

SUPPLEMENTARY MATERIAL

Title: Cardiovascular Outcomes of Early LDL-C Goal Achievement in Very-High-Risk Patients with ASCVD

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Supplementary Table 1. Instrumental definitions for ASCVD index event (inclusion criteria) and outcome MACEs

Inclusion criteria	
Myocardial infarction	<i>Patients who met all of the following conditions after January 1, 2000:</i> 1. Patients with recorded ICD-10 diagnosis codes I21 (Acute myocardial infarction) I22 (Subsequent myocardial infarction) I23 (Certain current complications following acute myocardial infarction) 2. Hospitalized patients, including those admitted through the emergency room 3. Patients who underwent CAG or PCI within 7 days of diagnosis code registration date
Unstable Angina	<i>Patients who met all of the following conditions after January 1, 2000:</i> 1. Patients with recorded ICD-10 diagnosis codes I20.0 (Unstable Angina)

	2. Hospitalized patients, including those admitted through the emergency room 3. Patients who underwent CAG or PCI within 7 days of diagnosis code registration date
Stable Angina	<i>Patients who met all of the following conditions after January 1, 2000:</i> 1. Patients with recorded ICD-10 diagnosis codes I20.8 (Other forms of angina pectoris) I20.9 (Angina pectoris, unspecified) I24 (Other acute ischemic heart diseases) I25.2 (Old myocardial infarction) I25.3 (Aneurysm of heart) I25.4 (Coronary artery aneurysm and dissection) I25.5 (Ischemic cardiomyopathy) I25.8 (Other forms of chronic ischemic heart disease) I25.9 (Chronic ischemic heart disease, unspecified) 2. Hospitalized patients, including those admitted through the emergency room

	3. Patients who underwent CAG or PCI within 7 days of diagnosis code registration date
Asymptomatic coronary artery disease	<i>Patients who met all of the following conditions after January 1, 2000:</i> 1. Patients with recorded ICD-10 diagnosis codes I25.0 (Atherosclerotic cardiovascular disease, so described) I25.1 (Atherosclerotic heart disease) I25.6 (Silent myocardial ischemia) 2. CAG test results indicating moderate or severe findings, or CCTA test results with values of 50% or higher <i>Patients with coronary artery stenosis of 50% or greater as determined by CAG or CCTA, who also met other ASCVD conditions, were excluded</i>
Ischemic stroke/transient	<i>Patients who met all of the following conditions after January 1, 2000:</i> 1. Patients with recorded ICD-10 diagnosis codes

nt ischemic attack	I63 (Cerebral infarction) G45.9 (Transient cerebral ischemic attack, unspecified) <i>Excluding hemorrhagic stroke</i> I60 (Subarachnoid hemorrhage) I61 (Intracerebral hemorrhage) I62 (Other nontraumatic intracranial hemorrhage) <i>Excluding lacunar infarction stroke</i> Patients with the terms 'Lacunar', 'Small Vessel', or 'SVD' mentioned in medical notes concerning stroke subtype classification information were excluded 2. Patients with at least one brain CT or MR imaging results within 30 days of diagnosis code registration date
Symptomatic PAD	<i>Patients who met all of the following conditions after January 1, 2000:</i> 1. Patients with recorded ICD-10 diagnosis codes I70 (Atherosclerosis) I73 (Other peripheral vascular diseases)

