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Clinical and Economic Analysis of Lipid Goal Attainments in Chinese Patients with Acute Coronary Syndrome Who Received Post-Percutaneous Coronary Intervention

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Aim: The recommended low-density lipoprotein cholesterol (LDL-C) levels of the guideline may be appropriate for Caucasian patients but not for other ethnic groups.

Methods: A cohort study was conducted in Hong Kong, and acute coronary syndrome (ACS) patients who received percutaneous coronary intervention (PCI) between 2005 and 2015 were enrolled. The primary outcomes of interest were the total cost of care and cardiovascular-related cost during one-year follow-up. The cost difference by lipid goal attainments was analyzed by Poisson regression with multivariate treatment effects. The clinical outcomes achieved by lipid goal attainments in terms of major adverse cardiovascular events were analyzed by multivariate Cox regression.

Results: Among the 4638 patients, 79.50%, 48.64%, and 36.14% attained the LDL-C goals of <2.6, <2.0, and <1.8 mmol/L for one year, respectively. Only about 16% patients achieved the $\geq 50\%$ reduction from baseline. None of these lipid goals was associated with a significant reduction in the total cost of care. We only identified the clinical benefits associated with the lipid goal of <2.6 mmol/L. Other more stringent lipid goals seemed to bring a significant economic burden on cardiovascular-related cost, but their clinical benefits were uncertain.

Conclusions: Lowering LDL-C to achieve the guideline-recommended target levels for post-PCI ACS patients may lead to fewer cardiovascular events, but it may not necessarily lead to economic benefits within one year of follow-up.

Key words: LDL-C, Cost analysis, Chinese, Cardiovascular events, Cost of care

Introduction

Epidemiologic studies and clinical trials constantly suggest that lipid management could reduce the risk of recurrent cardiovascular events[1-3]. In light of existing evidence, the United States[4, 5] and European[6, 7] guidelines recommended the lipid goals of 2.6 mmol/L (100 mg/dL) and <1.8 mmol/L (70 mg/dL) for high-risk patients, including those with prior history of coronary heart disease (CHD). The 2013 American College of Cardiology/American Heart Association guidelines recommended a low-density lipoprotein cholesterol (LDL-C) treatment target of $\geq 50\%$ reduction[8]. However, most clinical trial data were obtained from Caucasian patients[5, 8-12], and the concept of therapeutic LDL-C targets and proper use of lipid-lowering drugs may not be identical between Western and Asian populations[13]. A rapidly growing body of literature from Asian countries is challenging the "lower is better" hypothesis[14-19]. The main find-

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ing[20] from 13473 acute myocardial infarction (MI) patients in a large-scale, prospective, multicenter Korean MI registry found that patients who achieved the target LDL-C level of <70 mg/dL did not have lower risks for cardiovascular events regardless of statin therapy than patients who did not achieve the target LDL-C. The large-scale Japanese Coronary Revascularization Demonstrating Outcome Study in Kyoto[17] investigated 14866 patients who underwent coronary revascularization and found that the risk for major adverse cardiovascular events (MACEs) was significantly higher in the ≥ 120 mg/dl group than in patients with lipid goal levels between 80−99 mg/dL; however, the risk for MACEs was not significantly lower in the <80 mg/dL group. Another population-based study[14] using data from 31619 ischemic heart disease patients in Israel concluded that patients with LDL-C levels of 70−100 mg/dL had lower risks of MACEs than those with LDL-C levels at 100−130 mg/dL; however, they failed to observe any additional benefit in the patient group achieving LDL-C <70 mg/dL. According to our previous research findings[21, 22], we failed to identify the clinical benefits associated with the lipid goal of <1.8 mmol/L (70 mg/dL) in Chinese patients. There was an intense debate with regard to the Chinese guidelines on whether the recommended LDL-C reduction target for the high-risk atherosclerotic cardiovascular disease group should be set at LDL-C <1.8 mmol/L (70 mg/dl) or <2.0 mmol/L (80 mg/dl)[23, 24].

In real-world clinical practice, many patients fail to achieve their lipid goals, and the contributing factors vary between individuals, such as use of low doses, limited drug effectiveness, and poor drug adherence[25-27]. A retrospective cohort study in 29 countries across Asia, Western Europe, Eastern Europe, the Middle East, and Africa on 35121 patients taking lipid-lowering drugs found that LDL-C goal attainment was suboptimal worldwide, particularly in patients with high and very high cardiovascular risks[27]. Treating patients on the basis of guideline-recommended cholesterol levels or even below would lead to higher economic burden[28]. The Return on Expenditure Achieved for LIpid Therapy (REALITY) study in Europe[29] was among the first to study the association between attainment of treatment goals and lipid-lowering therapy. In Swedish patients, they found that those attaining the treatment goal of <3.0 mmol/L during the first year had a 28% higher cost of care[28] than nonachievers, but the cost of cardiovascular-related inpatient care in lipid goal achievers was 40% lower than nonachievers after 2–3 years. Compared with the ample pharmacoepidemiologic studies involving Caucasian patients, the economic burden of failure in lipid goal attainments in Asian countries[30] is not well addressed in literature. The REALITY study in Asia[31, 32] focused on the evaluation of the lipid goal attainment rate but left the question of economic burden unanswered.

Aim

The aim of the current research was to fill the knowledge gap regarding the following: 1) the lipid goal attainments (namely, the lipid goals of <2.6 mmol/L, <1.8 mmol/L, <2.0 mmol/L, and ≥ 50% LDL-C reduction) in Hong Kong; 2) the association of lipid goal attainments and MACEs; 3) the short- (one year) and long-term (five years) costs of failure in achieving the lipid goals, including the total cost of care and cardiovascular-related cost per person (among which the one-year cost was evaluated as the primary outcome, complemented with a sensitivity analysis on the five-year cost).

Methods

In an attempt to provide such data, we performed a noninterventional secondary cohort analysis of post-percutaneous coronary intervention (PCI) acute coronary syndrome (ACS) patients to assess the costs and consequences of lipid goal attainments under real-life conditions in Hong Kong, China. The current study was based on electronic health records (EHRs) from the Hong Kong Hospital Authority Clinical Data Analysis and Reporting System (CDARS) database.

Our study population consisted of all Chinese ACS patients (identified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) diagnosis codes of 411 and 410) aged above 21 years old who received a first documented PCI in the inclusion period between January 1, 2005, and November 30, 2015 from an acute public hospital, the PCI-capable hospital in the New Territories East Cluster of Hong Kong. The study population was continuously enrolled in CDARS for at least one year after their index PCI procedure and had at least one cholesterol measurement within the first-year follow-up. We defined MACEs in the current study as all-cause death, MI, unstable angina (UA), stroke, and revascularization[33, 34] from 30 days post-PCI to the one-year endpoint and identified MACEs by death records and ICD-9 CM codes of 410.x (MI); 411.x (UA); 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, and 434.91 (stroke); 36.01, 36.02, 36.05, 36.06, and 36.09 (PCI); and 36.1 (coronary artery bypass graft). If the patient died within one month after the PCI, he/she was excluded from

the analysis regarding the association of MACEs and the latest LDL-C goal before MACE because recurrent events that occurred within the first month might be largely related to the index PCI procedure[35-40]. The lipid goals under investigation were < 1.8 mmol/L (70 mg/dL), 2.6 mmol/L (100 mg/dL), < 2.0 mmol/L (80 mg/dl), and ≥ 50% reduction from baseline. The endpoint lipid goal at the one-year follow-up and the latest lipid goal before the first MACE were studied separately. The latest LDL-C measurement before the MACE was taken from the most recent laboratory results prior to the first MACE day, but it might not be necessarily the endpoint lipid measurement at the one-year follow-up. Considering that the measurement of LDL-C levels at the index ACS event was not a routine clinical practice in Hong Kong, the baseline LDL-C measurements were extracted from the laboratory results nearest to the index PCI procedure (within the period between 180 days prior to the index PCI day and 365 days after the index day). For patients who only had one laboratory result during the index day and after 365 days but had no prior LDL-C measurement between -180 and 0 days, their baseline LDL-C levels could be missing. The patients' prior disease history, including comorbidities of diabetes and hypertension, and prior cardiovascular disease (CVD) history were obtained from the ICD-9 CM codes in the system in the past six months prior to the index PCI procedure day.

