Gender-specific Goal Attainment of Low-density Lipoprotein Cholesterol among Patients with Coronary Artery Disease in Taiwan

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Abstract

Background: The attainment of target serum low-density lipoprotein cholesterol (LDL-C) levels among patients with coronary artery disease (CAD) in Taiwan remains unsatisfactory, which has become a critical issue in female patients with CAD who tend to be older and have more cardiovascular comorbidities, compared with male patients. The present study aims to investigate differences between genders in current LDL-C goal attainment rates, as well as prescription rates for high-intensity statins (HIS) and ezetimibe, among patients with CAD in the Lipid Clinic of our institution.

Methods: Between July 2018 and December 2019, the present study enrolled 100 patients with CAD who had a suboptimal serum LDL-C level >70 mg/dL. Each patient received well-organized treatment and counselling in the Lipid Clinic, according to the current Taiwan lipid guidelines.The LDL-C goal attainment rates and the prescription rates of HIS and ezetimibe were analyzed at every 3-month follow-up point.

Results: The baseline characteristics of patients with CAD were comparable for both genders, except that male patients had higher hemoglobin, creatinine, and creatine kinase than female patients. Of patients with CAD, female patients had a trend towards higher baseline serum LDL-C levels, a wider gap to reach target serum LDL-C levels and higher prescription rates for HIS/ezetimibe, compared with male patients, although these trends did not reach statistical significance. However, female patients with CAD showed a greater reduction of serum LDL-C levels while under treatment, compared with male patients with CAD. The LDL-C goal attainment rates were comparable for males and females.

Conclusion: The achievement of LDL-C goals was similar in both genders. This is the first study to demonstrate on a gender basis the current status of LDL-C goal attainment and prescription of HIS and ezetimibe in Taiwan.

Keywords: low-density lipoprotein cholesterol, gender, coronary artery disease

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Introduction

Coronary artery disease (CAD) is the main cause of death worldwide. Following ample evidence focused on the efficacy of primary and secondary prevention,[1,2] for atherosclerotic cardiovascular disease (ASCVD), lowering low-density lipoprotein cholesterol (LDL-C) with statin therapy is effective to reduce all-cause mortality and the occurrence of major adverse cardiovascular events (MACEs) in patients with CAD.[3,4] In addition, among high-risk patients, high-intensity statin (HIS) therapy provides more effective protection against death or MACEs than moderate-intensity statin therapy.[5,6]

The recently issued Taiwan lipid guidelines recommend that HIS therapy should be prescribed in patients with CAD, and that optimal serum levels of LDL-C in patients with CAD should be < 70 mg/dL.[7] In addition to statin therapy, several non-statin medications (e.g., ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors) in combination with statin provide further reduction in LDL-C.[8,9] Despite the guidelines' recommendations, the LDL-C goal attainment rates among patients with CAD remains suboptimal.[10,11] Potential reasons include poor disease awareness, suboptimal statin dosing, poor adherence, and an inadequate treatment response.

Though CAD is often thought of as a disease typically affecting males, it is nearly as common in females. Heart disease accounted for 24.2% and 21.8% of mortality in males and females, respectively, in the USA during 2017.[1] Generally, female patients with CAD tend to be older and have more comorbidities than male patients.[12] Additionally, female patients who survive a first myocardial infarction are more likely to develop heart failure or a second infarction, compared to male patients.[13] These findings suggest that prevention of ASCVD has become a critical issue in females. In the Dyslipidemia International Study (DYSIS), females were more likely to achieve target LDL-C goals, compared to males.[14] In contrast to the DYSIS study, female gender was identified as a predictor of non-attainment of LDL-C goals in the International ChoLesterol management Practice Study (ICLPS) and EUROpean Action on Secondary and Primary Prevention through Intervention to Reduce Events (EUROASPIRE IV) study.[15,16] Currently, there is only limited evidence regarding the gender-specific disparities in LDL-C goal attainment rates and the prescription rates of HIS/ezetimibe among patients with CAD in Taiwan. To address this knowledge gap, we designed a retrospective analysis of prospectively enrolled patients who had CAD and a suboptimal serum LDL-C level >70 mg/dL in the Lipid Clinic of our institution. We aimed to investigate differences between the genders regarding baseline LDL-C levels, responsiveness and change of LDL-C under statin treatment, and goal attainment rates for LDL-C levels at 3-, 6- , and 9-month follow-ups.