	I74 (Arterial embolism and thrombosis) 2. Patients who had undergone surgical procedures for arterial thrombosis and thrombosis, peripheral vascular procedures, or vascular angiography within 7 days of diagnosis code registration date
Outcome variables	
All-cause mortality	<i>Patients who met all of the following conditions after index date:</i> 1. Patients with documented in-hospital death dates and cancer-related death dates recorded at the hospital
Cardiac enzyme (Criteria used for selecting the outcome variable, though not	<i>Patients who met all of the following conditions after index date:</i> 1. Patients who had Troponin-I or CK-MB tests measured from the time of admission, including those admitted through the emergency room, up until before the PCI procedure

the main outcome)	2. Patients with Troponin-I or CK-MB test results surpassing the upper limit of the reference range 3. In case of multiple tests for CAG, PCI or CABG on the same date of visit, the earliest test result was considered
Myocardial infarction	<i>Patients who met all of the following conditions after the index date:</i> 1. Patients with recorded ICD-10 diagnosis codes I21 (Acute myocardial infarction) I22 (Subsequent myocardial infarction) I23 (Certain current complications following acute myocardial infarction) 2. Patients with recorded notes for CAG, PCI or CABG procedures 3. Cardiac enzyme during hospitalization <i>Cases of MI occurring within 4 weeks from the baseline admission date were excluded</i>

Stroke and TIA	<i>Patients who met all of the following conditions after the index date:</i> 1. Patients with recorded ICD-10 diagnosis codes I63 (Cerebral infarction) G45.9 (Transient cerebral ischemic attack, unspecified) 2. Patients with a brain CT or MR imaging results within 30 days after the index date <i>Cases of stroke/TIA occurring within 4 weeks from the baseline admission date were excluded</i>
Hospitalization for unstable angina	<i>Patients who met all of the following conditions after the index date:</i> 1. Patients who satisfied either condition A or B: A. During the tracking period for outcome occurrence, if newly added ICD-10 diagnosis included the following: I20.0 (Unstable angina) I24.0 (Coronary thrombosis not resulting in myocardial infarction)

	I24.9 (Acute ischemic heart disease, unspecified) <i>Excluding chronic stable angina</i> I25 (Chronic ischemic heart disease) B. In patients with predefined MI, if the maximum measured Troponin-I value during the outcome tracking period was less than 1.5 2. Patients with recorded notes for CAG, PCI or CABG procedures 3. Cardiac enzyme during hospitalization
Coronary Revascularization (PCI or CABG)	<i>Patients who met all of the following conditions after the index date:</i> 1. Patients in whom PCI or CABG procedures were conducted

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAG, coronary angiogram; CCTA, coronary computed tomography angiography; CK-MB, creatine kinase-MB; CT, computed tomography; ICD-10, International Classification of Diseases 10th Revision; MACE, major adverse cardiovascular event; MI, myocardial infarction; MR,

magnetic resonance; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Supplementary Table 2. ICD-10 codes for comorbidities and conditions

Condition	ICD-10 codes/operational definitions
Chronic Kidney Disease	N18 (chronic kidney disease) <i>or</i> eGFR equal to or lower than 90
Diabetes mellitus	E10–E14 (Diabetes mellitus) <i>or</i> HbA1c equal to or greater than 6.5%
Metabolic Syndrome	Individuals satisfying two or more of the following criteria were included: 1. Triglycerides equal to or greater than 150. 2. For males: HDL levels less than 40; for females: HDL levels less than 50. 3. SBP equal to or greater than 130, or DBP equal to or greater than 80. 4. Glucose equal to or greater than 100
Hypertension	I10 (Essential (primary) hypertension)

	I11 (Hypertensive heart disease) I12 (Hypertensive renal disease) I13 (Hypertensive heart and renal disease) I15 (Secondary hypertension) <i>or</i> Individuals with a history of prescription for: 1. Beta-blocker 2. RAAS inhibitor 3. Calcium channel blocker
Congestive heart failure	I42 (Cardiomyopathy) I43 (Cardiomyopathy in diseases classified elsewhere) I50 (Heart failure)
Atrial fibrillation disease	I48 (Atrial fibrillation and flutter)
Cancer	C00–C97 (Malignant neoplasms)
Rheumatoid arthritis	M05 (Rheumatoid arthritis with rheumatoid factor) M06 (Other rheumatoid arthritis)