The economic evaluation of interest was the total (direct) cost of care and the cardiovascular-related (inpatient and outpatient) cost from the provider perspective. The total cost of care included the costs for inpatient care, outpatient visits, revascularization procedures, lipid-lowering drugs, and laboratory tests (lipid tests) in the public sectors of Hong Kong. The cardiovascular-related cost in this evaluation was defined as the sum of all the costs of the first-year management of the patient for any cardiovascular-related events (identified by ICD-9 CM code 390. xx-459.xx), including inpatient hospitalization, accident and emergency department admission, and outpatient visits for cardiovascular conditions. The cost for inpatient care was estimated using the length of stay in the hospital from the CDARS and standardized daily cost. The estimation of in-hospital care cost by length of stay and cost per hospital bed day was a common practice by the World Health Organization[42], and the unit cost (cost per hospital bed day) was found in the Hong Kong Government Gazette.

Cost items were also available on all contacts with outpatient hospital services and each attendance at a general clinic would cost HKD 385 (USD 49.4) locally. The unit costs of all direct medical items were based on the 2013 Hong Kong Government Gazette (an official source for medical charges in local public hospitals[43]). All costs were estimated in Hong Kong dollars and were converted to US dollars by using the conversion rate USD 1 = HKD 7.8 as of March 9, 2018[44], when applicable.

Statistical Methods

Descriptive statistics were used to analyze the demographic data, baseline characteristics, and lipid profile parameters (**Table 1**). In **Supplementary Table 1**, the crude cost items of interest are presented. To identify the influential contributors to the total cost of care, **Supplementary Table 1** presents the rundown listing of all the target cost items per person, which include the following: the total cost of care, cardiovascular-related inpatient cost, cardiovascular-related outpatient cost, cardiovascular-related cost (including inpatient and outpatient costs), cost of lipid-lowering therapy (statins and other lipid-lowering drugs), and other management cost (deducting the cardiovascular-related cost from total cost of care). The differences in the abovementioned detailed costs between lipid goal achievers and nonachievers were examined using the treatment effect estimation of multivalued treatment effects[45, 46] by adjusting for available potential confounders such as age, sex, diabetes, hypertension, and prior CVD history (**Tables 2** and **3** for "analyzed sample," **Supplementary Table 2** and **Supplementary Table 3** for the "full sample," **Supplementary Table 4** for cardiovascular-related inpatient cost and cardiovascular-related outpatient cost). Considering that the costs were all positive and were not necessarily following the normality, we used the Poisson option inside the outcome model specification[47]. Multivariable Cox regression analyses (**Table 4**) were performed to assess the associations of MACEs with the LDL-C goal attainments before MACE after adjusting for age, sex, diabetes, hypertension, and prior CVD history.

Sensitivity Analysis

Two sensitivity analyses were conducted to test the robustness of our results. As noticed in the early literature[28], patients that reached the lipid goals showed a trend of cost reductions over time. To explore if the costs significantly decreased after one year after the index day, we also examined the average five-year total cost of care among the patients who underwent the index PCI between January 1, 2005, and November 30, 2010, and completed the five-year follow-up. The adjusted differences in the total cost of care and cardiovascular-related cost for this patient group could be found in **Table 5** and **Supplementary Table 5**. In absolute terms, the baseline LDL-C levels

Table 1. Descriptive of the subjects

	n (Column %)
Total	4638
Mean age (SD)	70.23 (10.99)
Sex: Male	3571 (76.99)
Previous CVD% (with respective ICD-9 CM code)	2223 (47.93)
Hypertensive disease (401-405)	451 (9.72)
Ischemic heart disease (410-414)	1278 (27.55)
Coronary Artery Disease (414)	36 (0.78)
CVA, stroke (434.91)	13 (0.28)
Atrial fibrillation (427.31)	46 (0.99)
Heart failure (428)	147 (3.17)
Carotid artery stenosis/occlusion (433)	3 (0.06)
Cerebral atherosclerosis/ischemic cerebrovascular disease (437)	6 (0.13)
Others	243 (5.24)
Comorbidity: Hypertension	901 (19.43)
Comorbidity: Diabetes	795 (17.14)
Baseline cholesterol	4182
Mean Total (SD)	4.65 (1.18)
Mean LDL-C (SD)	2.77 (1.05)
Mean HDL-C (SD)	1.16 (0.32)
Mean triglycerides (SD)	1.6 (0.97)
Baseline LDL-C category	4182
＜1.8mmol/L	675 (16.14)
1.8-2.6mmol/L	1328 (31.76)
＞2.6mmol/L	2179 (52.10)
LDL-C reduction ≥ 50% before MACE	633 (15.14)
LDL-C reduction ≥ 50% at one-year	667 (15.95)
Endpoint LDL-C goal attainments	
1.8 mmol/L	1676 (36.14)
2.0 mmol/L	2256 (48.64)
2.6 mmol/L	3687 (79.50)
Endpoint LDL-C	4638
＜1.8 mmol/L	1676 (36.14)
1.8-2.6 mmol/L	2011 (43.36)
＞2.6 mmol/L	951 (20.5)
Latest LDL-C goal attainments before MACE	
1.8 mmol/L	1642 (35.50)
2.0 mmol/L	2214 (47.87)
2.6 mmol/L	3644 (78.79)
Latest LDL-C category before MACE	4625
＜1.8 mmol/L	1642 (35.50)
1.8-2.6 mmol/L	2002 (43.29)
＞2.6 mmol/L	981 (21.21)
MACE	528 (11.38)
Recurrent PCI between 30 and 365 days	254 (5.56)
Recurrent ACS between 30 and 365 days	176 (3.75)
Stroke	31 (0.69)
Death between 30 and 365 days	54 (1.08)
Death within the first 30 days after index PCI	13 (0.30)

MACE, major adverse cardiovascular events; CVA, cerebrovascular accident; LDL-C, low-density lipoprotein cholesterol; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CDARS, clinical data analysis and reporting system; ICD-9 CM, International Classification of Diseases, Ninth Revision, Clinical Modification; CVD, cardiovascular diseases; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation.

seemed to largely influence the economic and clinical outcomes in terms of their initial effect on physicians' judgments. Therefore, a sensitivity analysis was conducted among patients with baseline LDL-C beyond 2.6 mmol/L to test the robustness of our results (**Tables 2**, **3**, and **4**).

All analyses were performed using Stata 14 (Stata Corporation Lp, College Station, TX). All the patients' information was de-identified in the database. The study was approved by the Joint Clinical Research Ethics Committee of The Chinese University of Hong Kong and New Territories East Cluster of Hong Kong, and the protocol was compliant with the Declaration of Helsinki.