Methods

Study design, population, and definition of CAD and HIS

This study was a retrospective analysis of prospectively enrolled patients in the Lipid Clinic, which was established in our institution since July 2018 and included three cardiologists and one endocrinologist as the principal investigators. The principal investigator meeting was held every two months to discuss any queries about the protocol setting and patient recruitment. All protocols of the present study were approved by the Institutional Review Board of our institution (Approval No. 18MMHIS083e), and written, informed consent was obtained from all participants.

Patients with CAD were defined as those who had >50% diameter stenosis of major epicardial coronary arteries, confirmed by coronary computed tomography (CT) angiography or coronary angiography, or had a history of acute coronary syndrome (ACS), identified by medical records of hospitalization and urgent coronary revascularization. According to the current

Taiwan lipid guidelines, atorvastatin 40-80 mg/day and rosuvastatin ≥20 mg/day are classified as HISs.[7] Furthermore, the target serum LDL-C level of patients with CAD is <70 mg/dL.[7] Patients with CAD were eligible for enrolment in the present study if they had a serum LDL-C level >70 mg/dL at baseline. We excluded patients who were intolerant to statin therapy or for whom it was contraindicated, those unable to receive regular blood examination, or who disagreed with sharing personal medical information. Finally, patients with CAD were divided into 2 groups: male patients and female patients (Figure 1).

Data collection and treatment

After enrolment, specially-trained study nurses collected all baseline data whenever feasible, including age, gender, weight, height, smoking habit, history of comorbidities, laboratory data, and concurrently prescribed medications. Body mass index was defined as weight in kilograms divided by the square of height in meters. Diagnosis of ischemic stroke (IS) was based on the neurologist's records with relevant image confirmation by brain computed tomography (CT) or magnetic resonance imaging. Diagnosis of peripheral artery disease (PAD) was confirmed by ankle-brachial index <0.9 or >1.4 and/or >50% diameter stenosis of peripheral arteries, as observed in CT angiography. Diagnosis of diabetes mellitus (DM) was based on medical records and prescribed medications. Familial hypercholesterolemia (FH) was identified when patients had a pathogenic genotype confirmed by gene test or had a Dutch Lipid Clinic Network (DLCN) score >81.[7] Other medical histories, including hypertension (HTN), heart failure, and dialysis were identified based on medical records. The concurrent medications were recorded in detail, including angiotensin-converting enzyme