Psoriasis	L40 (Psoriasis)
HIV	B20–B24 (Human immunodeficiency virus [HIV] disease) <i>or</i> Code for Rare and Intractable Disease Special Calculation Exception: V103 (HIV disease)
Hypothyroidism	E02 (Subclinical iodine-deficiency hypothyroidism) E03 (Other hypothyroidism) E06.3 (Autoimmune thyroiditis)
Hyperthyroidism	E05 (Thyrotoxicosis [hyperthyroidism])
Liver Disease	B18 (Chronic viral hepatitis) B19 (Unspecified viral hepatitis) K70–K77 (Diseases of liver)

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density cholesterol; HIV, human immunodeficiency virus; ICD-10, International Classification of Diseases 10th Revision; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

Supplementary Table 3. Medication list

Drug class	Active ingredient(s) in medication
Statin	Atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin calcium, pravastatin sodium, rosuvastatin, simvastatin
Ezetimibe	Ezetimibe
Fibrate	Bezafibrate, fenofibrate, gemfibrozil
Niacin	Acipimox
Cholestyramine	Cholestyramine resin
PCSK9 inhibitor	Aliroumab, evolocumab
Aspirin	Aspirin
P2Y12 inhibitor	Clopidogrel, prasugrel, ticagrelor, ticlopidine hydrochloride (HCl)
Beta-blocker	Arotinolol HCl, atenolol, bevantolol, bisoprolol fumarate, carvedilol, celiprolol HCl, nebivolol, propranolol, propranolol HCl, s-atenolol

RAAS inhibitor	Alacepril, benazepril, candesartan cilexetil, captopril, cilazapril, enalapril, enalapril maleate, eprosartan mesylate, fimasartan, fimasartan potassium, fosinopril, imidapril, irbesartan, lisinopril, losartan, moexipril hydrochloride, olmesartan, olmesartan medoxomil, perindopril tert-butylamine, quinapril, ramipril, telmisartan, temocapril, valsartan, zofenopril, zofenopril calcium
Calcium channel blocker	Amlodipine, benidipine, cilnidipine, diltiazem HCl, felodipine, lacidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, s-amlodipine
Estrogen/hormone replacement therapy	Chlormadinone acetate, estradiol valerate, hydroxyprogesterone caproate, medroxyprogesterone acetate, megestrol acetate, raloxifene HCl

Abbreviations: HCl, hydrochloride; PCSK9, proprotein convertase subtilisin/kexin type 9; RAAS, renin-angiotensin-aldosterone system.

Supplementary Table 4. Crude incidence rate and hazard ratios of MACE associated with early LDL-C goal satisfaction in patient subgroups

LDL-C groups	Number of events	PY	Crude incidence rate (per 100 PY)	Crude HR (95% CI)	Adjusted HR¹ (95% CI)
Stable angina subgroup					
<i>Primary endpoint</i>					
Early target LDL-C group	268	11,082.6	2.42	0.83 (0.72, 0.96)	0.84 (0.72, 0.97)
Non-early target LDL-C group	633	22,177.2	2.85	1.00 (Reference)	1.00 (Reference)
<i>Secondary endpoint</i>					
Early target LDL-C group	129	11,828.5	1.09	0.82 (0.66, 1)	0.81 (0.66, 1)

Non-early target LDL-C group	329	24,129.3	1.36	1.00 (Reference)	1.00 (Reference)
Asymptomatic CAD subgroup					
<i>Primary endpoint</i>					
Early target LDL-C group	115	4,100.4	2.80	1.06 (0.85, 1.32)	1.04 (0.82, 1.31)
Non-early target LDL-C group	242	9,170.6	2.64	1.00 (Reference)	1.00 (Reference)
<i>Secondary endpoint</i>					
Early target LDL-C group	66	4,403.2	1.50	1 (0.75, 1.34)	0.98 (0.72, 1.32)
Non-early target LDL-C group	149	9,783.1	1.52	1.00 (Reference)	1.00 (Reference)
IS/TIA subgroup					