Results

Our analysis involves 4638 patients (mean age ± standard deviation (SD): 70.23 ± 10.99 years) who have at least one LDL-C measurement via one-year follow-up (**Table 1**); these patients are referred to as the "full sample" in **Supplementary Tables 1**, **2**, **3**, and **4**. There were 76.99% males, 19.43% of which were hypertensive, 17.14% were diabetic patients, and 47.93% had previous CVD. At the one-year endpoint, approximately 80% and 50% of patient reached the LDL-C goals of 2.6 and 2.0 mmol/L, respectively, and 36.14% were well controlled under 1.8 mmol/L. Among the 4182 patients who had available baseline LDL-C levels, 52.10% had their initial LDL-C levels above 2.6 mmol/L, and only 15.95% achieved ≥ 50% reduction. Among all patients, 515 (11.10%) had at least one incidence of MACE between 30 and 365 days after the index procedure. Thirteen patients died within the first month, and these patients were excluded when we analyzed the latest lipid goal attainment before MACE. After the exclusion, 4625 patients comprised the "analyzed sample" (**Tables 2**, **3**, and **4**).

Supplementary Table 1 reports the crude costs by lipid goal attainments at the one-year endpoint and before their first MACE between the 30th and 365th day, respectively. From the observed crude numbers of **Supplementary Table 1**, the lipid goal achievers of < 1.8 mmol/L carry the highest total cost of care compared with the nonachievers, and the lipid category of 1.8–2.6 mmol/L seems to be more desirable in terms of costs. The adjusted cost differences in the total cost of care and cardiovascular-related cost are presented in **Tables 2** and **3** (**Supplementary Tables 2** and **3** for the results of the "full sample") and were controlled for baseline characteristics. After this adjustment, none of the lipid goal attainments of < 2.6 mmol/L, < 2.0 mmol/L, < 1.8 mmol/L, or ≥ 50% reduction was associated with any reduction in the total cost of care during the one-year follow-up. After excluding the cardiovascular-related management costs (in **Table 3**), the lipid goal attainment of 2.6 mmol/L either at the one-year endpoint or before MACE seems to be a cost-saving strategy, particularly the category of 1.8–2.6 mmol/L. This finding could imply that among all the detailed cost items, the cardiovascular-related management cost, particularly the cardiovascular-related inpatient cost (shown in **Supplementary Table 4**), is the most affected by the lipid goal attainments. Assuming that patients who could attain the lipid goals remarkably differed in baseline characteristics from those who could not, we adjusted for all the available covariates and performed a sensitivity analysis among high-risk patients with LDL-C > 2.6 mmol/L at baseline. We constantly find that lowering patients' LDL-C levels to a more stringent goal leads to an increase in cardiovascular-related cost (**Table 2**). Upon realizing that the endpoint lipid goal attainment (at the one-year endpoint) was not necessarily the latest lipid goal before the MACE, we evaluated the cost difference by using the latest lipid goal attainments before MACE (**Table 2**) and the cost difference by lipid goal attainment at the one-year endpoint (**Supplementary Table 2**). It was still noted that the patients attaining more stringent lipid goals had higher costs in cardiovascular-related management. After excluding the cardiovascular-related (inpatient and outpatient) costs, both LDL-C goal attainment groups of < 2.6 and < 2.0 mmol/L could substantially increase the cost savings (**Table 3**). We expected that those having LDL-C levels below each lipid goal would be on more intensive lipid treatments than those above the goal, and this situation would contribute to the increased cost of reaching a lower level of LDL-C. However, from this current observation, the cardiovascular-related inpatient cost (**Supplementary Table 4**) is a more influential contributor to the total cost of care than the intensive lipid treatment cost (**Table 3**). In **Table 5**, among 2686 patients with a complete 5-year follow-up, no significant differences in any cost items between lipid goal achievers and nonachievers were observed starting from the second year.

Table 4 shows the results from the multivariate Cox regression analysis of the first occurrence of MACE. Separate regressions were performed for lipid goal attainments before MACEs in the analyzed sample and in the patient group with baseline LDL-C above 2.6 mmol/L. The LDL-C goal of < 2.6 mmol/L was associated with a reduction in MACE but not the goals of 1.8 mmol/L, 2.0 mmol/L, and ≥ 50% reduction. Lowering the LDL-C level attainment from 2.6 mmol/L to 1.8 mmol/L did not improve the clinical

Table 2. Adjusted cost difference in the total cost of care and cardiovascular-related cost by lipid goal attainments

		Total cost of care (HKD)			Cardiovascular-related cost (HKD)		
	N	Adjusted Coefficient*	(95% Confidence Interval)	*p*-value	Adjusted Coefficient*	(95% Confidence Interval)	*p*-value
Analyzed sample							
Latest LDL-C before MACE achieving the goal of 2.6 mmol/L	4625						
Not at goal	947	Ref			Ref		
At goal	3678	-4994.14	(-13597.38, 3609.10)	0.255	4846.70	(1355.73, 8337.66)	0.007
Latest LDL-C before MACE achieving the goal of 1.8 mmol/L	4625						
Not at goal	2950	Ref			Ref		
At goal	1675	1385.40	(-5911.87, 8682.68)	0.710	3414.99	(-487.42, 7317.40)	0.086
Latest LDL-C before MACE achieving the goal of 2.0 mmol/L	4625						
Not at goal	2374	Ref			Ref		
At goal	2251	-1893.70	(-8656.95, 4869.55)	0.583	3565.83	(-25.09, 7156.76)	0.052
Latest LDL-C before MACE achieving the reduction of ≥ 50%	4180						
Not at goal	3547	Ref			Ref		
At goal	633	7485.89	(-5483.54, 20455.32)	0.258	5861.97	(-1088.23, 12812.17)	0.098
Latest LDL-C before MACE category	4625						
＞2.6 mmol/L	947	Ref			Ref		
1.8-2.6 mmol/L	2003	-6770.82	(-15760.27, 2218.63)	0.140	3918.44	(-26.17, 7863.05)	0.052
＜1.8 mmol/L	1675	-2937.15	(-12802.03, 6927.73)	0.560	6005.66	(1690.23, 10321.08)	0.006
Among those baseline LDL-C ＞2.6 mmol/L	2177						
Latest LDL-C before MACE achieving the goal of 2.6 mmol/L	2177						
Not at goal	585	Ref			Ref		
At goal	1592	-9274.95	(-20211.78, 1661.87)	0.096	3009.52	(-1782.19, 7801.23)	0.218
Latest LDL-C before MACE achieving the goal of 1.8 mmol/L	2177						
Not at goal	1535	Ref			Ref		
At goal	642	-960.01	(-11895.72, 9975.70)	0.863	3486.48	(-2322.27, 9295.23)	0.239
Latest LDL-C before MACE achieving the goal of 2.0 mmol/L	2177						
Not at goal	1275	Ref			Ref		
At goal	903	-2112.09	(-11778.81, 7554.62)	0.668	5159.30	(-309.52, 10628.12)	0.064
Latest LDL-C before MACE achieving the reduction of ≥ 50%	2177						
Not at goal	1603	Ref			Ref		
At goal	574	7611.84	(-4473.77, 19697.46)	0.217	6751.11	(-297.54, 13799.76)	0.060
Latest LDL-C before MACE category	2177						
＞2.6 mmol/L	585	Ref			Ref		
1.8-2.6 mmol/L	950	-10335.72	(-21762.04, 1090.59)	0.076	2157.93	(-3304.57, 7620.44)	0.439
＜1.8 mmol/L	642	-7167.12	(-20738.06, 6403.83)	0.301	4521.06	(-1791.19, 10833.30)	0.160