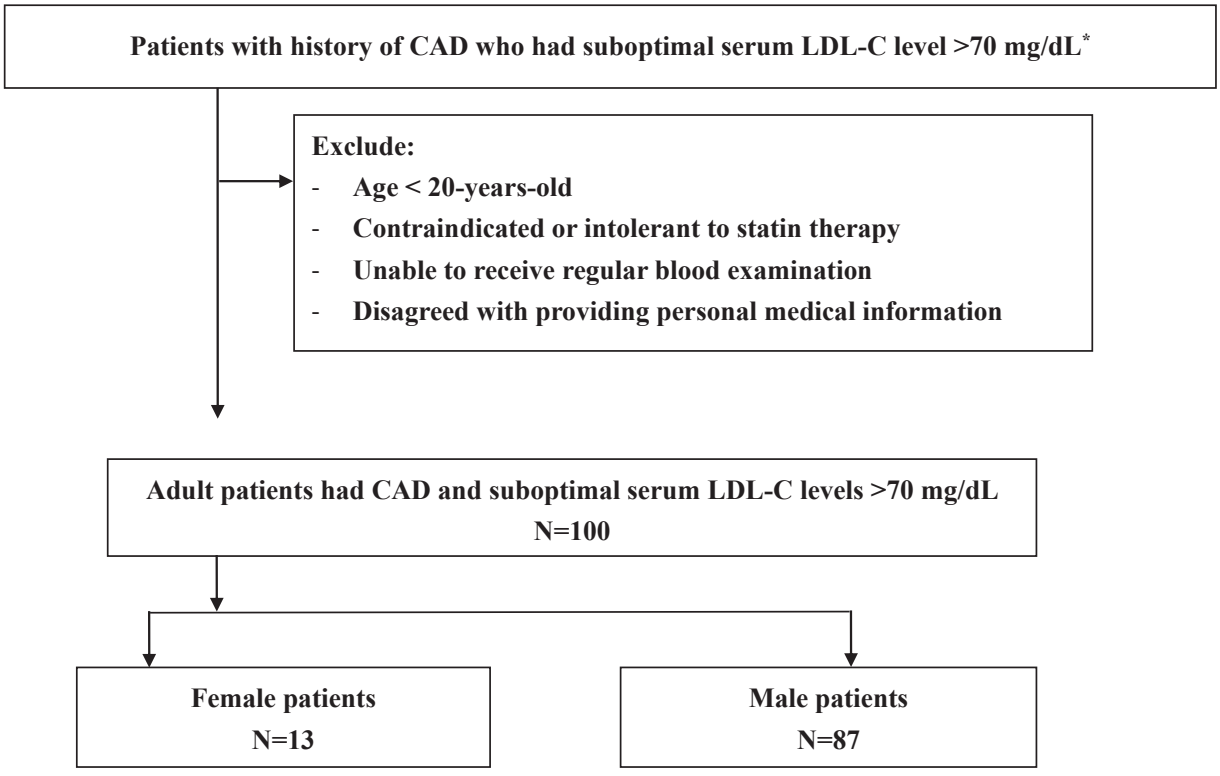


Figure 1. Diagram of patient selection. (*According to "2017 Taiwan lipid guidelines in high risk patients) (CAD = coronary artery disease; LDL-C = low-density lipoprotein cholesterol)

inhibitors/angiotensin receptor blockers (ACEIs/ARBs), antiplatelets (i.e., aspirin and P2Y12 inhibitors), beta-blockers, calcium-channel blockers, statins, ezetimibe, fibrates, and insulin.

All participants in the present study were followed up and underwent blood examination every 3 months for a total duration of 9 months. Each patient with CAD received well-organized treatment and counselling in the Lipid Clinic, covering life-style modification, lipid-lowering therapy (LLT) according to the recommendations of the current Taiwan lipid guidelines,[7] and drug adherence support. All patients in the present study received initiation or adjustment of statin therapy after enrolment. Other LLTs, including ezetimibe, fibrates and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were prescribed according to actual clinical situation and physician-patient discussion. At each visit, the patients' prescribed LLT and lipid profiles, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and LDL-C were recorded.

Study outcomes

The study outcomes in the present study included the prescription rates of HIS and ezetimibe, and the LDL-C goal attainment rates in patients with CAD at every 3-month follow-up.

Statistical analysis

Continuous and categorical variables are presented as means (±standard deviations) or numbers (percentages), respectively. Comparisons were performed using the unpaired Student t test or Wilcoxon rank sum test for continuous variables, and the chi-square or Fisher's exact test for categorical variables, as appropriate. The baseline characteristics of male patients with CAD were compared with female patients with CAD. The prescription rates of HIS and ezetimibe, and LDL-C goal attainment rates were analyzed at every 3-month follow-up. Significance was set at $p < 0.05$ (2-tailed). SAS statistical software (Version 9.2 for Windows; SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Patients' baseline characteristics

