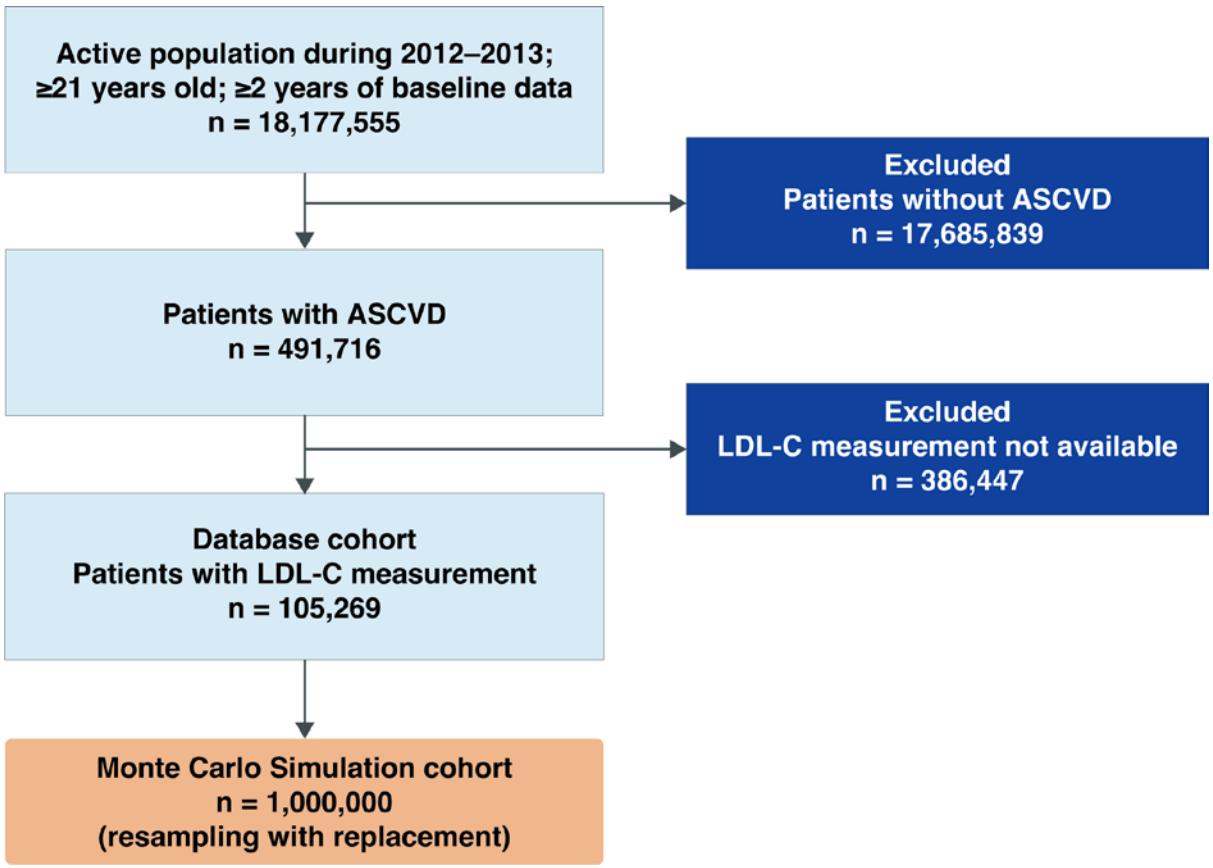
eFigure 1. Determination of Treatment Status as of the Index Date



Blue bars representing Treatment Status T1 and T2 (medication supply via filled Rx on or within 30 days prior to the index date) define the patient as being treated as of the index date. The red bar representing Treatment Status T3 (medication supply via filled Rx more than 30 days prior to the index date) defines the patient as not being treated as of the index date.