MACE, major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; HKD, Hong Kong dollars; Ref, reference.
*Adjusted for age, sex, diabetes, hypertension, and prior cardiovascular history

Table 3. Adjusted cost difference in other management cost and the cost of lipid-lowering therapy by lipid goal attainments

		Other management cost (defined as total cost of care excluding the cardiovascular-related (inpatient and outpatient) cost) (HKD)				Cost of lipid-lowering therapy (statin and other lipid-lowering drugs) (HKD)			
	N	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value
Analyzed sample									
Latest LDL-C before MACE achieving the goal of 2.6 mmol/L	4625								
Not at goal	947	Ref				Ref			
At goal	3678	-9937.53	-17166.93	-2708.14	0.007	66.43	-35.63	168.50	0.202
Latest LDL-C before MACE achieving the goal of 1.8 mmol/L	4625								
Not at goal	2950	Ref				Ref			
At goal	1675	-2252.01	-7796.22	3292.19	0.426	272.35	183.19	361.51	<0.001
Latest LDL-C before MACE achieving the goal of 2.0 mmol/L	4625								
Not at goal	2374	Ref				Ref			
At goal	2251	-5538.07	-10675.99	-400.16	0.035	222.30	139.32	305.29	<0.001
Latest LDL-C before MACE achieving the reduction of ≥ 50%	4180								
Not at goal	3547	Ref				Ref			
At goal	633	1578.91	-8297.82	11455.64	0.754	667.28	508.35	826.21	<0.001
Latest LDL-C before MACE category	4625								
>2.6 mmol/L	947	Ref				Ref			
1.8-2.6 mmol/L	2003	-10721.37	-18081.72	-3361.01	0.004	-65.52	-173.06	42.03	0.232
<1.8 mmol/L	1675	-9176.30	-17309.22	-1043.37	0.027	227.61	109.81	345.41	<0.001
Among those baseline LDL-C >2.6 mmol/L									
Latest LDL-C before MACE achieving the goal of 2.6 mmol/L	2177								
Not at goal	585	Ref				Ref			
At goal	1592	-12256.63	-21228.51	-3284.75	0.007	27.61	-123.97	179.20	0.721
Latest LDL-C before MACE achieving the goal of 1.8 mmol/L	2177								
Not at goal	1535	Ref				Ref			
At goal	642	-4403.03	-12882.10	4076.04	0.309	325.712	167.917	483.507	<0.001
Latest LDL-C before MACE achieving the goal of 2.0 mmol/L	2177								
Not at goal	1275	Ref				Ref			
At goal	903	-7310.54	-14527.17	-93.91	0.047	275.38	135.93	414.82	<0.001
Latest LDL-C before MACE achieving the reduction of ≥ 50%	2177								
Not at goal	1603	Ref				Ref			
At goal	574	835.75	-7993.07	9664.57	0.853	757.21	582.19	932.24	<0.001
Latest LDL-C before MACE category	2177								
>2.6 mmol/L	585	Ref				Ref			
1.8-2.6 mmol/L	950	-12471.43	-21536.32	-3406.54	0.007	-116.61	-276.62	43.41	0.153
<1.8 mmol/L	642	-11605.88	-22613.40	-598.36	0.039	250.92	60.07	441.77	0.010

MACE, major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; HKD, Hong Kong dollars; Ref, reference; CI, confidence interval.
*Adjusted for age, sex, diabetes, hypertension, and prior cardiovascular history

Table 4. Association of MACEs and lipid goal attainments

	n	Adjusted Hazard Ratio*	(95% Confidence Interval)	*p*-value
Analyzed sample				
Latest LDL-C before MACE achieving the goal of 2.6 mmol/L	4625			
Not at goal	981	1		
At goal	3644	0.76	(0.62, 0.93)	0.007
Latest LDL-C before MACE achieving the goal of 1.8 mmol/L	4625			
Not at goal	2983	1		
At goal	1642	0.97	(0.81, 1.17)	0.779
Latest LDL-C before MACE achieving the goal of 2.0 mmol/L	4625			
Not at goal	2411	1		
At goal	2214	0.93	(0.78, 1.10)	0.385
Latest LDL-C before MACE achieving the goal of ≥ 50% reduction	4180			
Not at goal	3547	1		
At goal	633	0.77	(0.58, 1.03)	0.074
Latest LDL-C category before MACE	4625			
< 1.8 mmol/L	1642	1		
1.8-2.6 mmol/L	2003	0.92	(0.75, 1.12)	0.396
> 2.6 mmol/L	981	1.25	(1.00, 1.57)	0.051
Among those with baseline LDL-C > 2.6 mmol/L				
Latest LDL-C before MACE achieving the goal of 2.6 mmol/L	2177			
Not at goal	585	1		
At goal	1592	0.56	(0.42, 0.74)	< 0.001
Latest LDL-C before MACE achieving the goal of 1.8 mmol/L	2177			
Not at goal	1535	1		
At goal	642	0.78	(0.57, 1.06)	0.108
Latest LDL-C before MACE achieving the goal of 2.0 mmol/L	2177			
Not at goal	1275	1		
At goal	903	0.83	(0.63, 1.10)	0.186
Latest LDL-C before MACE achieving the goal of ≥ 50% reduction	2177			
Not at goal	1603	1		
At goal	574	0.72	(0.52, 1.00)	0.051
Latest LDL-C category before MACE	2177			
< 1.8 mmol/L	642	1		
1.8-2.6 mmol/L	950	1.00	(0.71, 1.41)	0.983
> 2.6 mmol/L	585	1.79	(1.26, 2.55)	0.001

MACE, major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol.
*Adjusted for age, sex, diabetes, hypertension, and prior cardiovascular history

outcomes.

Discussion

To our knowledge, this study was the first to investigate the economic burden of failure in achieving the lipid goals in an Asian/Chinese population. Our findings suggested that any LDL-C goal attainments of < 2.6 mmol/L, < 2.0 mmol/L, < 1.8 mmol/L, and ≥ 50% reduction did not necessarily bring any reduction in the total cost of care during a one-year follow-up; this finding was in line with the prior cost analysis in Sweden[28]. This was possible because the higher cardiovascular-related cost targeting for more stringent lipid goals offset the savings in other management cost and boosted the total cost of care. In the current analysis, the latest lipid goal attainments before MACEs might not be the same as the lipid goal at the one-year endpoint because lipids changed acutely after MACE[48, 49]. Therefore, we also tested the cost difference by the latest lipid goal attainments before MACE. The results seemed to be robust to what was found before. Owing to the limitations of the observational study, we could not clarify the causes

Table 5. Adjusted cost difference of the total cost of care and cardiovascular-related cost by lipid goal attainments among 2686 patients with complete five-year follow-up