<i>Primary endpoint</i>					
Early target LDL-C group	341	2,241.3	15.21	1.12 (0.99, 1.27)	1.05 (0.92, 1.19)
Non-early target LDL-C group	895	7,316.8	12.23	1.00 (Reference)	1.00 (Reference)
<i>Secondary endpoint</i>					
Early target LDL-C group	332	2,285.1	14.53	1.14 (1.01, 1.3)	1.08 (0.95, 1.24)
Non-early target LDL-C group	862	7,567.4	11.39	1.00 (Reference)	1.00 (Reference)

Footnote: ¹Adjusted for age, sex, diabetes mellitus, smoking, aspirin or P2Y12

inhibition, beta-blockers, RAAS inhibitors, chronic kidney disease, statin use (3 groups), and non-statin lipid-lowering treatment.

Abbreviations: CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; IS, ischemic stroke; LDL-C, low density lipoprotein cholesterol; MACE, major adverse cardiovascular event; PY, patient years; TIA, transient ischemic attack.

Supplementary Table 5. Sensitivity analysis outcomes (IS/TIA subgroup)

LDL-C groups	Number of events	PY	Crude incidence rate (per 100 PY)	Crude HR (95% CI)	Adjusted HR¹ (95% CI)
Primary MACE risk among subtypes of IS/TIA					
Large artery atherosclerosis	454	2,644.7	17.17	0.89 (0.73, 1.08)	0.90 (0.74, 1.11)
Cardioembolic	78	745.1	10.47	0.91 (0.55, 1.51)	0.92 (0.53, 1.58)
Other undetermined etiology	128	991.8	12.91	1.22 (0.83, 1.79)	1.18 (0.79, 1.75)
Primary MACE risk among redefined stroke populations					
<i>Excluded cancer patients</i>					
Early target LDL-C group	298	2,060.2	14.46	1.15 (1, 1.31)	1.1 (0.96, 1.27)

Non-early target LDL-C group	764	6,763.3	11.30	1.00 (Reference)	1.00 (Reference)
<i>Included lacunar stroke patients</i>					
Early target LDL-C group	411	3,166.9	12.98	1.07 (0.95, 1.2)	1.03 (0.91, 1.15)
Non-early target LDL-C group	1046	9,303.7	11.24	1.00 (Reference)	1.00 (Reference)
Safety endpoint (Hemorrhagic stroke)					
Early target LDL-C group	15	3,183.1	0.47	0.93 (0.51, 1.66)	1.09 (0.57, 2.09)
Non-early target LDL-C group	49	10,288.6	0.48	1.00 (Reference)	1.00 (Reference)
Differential LDL-C goal cut-offs					
<100 mg/dL	1,057	7,689.3	13.75	1.23 (1.05, 1.45)	1.14 (0.96, 1.36)
≥100 mg/dL	179	1,868.7	9.58	1.00 (Reference)	1.00 (Reference)