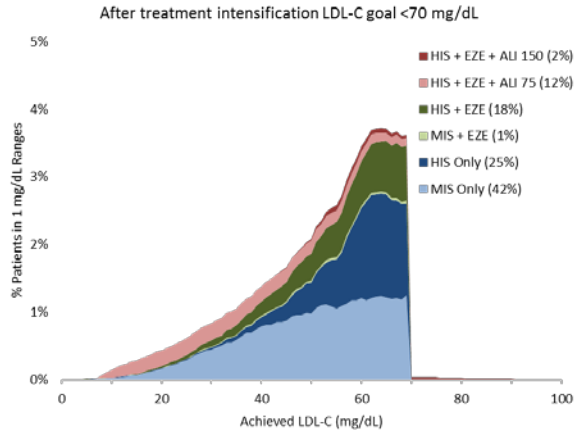
LDL-C, low-density lipoprotein cholesterol; Rx, prescription

eFigure 2. Flowchart of the Cohort Selection for the Study

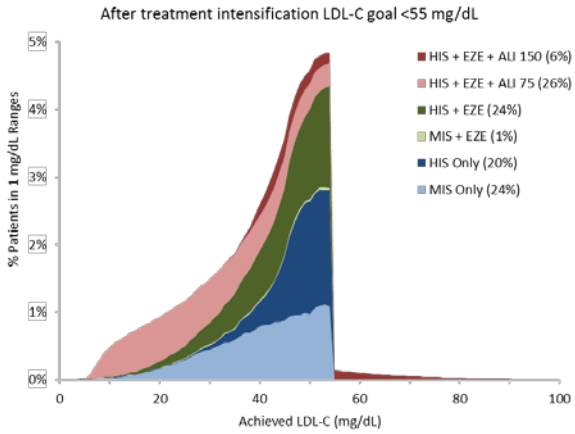


ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

eFigure 3. LLT Use and LDL-C Level Distribution After Treatment Intensification With an LDL-C Threshold of <55 mg/dL Compared With <70 mg/dL



%	<10	10-25	25-40	40-55	55-70	>70
No Statin	--	--	--	--	--	--
Statin Only	0.1	1.9	8.5	19.7	37.0	--
+ezetimibe	<0.1	0.3	1.9	5.5	10.9	--
+alirocumab	0.1	3.1	3.7	3.3	3.1	0.7
Total	0.2	5.3	14.1	28.7	51.0	0.7



%	<10	10-25	25-40	40-55	55-70	>70
No Statin	--	--	--	--	--	--
Statin Only	0.1	1.9	9.6	32.2	--	--
+ezetimibe	<0.1	1.1	6.3	17.5	--	--
+alirocumab	0.9	9.1	9.5	9.6	1.4	0.8
Total	1.0	12.1	25.3	59.2	1.4	0.8

The vertical axis in above graphs represents percent patients per 1 mg/dL range.

ALI 75, alirocumab 75 mg; ALI 150, alirocumab 150 mg; EZE, ezetimibe; HIS, high-intensity statin; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MIS, moderate- to low-intensity statin.

eMethods. Estimation of Sampling Weights for Bootstrap Sampling

Sampling weights were utilized in the bootstrap-sampling process in order to account for quantifiable differences in the characteristics of the database cohort relative to generalizable sources and allow for findings that are more representative of the overall US population. The sampling weights represented adjustment factors based on patient demographic and clinical profiles and were derived in the following manner: the database cohort was initially divided into mutually exclusive strata based on status representing presence of coronary heart disease (CHD; including recent acute coronary syndrome and other CHD), ischemic stroke, peripheral arterial disease (PAD), diabetes mellitus (DM), dichotomous age groups (21 to 64 years versus ≥65 years), and gender. An example of strata would be a profile representing male, aged ≥65 years, with CHD and DM.

Differential weights by these mutually exclusive strata were then estimated via an optimization algorithm to minimize the difference between estimated totals for aggregate categories (not mutually exclusive) representing CHD, ischemic stroke, PAD, DM, age groups, and gender, and their reported prevalence in the USA based on American Heart Association Heart Disease and Stroke Statistics[1] and the US Census Bureau[2]. Estimation of sampling weights via optimization methodology was conducted using Excel Solver. The methodology helped account for differential scaling by patient profiles and eliminated double counting due to overlap between conditions. Validation checks were then conducted by applying the estimated sampling weights at a patient level to the database cohort, multiplying by the ratio of US population to database N, summing across aggregate profiles (not mutually exclusive; e.g., CHD, aged ≥65 years, etc.), and comparing them back with the presumed inputs representing published data.

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