		Total cost of care (HKD)			Cardiovascular-related cost (HKD)		
	N	Adjusted Coefficient*	(95% Confidence Interval)	*p*-value	Adjusted Coefficient*	(95% Confidence Interval)	*p*-value
Endpoint LDL-C achieving the goal of 2.6 mmol/L	2686						
1st year: At goal vs Not at goal	2686	6548.52	(-3441.94, 16538.97)	0.20	10495.13	(5846.36, 15143.89)	<0.001
2nd year: At goal vs Not at goal	2686	1433.02	(-6835.65, 9701.69)	0.73	-1637.26	(-5892.56, 2618.05)	0.45
3rd year: At goal vs Not at goal	2686	1404.19	(-6251.35, 9059.74)	0.72	-7.59	(-3437.71, 3422.53)	1.00
4th year: At goal vs Not at goal	2686	-4251.30	(-11714.31, 3211.71)	0.26	-1776.81	(-5662.26, 2108.64)	0.37
5th year: At goal vs Not at goal	2686	-748.84	(-7558.02, 6060.34)	0.83	-1529.18	(-5146.36, 2088.00)	0.41
Endpoint LDL-C achieving the goal of 1.8 mmol/L	2686						
1st year: At goal vs Not at goal	2686	12764.70	(1199.33, 24330.08)	0.03	8367.48	(1343.69, 15391.27)	0.02
2nd year: At goal vs Not at goal	2686	10694.72	(1936.13, 19453.32)	0.02	739.51	(-2118.36, 3597.39)	0.61
3rd year: At goal vs Not at goal	2686	4185.83	(-3570.15, 11941.81)	0.29	2323.03	(-1117.32, 5763.37)	0.19
4th year: At goal vs Not at goal	2686	-2747.02	(-9003.42, 3509.38)	0.39	-1263.53	(-4107.77, 1580.71)	0.38
5th year: At goal vs Not at goal	2686	367.42	(-6025.01, 6759.85)	0.91	21.21	(-2939.33, 2981.74)	0.99
Endpoint LDL-C achieving the goal of 2.0 mmol/L	2686						
1st year: At goal vs Not at goal	2686	8031.90	(-2052.35, 18116.14)	0.12	7683.58	(1678.83, 13688.32)	0.01
2nd year: At goal vs Not at goal	2686	6080.24	(-1372.17, 13532.65)	0.11	-167.99	(-2973.12, 2637.14)	0.91
3rd year: At goal vs Not at goal	2686	1853.03	(-5091.22, 8797.29)	0.60	1056.23	(-1890.38, 4002.83)	0.48
4th year: At goal vs Not at goal	2686	-6025.85	(-11884.44, -167.25)	0.04	-2474.41	(-5301.74, 352.93)	0.09
5th year: At goal vs Not at goal	2686	-405.39	(-6530.61, 5719.83)	0.90	-1076.21	(-3926.35, 1773.94)	0.46
Endpoint LDL-C achieving the reduction of 50%	2412						
1st year: At goal vs Not at goal	2412	16472.69	(-2613.22, 35558.59)	0.09	10607.64	(297.47, 20917.80)	0.04
2nd year: At goal vs Not at goal	2412	-3062.50	(-11721.47, 5596.48)	0.49	-1222.43	(-4448.06, 2003.20)	0.46
3rd year: At goal vs Not at goal	2412	-1969.65	(-13188.12, 9248.82)	0.73	-182.27	(-5121.42, 4756.89)	0.94
4th year: At goal vs Not at goal	2412	-4115.05	(-13228.67, 4998.58)	0.38	-2179.64	(-5794.71, 1435.42)	0.24
5th year: At goal vs Not at goal	2412	2065.28	(-10846.31, 14976.88)	0.75	-1675.69	(-5453.84, 2102.45)	0.38

MACE, major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; HKD, Hong Kong dollars; Ref, reference.
*Adjusted for age, sex, diabetes, hypertension, and prior cardiovascular history

of the additional cardiovascular-related cost in the "treat-to-target" approaches for the LDL-C goals of < 2.0 mmol/L, <1.8 mmol/L, and ≥ 50% reduction compared with the less intensive LDL-C goal of <2.6 mmol/L. One possible reason could be that physicians aggressively treated patients who were at higher risk at baseline to reach a more stringent lipid goal, thus causing additional economic burden. Bearing this potential explanation in mind, we looked at the cost differences in high-risk patients with baseline LDL-C beyond 2.6 mmol/L and still found that lipid categories of 1.8 mmol/L, 2.0 mmol/L, 2.6 mmol/L, and ≥ 50% reduction denoted higher cardiovascular-related costs. The other possible explanation could be that the cost of higher intensive lipid treatment may have been substantially greater because of the use of branded atorvastatin and rosuvastatin rather than generic simvastatin. However, as shown in **Table 3**, the cost of lipid-lowering drugs alone was perceived to have little effect on the total cost of care. Normally the future costs were less than the immediate costs, although the future clinical benefits of a longer follow-up were generally less significant than the immediate benefits[50]. As a consequence, we took a closer look at the time series changes among patients with five-year follow-up because one Swedish study found that the cardiovascular-related costs for goal-attaining patients decreased significantly 2–3 years after the treatment started[28]. However, our results did not show the same "cost reduction" trend in lipid goal achievers. Starting from the second year, there were no significant cost differences between the lipid goal achievers and nonachiev-

ers.

Taken together, if attainment of a more stringent lipid goal accompanied a higher cardiovascular-related cost, it would be important to determine if the attainment of the lower lipid goal could also lead to improved clinical outcomes. Therefore, we examined if the lipid goal attainments of 1.8 mmol/L, 2.0 mmol/L, 2.6 mmol/L, and ≥ 50% reduction could lead to significant reduction in MACEs after controlling for known baseline variables. Our results suggested that only the lipid goal of 2.6 mmol/L was associated with a reduction in MACEs during the one-year follow-up. Patients attaining the lipid goals of 1.8 mmol/L, 2.0 mmol/L, or ≥ 50% reduction were not having fewer MACEs, and lowering the patient's LDL-C from 1.8–2.6 mmol/L further to <1.8 mmol/L did not seem to be associated with any significant clinical benefits. On the basis of our exploration on the clinical benefits and costs of lipid goal attainments in Hong Kong Chinese patients, our study questioned if the lipid goal of 2.6 mmol/L could be a better fit for Chinese patients, with significant clinical benefits and lower cardiovascular-related management costs, and raised the question of the most cost-effective lipid goal, which would need to be addressed by a prospective clinical trial. Despite the sensitivity analysis, our study has a limitation associated with real-world data (RWD). It may provide a large sample size and can be more representative of the general population, but we were unable to adjust for the confounders that were not captured in real-world clinical practice. The following could be a more cautious interpretation of our results: the reason for aiming for a more stringent lipid goal (for example, <1.8 mmol/L) was due to the fact that patients had multiple risk factors such as obesity, smoking, and comorbidities. This possibility was beyond our scope, and our findings were limited to the nature of the type of RWD generated from EHRs.

Given its retrospective nature, the study was limited to the following aspects. First, the main problem with the basic data was that it was retrospective and observational and had very limited power to challenge the evidence of a randomized controlled trial. The groups of patients above and below the various lipid goals during follow-up were not matched at the start when they were first identified as a CVD patient and probably differed in terms of true and original baseline lipids. Therefore, it is important to be very cautious when comparing these groups. Second, several risk factors, such as body mass index and smoking status, which might be relevant to lipid goal attainments and MACEs, were not available for the current analysis. Therefore, patients who attained the respective lipid goal could differ from those who did not attain the goal. Although we adopted the estimation of multivalued treatment effects, adjusted for the confounders at baseline, and performed sensitivity analysis, it should be still viewed as a potential violation to our results because we lacked an evaluation of the patients' full risk profile at baseline. Third, we observed the higher cardiovascular-related costs associated with lower lipid goals but failed to identify the reason leading to the difference.