Of 100 patients with CAD who participated in this present study, 87% were males and 13% were females (Figure 1). The mean age of male patients was 60.6 ± 8.6 years, while that of female patients was 62.5 ± 12.9 years. The baseline characteristics of medical history, prescribed medications, and laboratory data were comparable between males and females, except that male patients had higher hemoglobin-, creatinine- and creatine kinase levels than female patients (Table 1). The percentages of statin and HIS use at baseline in male patients were, respectively, 71.3% and 25.3%, while those in female patients were, respectively, 76.9% and 23.1%. Among male patients with CAD, the baseline serum LDL-C levels in statin users and statin non-users were 106.6 ± 33.5 mg/dL and 134.5 ± 31.4 mg/dL, respectively. Among female patients with CAD, the baseline serum LDL-C levels in statin users and statin non-users were 115.6 ± 37.3 mg/dL and 163.7 ± 29.1 mg/dL, respectively (Table 1). The percentages of LDL-C reduction needed among male patients with CAD were 29.9 ± 15.7% in statin users and 45.6 ± 11.0% in statin non-users, while among female patients with CAD they were 34.8 ± 17.0% in statin users and 56.2 ± 8.5% in statin non-users (Table 1).

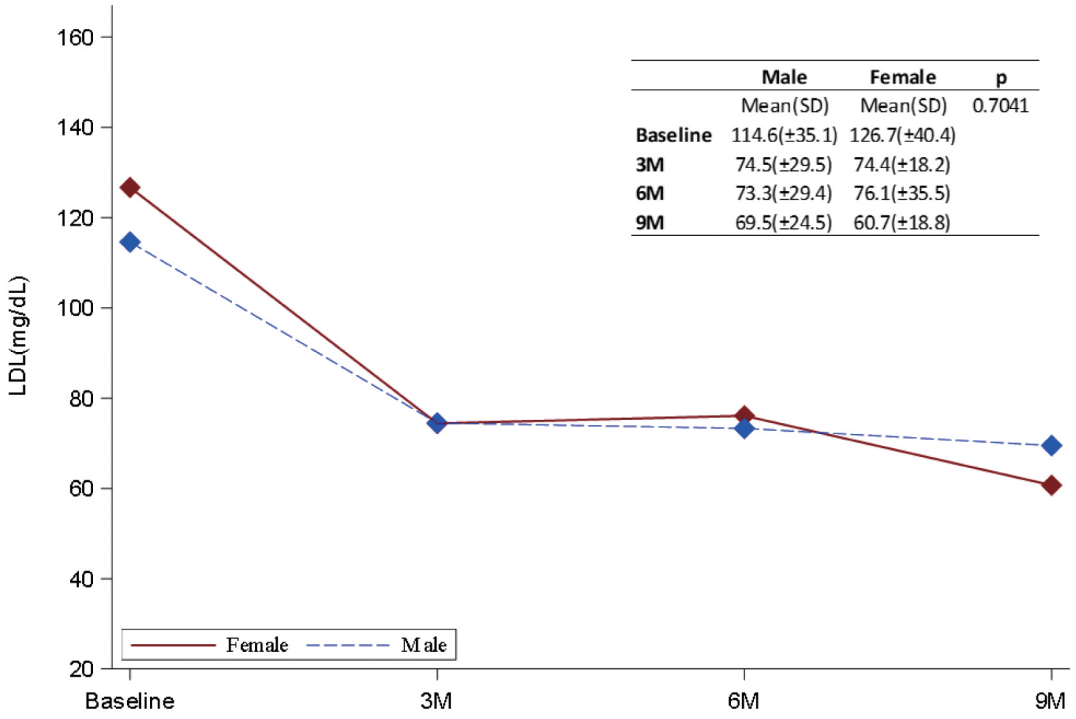
Percent attainment of serum LDL-C reduction goals, and prescription rates of HIS and ezetimibe during follow-up:

The serum LDL-C levels in male patients with CAD at 3-, 6-, and 9-month follow-up were, respectively, 74.4 ± 18.2 mg/dL, 73.3 ± 29.4 mg/dL, and 69.5 ± 24.5 mg/dL, while those in female patients with CAD were, respectively, 74.5 ± 29.5 mg/dL, 76.1 ± 35.5 mg/dL, and 60.7 ± 18.4 mg/dL (Figure 2). The percent reductions in serum LDL-C in male patients with CAD at the 3-, 6-, and 9-month follow-up were, respectively, 32.4 ± 23.1%, 34.7 ± 29.4%, and 40.7 ± 22.8%,

Table 1. Baseline characteristics of patients with CAD in the Lipid Clinic

		Total N=100	Females N=13	Males N=87	*p**
Age		60.9(9.2)	62.5(12.9)	60.6(8.6)	0.61
BMI (Kg/m2)		26.1(4)	25.7(4)	26.2(4)	0.67
Medical history	**Current smoker**	19(19)	0(0)	19(21.8)	0.12
	Hypertension	68(68)	11(84.6)	57(65.5)	0.17
	Diabetes	41(41)	5(38.5)	36(41.4)	0.84
	PAD	9(9)	1(7.7)	8(9.2)	1.00
	Ischemic stroke	4(4)	1(7.7)	3(3.4)	0.43
	Dialysis	2(2)	0(0)	2(2.3)	1.00
	Heart failure	16(16)	0(0)	16(18.4)	0.12
	FH	1(1)	1(7.7)	0(0)	0.13
Prescribed medications	**Antiplatelets**	93(93)	11(84.6)	82(94.3)	0.20
	- Aspirin	72(72)	9(69.2)	63(72.4)	0.81
	- P2Y12 inhibitor	57(57)	5(38.5)	52(59.8)	0.15
	Beta-blocker	75(75)	10(76.9)	65(74.7)	0.86
	Calcium channel blocker	18(18)	4(30.8)	14(16.1)	0.24
	ACEI / ARB	66(66)	10(76.9)	56(64.4)	0.37
	Insulin	9(9)	1(7.7)	8(9.2)	1.00
	Any statin **HIS**	72(72) 25(25)	10(76.9) 3(23.1)	62(71.3) 22(25.3)	0.67 1.00
	Ezetimibe	8(8)	3(23.1)	5(5.7)	0.07
	Fibrate	4(4)	0(0)	4(4.6)	1.00
Laboratory and Physiological data	**LVEF (%)**	60.8(8.2)	62(11.3)	60.6(7.7)	0.59
	Hb (g/dL)	14.2(1.6)	12.8(1.1)	14.4(1.6)	0.00
	Glucose AC (mg/dL)	119.3(34.4)	108.3(29.3)	120.9(34.9)	0.22
	HbA1c (%)	6.6(1.4)	6.9(1.6)	6.5(1.3)	0.42
	Cr (mg/dL)	1.2(1.1)	0.8(0.2)	1.3(1.1)	0.00
	eGFR (ml/min)	71.6(21.3)	72.9(18.7)	71.4(21.8)	0.81
	AST (U/L)	25.6(12.1)	24(7.5)	25.8(12.7)	0.48
Lipid profiles	**TC (mg/dL)**	187.8(42.1)	204.1(49.1)	185.3(40.7)	0.13
	TG (mg/dL)	159(74.4)	167.8(48.2)	157.7(77.7)	0.65
	HDL-C (mg/dL)	42.4(9.6)	46.1(8.3)	41.9(9.7)	0.14
	LDL-C (mg/dL)	116.2(35.9)	126.7(40.4)	114.6(35.1)	0.26
	- LDL-C in statin non-users	137.6(32)	163.7(29.1)	134.5(31.4)	0.14
	- LDL-C in statin users	107.8(34)	115.6(37.3)	106.6(33.5)	0.44
%LDL-C needed to reduce	**Statin users**	30.6(15.9)	34.8(17)	29.9(15.7)	0.37
	Statin non-users	46.7(11.2)	56.2(8.5)	45.6(11)	0.12

Abbreviation: ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AST = aspartate aminotransferase; BMI=body mass index; CAD = coronary artery disease; Cr = creatinine; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; Hb = hemoglobin; HDL-C = high-density lipoprotein cholesterol; HIS = high-intensity statin; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; SD = standard deviation; TC = total cholesterol; TG = triglyceride. (*Male patients with CAD vs. female patients with CAD). Data are numbers (%) for male gender, medical history, and prescribed medications, and means (SD) for all others.