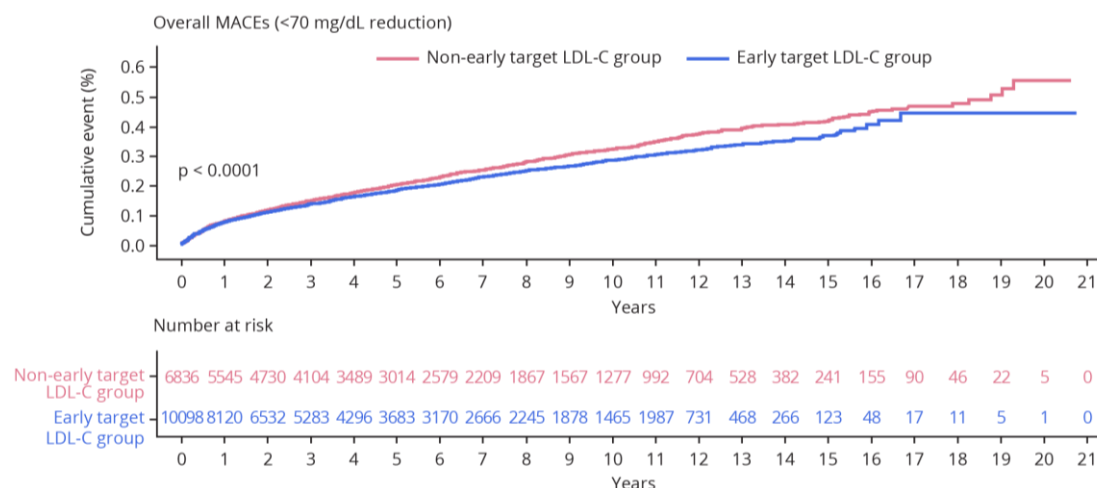
≥50% reduction and <100 mg/dL	343	2,469.3	13.89	1.08 (0.95, 1.22)	1.05 (0.92, 1.19)
Others	893	7,088.7	12.60	1.00 (Reference)	1.00 (Reference)

Footnote: ¹Adjusted for age, sex, diabetes mellitus, smoking, aspirin or P2Y12

inhibition, beta-blockers, RAAS inhibitors, chronic kidney disease, statin use (3 groups), and non-statin lipid-lowering treatment.

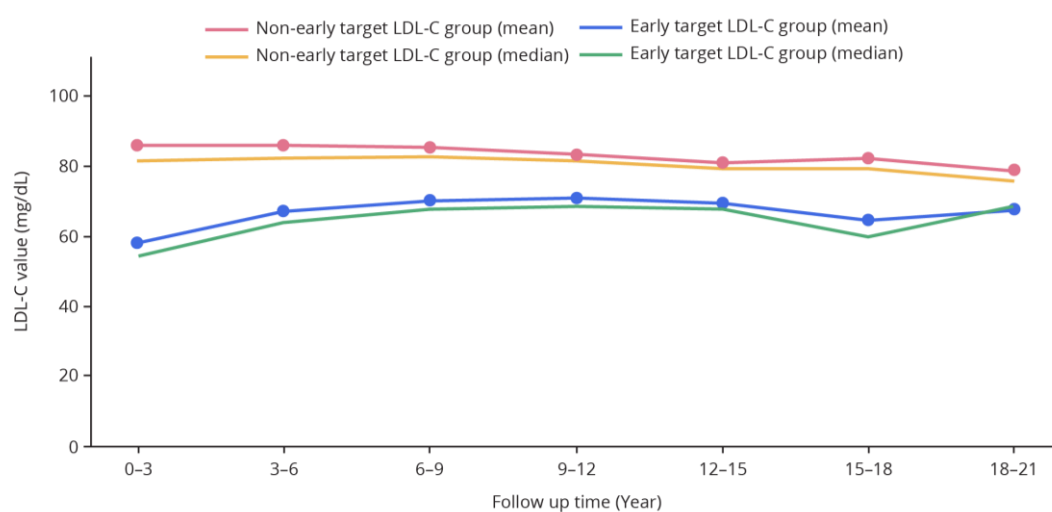
Abbreviations: HR, hazard ratio; IS/TIA, ischemic stroke/transient ischemic attack; LDL-C, low density lipoprotein cholesterol; MACE, major adverse cardiovascular event; PY, patient years; RAAS, renin-angiotensin-aldosterone system.

Supplementary Figure 1. Comparison of cumulative incidence of primary composite MACEs <70 mg/dL between the early target LDL-C group and the non-early target LDL-C group



Abbreviations: LDL-C, low density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

Supplementary Figure 2. Long-term LDL-C measurements for the early target LDL-C group and the non-early target LDL-C group



Abbreviations: LDL-C, low density lipoprotein cholesterol.