Conclusion

In this first examination of the clinical outcomes and economic burden of lipid goal attainments in post-PCI Chinese patients with ACS, we found that none of the LDL-C goals of <2.6 mmol/L, <2.0 mmol/L, <1.8 mmol/L, and ≥ 50% reduction could lead to the reduction of the total costs of care within one-year follow-up. Furthermore, we found that any further lipid decrease could bring a remarkable economic burden on cardiovascular-related management. However, we failed to identify the clinical benefits associated with lipid goals of <1.8 mmol/L, 2.0 mmol/L, and ≥ 50% reduction despite of the higher cardiovascular-related costs related to these groups of patients.

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Supplementary Table 1. Crude cost items by lipid goal attainments

Lipid goal attainments	*N*	All management cost		All management cost excluding all the cardio-related cost		Cardiovascular-related inpatient cost	
		HKD	(USD)	HKD	(USD)	HKD	(USD)
Full sample (*n* = 4638)	4638	84021.88	(10772.04)	37598.98	(4820.38)	34294.78	(4396.77)
Endpoint LDL-C achieving the goal of 2.6 mmol/L							
Not at goal	950	85979.66	(11023.03)	44935.63	(5760.98)	29061.01	(3725.77)
At goal	3688	83516.90	(10707.30)	35706.62	(4577.77)	35644.75	(4569.84)
Endpoint LDL-C achieving the goal of 1.8 mmol/L	4638						
Not at goal	2962	82682.57	(10600.33)	38365.84	(4918.70)	32431.62	(4157.90)
At goal	1676	86388.86	(11075.49)	36243.71	(4646.63)	37587.55	(4818.92)
Endpoint LDL-C achieving the goal of 2.0 mmol/L	4638						
Not at goal	2382	83143.60	(10659.44)	39861.10	(5110.40)	31382.20	(4023.36)
At goal	2256	84949.21	(10890.92)	35210.52	(4514.17)	37370.04	(4791.03)
Endpoint LDL-C achieving the reduction of ≥ 50%	4182						
Not at goal	3549	85297.01	(10935.51)	38541.63	(4941.24)	34225.65	(4387.90)
At goal	633	82223.61	(10541.49)	33773.27	(4329.91)	37244.65	(4774.95)
Endpoint LDL-C category	4638						
> 2.6 mmol/L	950	85979.66	(11023.03)	44935.63	(5760.98)	29061.01	(3725.77)
1.8-2.6 mmol/L	2012	81123.37	(10400.43)	35258.99	(4520.38)	34025.58	(4362.25)
< 1.8 mmol/L	1676	86388.86	(11075.49)	36243.71	(4646.63)	37587.55	(4818.92)
Analyzed sample (*n* = 4625)							
Latest LDL-C before MACE achieving the goal of 2.6 mmol/L	4625	83927.13	(10759.89)	37691.60	(4832.26)	34133.48	(4376.09)
Not at goal	981	89092.49	(11422.11)	46677.64	(5984.31)	30467.26	(3906.06)
At goal	3644	82536.57	(10581.61)	35272.47	(4522.11)	35120.47	(4502.62)
Latest LDL-C before MACE achieving the goal of 1.8 mmol/L	4625						
Not at goal	2983	83178.75	(10663.94)	38433.26	(4927.34)	32886.29	(4216.19)
At goal	1642	85286.70	(10934.19)	36344.23	(4659.52)	36399.25	(4666.57)
Latest LDL-C before MACE achieving the goal of 2.0 mmol/L	4625						
Not at goal	2411	84468.93	(10829.35)	40280.41	(5164.16)	32329.59	(4144.82)
At goal	2214	83337.12	(10684.25)	34872.44	(4470.83)	36097.89	(4627.93)
Latest LDL-C before MACE achieving the reduction of ≥ 50%	4180						
Not at goal	3547	85314.22	(10937.72)	38563.37	(4944.02)	34233.07	(4388.86)
At goal	633	82223.61	(10541.49)	33773.27	(4329.91)	37244.65	(4774.95)
Latest LDL-C before MACE category	4625						
> 2.6 mmol/L	981	89092.49	(11422.11)	46677.64	(5984.31)	30467.26	(3906.06)
1.8-2.6 mmol/L	2002	80280.96	(10292.43)	34393.44	(4409.41)	34071.63	(4368.16)
< 1.8 mmol/L	1642	85286.70	(10934.19)	36344.23	(4659.52)	36399.25	(4666.57)

MACE indicates major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; HKD, Hong Kong Dollars; USD, United States Dollars.

(Cont. Supplementary Table 1)

Lipid goal attainments	Cardiovascular-related outpatient cost		Cardiovascular-related inpatient and outpatient cost		Lipid-lowering therapy (statins and other lipid-lowering drugs)	
	HKD	(USD)	HKD	(USD)	HKD	(USD)
Full sample (*n* = 4638)	12010.26	(1539.78)	45954.70	(5891.63)	764.78	(98.05)
Endpoint LDL-C achieving the goal of 2.6 mmol/L						
Not at goal	11835.23	(1517.34)	40731.76	(5222.02)	675.92	(86.66)
At goal	12055.40	(1545.56)	47301.87	(6064.34)	787.70	(100.99)
Endpoint LDL-C achieving the goal of 1.8 mmol/L						
Not at goal	11701.03	(1500.13)	43767.36	(5611.20)	640.65	(82.14)
At goal	12556.75	(1609.84)	49820.39	(6387.23)	984.14	(126.17)
Endpoint LDL-C achieving the goal of 2.0 mmol/L						
Not at goal	11679.77	(1497.41)	42828.18	(5490.79)	635.40	(81.46)
At goal	12359.20	(1584.51)	49255.83	(6314.85)	901.39	(115.56)
Endpoint LDL-C achieving the reduction of ≥ 50%						
Not at goal	12504.82	(1603.18)	46712.21	(5988.74)	638.31	(81.83)
At goal	11205.70	(1436.63)	48450.35	(6211.58)	1484.50	(190.32)
Endpoint LDL-C category						
> 2.6 mmol/L	11835.23	(1517.34)	40731.76	(5222.02)	675.92	(86.66)
1.8-2.6 mmol/L	11637.57	(1492.00)	45202.89	(5795.24)	623.98	(80.00)
< 1.8 mmol/L	12556.75	(1609.84)	49820.39	(6387.23)	984.14	(126.17)
Analyzed sample (*n* = 4625)						
Latest LDL-C before MACE achieving the goal of 2.6 mmol/L	12040.65	(1543.67)	46010.37	(5898.76)	766.83	(98.31)
Not at goal	11909.24	(1526.83)	42298.15	(5422.84)	714.08	(91.55)
At goal	12076.03	(1548.21)	47009.73	(6026.89)	781.03	(100.13)
Latest LDL-C before MACE achieving the goal of 1.8 mmol/L						
Not at goal	11764.48	(1508.27)	44578.84	(5715.24)	667.50	(85.58)
At goal	12542.37	(1608.00)	48611.00	(6232.18)	947.28	(121.45)
Latest LDL-C before MACE achieving the goal of 2.0 mmol/L						
Not at goal	11749.64	(1506.36)	43994.11	(5640.27)	658.84	(84.47)
At goal	12357.57	(1584.30)	48206.02	(6180.26)	884.43	(113.39)
Latest LDL-C before MACE achieving the reduction of ≥ 50%						
Not at goal	12511.87	(1604.09)	46738.55	(5992.12)	652.17	(83.61)
At goal	11205.70	(1436.63)	48450.35	(6211.58)	1454.30	(186.45)
Latest LDL-C before MACE category						
> 2.6 mmol/L	11909.24	(1526.83)	42298.15	(5422.84)	714.08	(91.55)
1.8-2.6 mmol/L	11693.55	(1499.17)	45696.40	(5858.51)	644.68	(82.65)
< 1.8 mmol/L	12542.37	(1608.00)	48611.00	(6232.18)	947.28	(121.45)