	Male	Female	p
	Mean(SD)	Mean(SD)	0.7041
Baseline	114.6(±35.1)	126.7(±40.4)	
3M	74.5(±29.5)	74.4(±18.2)	
6M	73.3(±29.4)	76.1(±35.5)	
9M	69.5(±24.5)	60.7(±18.8)	

Figure 2. Serum LDL-C levels in both genders at 3-, 6-, and 9-month follow-ups. Abbreviations: LDL-C = low-density lipoprotein cholesterol; M = month; SD = standard deviation.

while those in female patients with CAD were, respectively, 35.4 ± 26.9%, 40.6 ± 49.0%, and 61.6 ± 10.2% (Figure 3). The LDL-C goal attainment rates in male patients with CAD at 3-, 6-, and 9-month follow-up were, respectively, 58.3%, 62.3%, and 62.0%, while those in female patients with CAD were, respectively, 61.5%, 60.0% and 66.7% (Figure 4). The prescription rates of HIS in male patients with CAD at 3-, 6-, and 9-month follow-up were, respectively, 78.8%, 77%, and 86%, while those in female patients with CAD were, respectively, 76.9%, 90.0% and 100% (Figure 5). The prescription rates of ezetimibe in male patients with CAD at 3-, 6-, and 9-month follow-up were, respectively, 50.6%, 67.6%, and 82%, while those in female patients with CAD were, respectively, 53.8%, 80% and 83% (Figure 6).

Discussion

In the present study, we observed that female patients with CAD trended towards higher baseline serum LDL-C levels and a wider gap to reach target serum LDL-C levels than male patients with CAD, irrespective of statin use at enrolment. In addition, female patients with CAD trended towards receiving HIS more frequently than male patients with CAD, while the prescription rates of ezetimibe were comparable in both genders. Female patients with CAD had a better responsiveness and a greater LDL-C reduction under LLT than male patients with CAD, so that the LDL-C goal attainment rates were comparable in both genders. To the best of our knowledge, this is the first study to illuminate the current status of LDL-C goal attainment and examine the prescription of HIS and ezetimibe in both genders in Taiwan.

Numerous studies in different countries have focused on lipid management among high-risk populations and have reported suboptimal results. The rates for attainment of LDL-C under 70 mg/dL were 8.5% in Germany,[18] 13.9% in France[19]