Supplementary Table 2. Adjusted cost difference in total cost of care and cardiovascular-related cost by lipid goal attainments

		Total cost of care (HKD)				Cardiovascular-related inpatient and outpatient cost (HKD)			
	N	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value
Full sample									
Endpoint LDL-C achieving the goal of 2.6 mmol/L	4638								
Not at goal	950	Ref				Ref			
At goal	3688	-759.60	-9253.72	7734.53	0.861	6739.87	3337.06	10142.69	<0.001
Endpoint LDL-C achieving the goal of 1.8 mmol/L	4638								
Not at goal	2962	Ref				Ref			
At goal	1676	2891.58	-4362.46	10145.62	0.435	5358.43	1418.34	9298.53	0.008
Endpoint LDL-C achieving the goal of 2.0 mmol/L	4638								
Not at goal	2382	Ref				Ref			
At goal	2256	1162.69	-5568.53	7893.90	0.735	5765.66	2188.53	9342.79	0.002
Endpoint LDL-C achieving the reduction of ≥50%	4182								
Not at goal	3549	Ref				Ref			
At goal	633	10673.08	-2193.27	23539.42	0.104	7790.72	949.94	14631.51	0.026
Endpoint LDL-C category	4638								
>2.6 mmol/L	950	Ref				Ref			
1.8-2.6 mmol/L	2012	-2594.92	-11501.67	6311.83	0.568	5078.77	1283.27	8874.28	0.009
<1.8 mmol/L	1676	1232.23	-8507.65	10972.12	0.804	8751.29	4436.00	13066.58	<0.001
Among those with baseline LDL-C >2.6 mmol/L (*n* =2179)									
Endpoint LDL-C achieving the goal of 2.6 mmol/L	2179								
Not at goal	549	Ref				Ref			
At goal	1630	-916.76	-11958.09	10124.56	0.871	6964.52	2373.71	11555.33	0.003
Endpoint LDL-C achieving the goal of 1.8 mmol/L	2179								
Not at goal	1512	Ref				Ref			
At goal		833.85	-9921.49	11589.19	0.879	5357.43	-323.41	11038.27	0.065
Endpoint LDL-C achieving the goal of 2.0 mmol/L	2179								
Not at goal	1250	Ref				Ref			
At goal	929	314.59	-9539.14	10168.31	0.950	6407.34	994.74	11819.93	0.020
Endpoint LDL-C achieving the reduction of ≥50%	2179								
Not at goal	1577	Ref				Ref			
At goal	602	11674.81	-296.01	23645.63	0.056	8915.78	2036.57	15794.99	0.011
Endpoint LDL-C category	2179								
>2.6 mmol/L	549	Ref				Ref			
1.8-2.6 mmol/L	963	-1296.78	-12985.19	10391.63	0.828	5735.21	485.86	10984.55	0.032
<1.8 mmol/L	660	-229.20	-13649.60	13191.20	0.973	8709.78	2657.14	14762.41	0.005

MACE indicates major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; HKD, Hong Kong Dollars; Ref, reference; CI, confidence interval.
*Adjusted for age, sex, diabetes, hypertension, and prior cardiovascular history

Supplementary Table 3. Adjusted cost difference in other management cost and cardiovascular-related cost al by lipid goal attainments

		Other management cost (defined as total cost of care excluding the cardiovascular-related (inpatient and outpatient) cost) (HKD)				Cost of lipid-lowering therapy (statins and other lipid-lowering drugs) (HKD)			
	N	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value
Full sample									
Endpoint LDL-C achieving the goal of 2.6 mmol/L	4638								
Not at goal	950	Ref				Ref			
At goal	3688	-7649.69	-14780.03	-519.35	0.035	111.84	11.39	212.30	0.029
Endpoint LDL-C achieving the goal of 1.8 mmol/L	4638								
Not at goal	2962	Ref				Ref			
At goal	1676	-2295.23	-7762.20	3171.74	0.411	336.07	247.01	425.12	<0.001
Endpoint LDL-C achieving the goal of 2.0 mmol/L	4638								
Not at goal	2382	Ref							
At goal	2256	-4634.13	-9738.11	469.84	0.075	265.48	183.11	347.84	<0.001
Endpoint LDL-C achieving the reduction of ≥50%	4182								
Not at goal	3549	Ref				Ref			
At goal	633	2870.41	-6875.75	12616.56	0.564	721.86	565.70	878.02	<0.001
Endpoint LDL-C category	4638								
>2.6 mmol/L	950	Ref				Ref			
1.8-2.6 mmol/L	2012	-7974.68	-15298.58	-650.78	0.033	-50.31	-155.59	54.96	0.349
<1.8 mmol/L	1676	-7555.90	-15534.01	422.20	0.063	300.77	184.00	417.54	<0.001
Among those baseline LDL-C >2.6 mmol/L									
Endpoint LDL-C achieving the goal of 2.6 mmol/L	2179								
Not at goal	549	Ref				Ref			
At goal	1630	-7662.03	-16812.44	1488.38	0.101	93.92	-56.79	244.63	0.222
Endpoint LDL-C achieving the goal of 1.8 mmol/L	2179								
Not at goal	1512	Ref				Ref			
At goal		-4392.23	-12755.67	3971.20	0.303	402.64	246.53	558.76	<0.001
Endpoint LDL-C achieving the goal of 2.0 mmol/L	2179								
Not at goal	1250	Ref				Ref			
At goal	929	-6035.74	-13535.69	1464.20	0.115	329.98	191.73	468.22	<0.001
Endpoint LDL-C achieving the reduction of ≥50%	2179								
Not at goal	1577	Ref				Ref			
At goal	602	2805.23	-5949.90	11560.35	0.530	813.85	642.16	985.54	<0.001
Endpoint LDL-C category	2179								
>2.6 mmol/L	549	Ref				Ref			
1.8-2.6 mmol/L	963	-6818.40	-16262.66	2625.86	0.157	-83.74	-241.19	73.71	0.297
<1.8 mmol/L	660	-8657.79	-19624.15	2308.57	0.122	347.44	157.97	536.90	<0.001

MACE indicates major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; HKD, Hong Kong Dollars; Ref, reference; CI, confidence interval.

*Adjusted for age, sex, diabetes, hypertension, and prior cardiovascular history

Supplementary Table 4. Adjusted cost difference in cardiovascular-related inpatient and outpatient costs al by lipid goal attainments

		Cardiovascular-related inpatient cost (HKD)				Cardiovascular-related outpatient cost (HKD)			
	N	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value
Full sample									
Endpoint LDL-C achieving the goal of 2.6 mmol/L	4638								
Not at goal	950	Ref				Ref			
At goal	3688	6563.44	3567.08	9559.81	<0.001	404.88	-764.31	1574.07	0.497
Endpoint LDL-C achieving the goal of 1.8 mmol/L	4638								
Not at goal	2962	Ref				Ref			
At goal	1676	4583.37	921.54	8245.20	0.01	784.66	-106.42	1675.74	0.084
Endpoint LDL-C achieving the goal of 2.0 mmol/L	4638								
Not at goal	2382	Ref				Ref			
At goal	2256	5343.24	2032.67	8653.81	0.002	674.53	-174.16	1523.21	0.119
Endpoint LDL-C achieving the reduction of 50%	4182								
Not at goal	3549	Ref				Ref			
At goal	633	7821.31	1379.81	14262.81	0.02	-48.28	-1176.01	1079.44	0.933
Endpoint LDL-C category	4638								
>2.6 mmol/L	950	Ref				Ref			
1.8-2.6 mmol/L	2012	-2815.61	-6868.01	1236.78	0.173	-780.33	-1694.82	134.16	0.094
<1.8 mmol/L	1676	-8168.68	-12054.67	-4282.69	0.00	-797.55	-2091.59	496.49	0.227
Analyzed sample									
Latest LDL-C before MACE achieving the goal of 2.6 mmol/L	4625								
Not at goal	947	Ref				Ref			
At goal	3678	4640.73	1550.45	7731.00	0.003	310.31	-854.52	1475.14	0.602
Latest LDL-C before MACE achieving the goal of 1.8 mmol/L	4625								
Not at goal	2950	Ref				Ref			
At goal	1675	3026.64	-574.43	6627.71	0.10	698.51	-205.20	1602.23	0.130
Latest LDL-C before MACE achieving the goal of 2.0 mmol/L	4625								
Not at goal	2374	Ref				Ref			
At goal	2251	3177.62	-121.41	6476.64	0.059	569.77	-286.25	1425.79	0.192
Latest LDL-C before MACE achieving the reduction of 50%	4180								
Not at goal	3547	Ref				Ref			
At goal	633	6407.96	-189.79	13005.72	0.06	-556.08	-1639.01	526.85	0.314
Latest LDL-C before MACE category	4625								
>2.6 mmol/L	947	Ref				Ref			
1.8-2.6 mmol/L	2003	3939.56	402.93	7476.19	0.029	-34.05	-1246.45	1178.34	0.956
<1.8 mmol/L	1675	5625.88	1740.87	9510.88	<0.001	679.57	-617.86	1977.01	0.305

(Cont. Supplementary Table 4)

		Cardiovascular-related inpatient cost (HKD)				Cardiovascular-related outpatient cost (HKD)			
	N	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value
Among those baseline LDL-C ＞2.6 mmol/L									
Endpoint LDL-C achieving the goal of 2.6 mmol/L	2179								
Not at goal	549	Ref				Ref			
At goal	1630	7425.07	3397.85	11452.29	＜0.001	-522.06	-2070.39	1026.28	0.509
Endpoint LDL-C achieving the goal of 1.8 mmol/L	2179								
Not at goal	1512	Ref				Ref			
At goal		5010.12	-258.74	10278.98	0.062	317.90	-860.70	1496.49	0.597
Endpoint LDL-C achieving the goal of 2.0 mmol/L	2179								
Not at goal	1250	Ref				Ref			
At goal	929	6119.90	1068.21	11171.58	0.02	251.80	-853.84	1357.44	0.655
Endpoint LDL-C achieving the reduction of 50%	2179								
Not at goal	1577	Ref				Ref			
At goal	602	8597.60	2094.39	15100.81	0.01	288.93	-923.39	1501.25	0.640
Endpoint LDL-C category	2179								
＞2.6 mmol/L	549	Ref				Ref			
1.8-2.6 mmol/L	963	-2348.39	-8314.18	3617.40	0.44	-616.14	-1796.81	564.54	0.306
＜1.8 mmol/L	660	-8779.03	-14217.25	-3340.82	0.002	131.12	-1569.10	1831.34	0.880
Latest LDL-C before MACE achieving the goal of 2.6 mmol/L	2177								
Not at goal	585	Ref				Ref			
At goal	1592	3885.39	-384.12	8154.91	0.074	-878.64	-2371.55	614.28	0.249
Latest LDL-C before MACE achieving the goal of 1.8 mmol/L	2177								
Not at goal	1535	Ref				Ref			
At goal	642	3319.74	-2132.71	8772.18	0.23	161.66	-1008.74	1332.06	0.787
Latest LDL-C before MACE achieving the goal of 2.0 mmol/L	2177								
Not at goal	1275	Ref				Ref			
At goal	903	4957.06	-163.92	10078.04	0.058	193.57	-915.19	1302.34	0.732
Latest LDL-C before MACE achieving the reduction of 50%	2177								
Not at goal	1603	Ref				Ref			
At goal	574	6942.93	231.22	13654.65	0.04	-202.58	-1382.28	977.12	0.736
Latest LDL-C before MACE category	2177								
＞2.6 mmol/L	585	Ref				Ref			
1.8-2.6 mmol/L	950	3250.41	-1686.73	8187.55	0.197	-1086.36	-2671.65	498.94	0.179
＜1.8 mmol/L	642	5005.76	-774.48	10786.01	0.09	-485.87	-2131.76	1160.02	0.563

MACE indicates major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; HKD, Hong Kong Dollars; Ref, reference; CI, confidence interval.
*Adjusted for age, sex, diabetes, hypertension, and prior cardiovascular history

Supplementary Table 5. Adjusted cost difference by lipid goal attainments among 2686 patients with complete five-year follow-up

	Total cost of care (HKD)				Cardiovascular-related cost (HKD)			
	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value	Adjusted Coefficient*	Lower limit for 95% CI	Lower limit for 95% CI	*p*-value
Endpoint LDL-C category								
1st year:								
>2.6 mmol/L	Ref				Ref			
1.8-2.6 mmol/L	1510.38	-9054.15	12074.92	0.78	8280.74	3097.21	13464.26	<0.001
<1.8 mmol/L	13910.13	710.44	27109.82	0.04	13887.91	6831.99	20943.83	<0.001
2nd year:								
>2.6 mmol/L	Ref				Ref			
1.8-2.6 mmol/L	-3520.93	-11949.96	4908.09	0.41	-2387.03	-6707.04	1932.98	0.28
<1.8 mmol/L	8408.82	-2255.99	19073.64	0.12	-753.36	-5383.72	3876.99	0.75
3rd year:								
>2.6 mmol/L	Ref				Ref			
1.8-2.6 mmol/L	-211.90	-8450.38	8026.58	0.96	-1234.08	-4663.44	2195.28	0.48
<1.8 mmol/L	4022.09	-5283.34	13327.51	0.40	1649.37	-2653.99	5952.72	0.45
4th year:								
>2.6 mmol/L	Ref				Ref			
1.8-2.6 mmol/L	-3680.62	-11771.91	4410.68	0.37	-1411.23	-5648.60	2826.13	0.51
<1.8 mmol/L	-5277.79	-13619.73	3064.16	0.21	-2267.74	-6382.58	1847.10	0.28
5th year:								
>2.6 mmol/L	Ref				Ref			
1.8-2.6 mmol/L	-1029.39	-8780.01	6721.23	0.79	-1541.59	-5687.27	2604.09	0.47
<1.8 mmol/L	-342.22	-8003.73	7319.29	0.93	-1061.03	-4991.50	2869.43	0.60

MACE indicates major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; HKD, Hong Kong Dollars; Ref, reference; CI, confidence interval.

*Adjusted for age, sex, diabetes, hypertension, and prior cardiovascular history