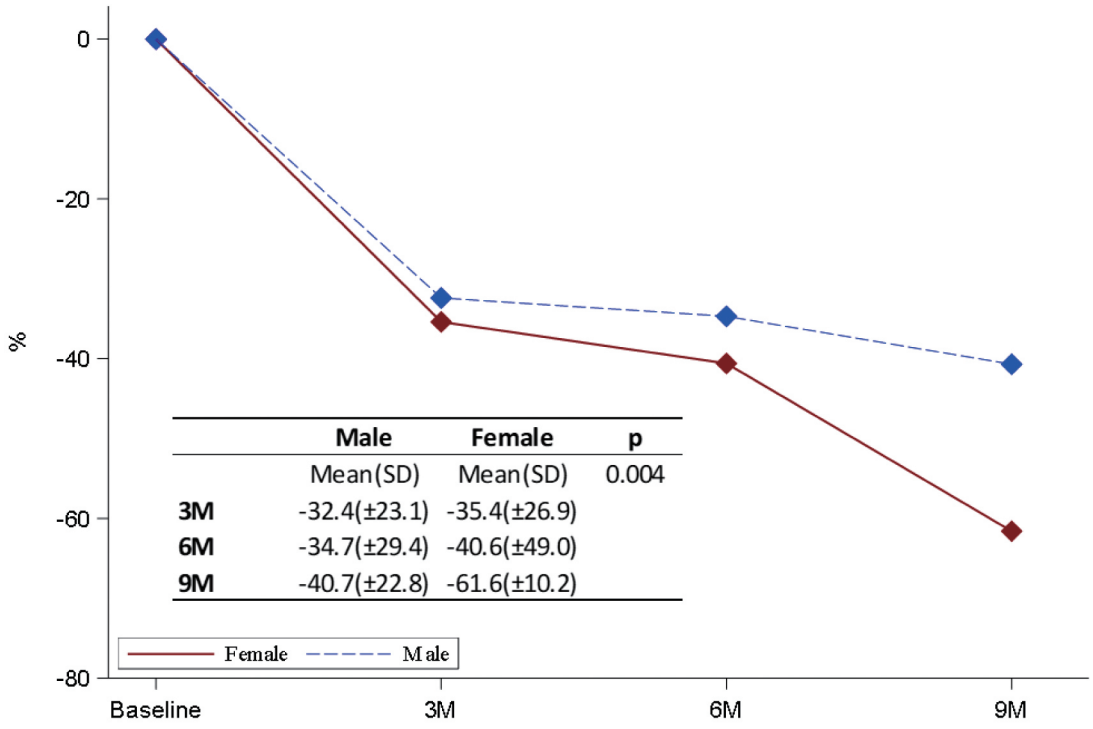


Figure 3. Reduction percentages of serum LDL-C levels in both genders at 3-, 6-, and 9-month follow-ups. Abbreviations: M = month; SD = standard deviation.

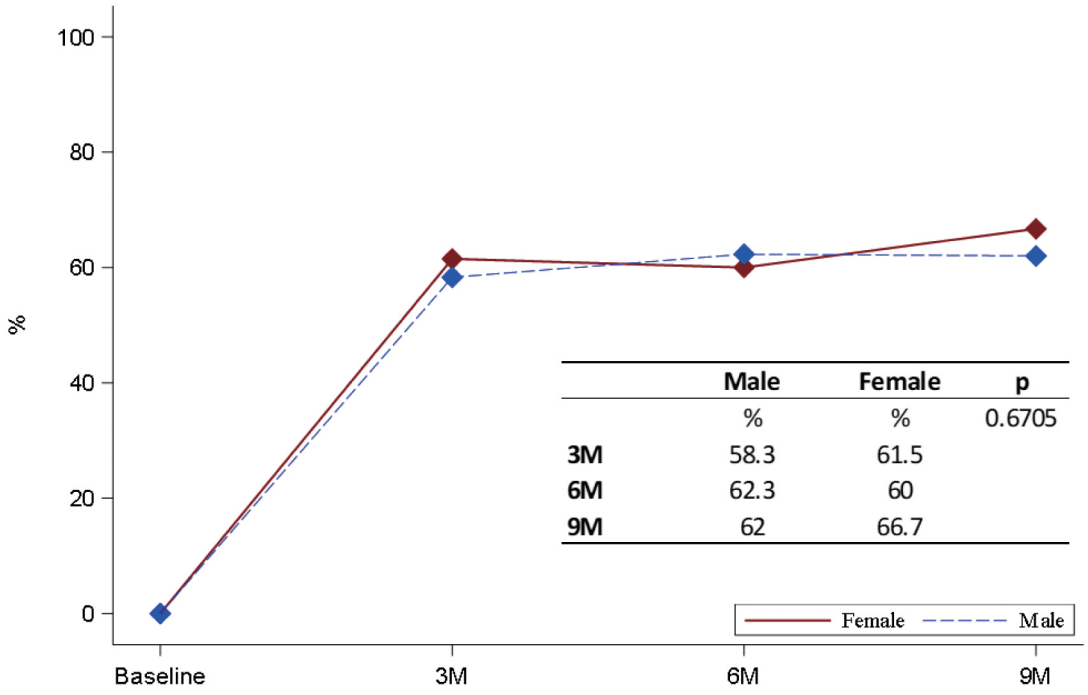
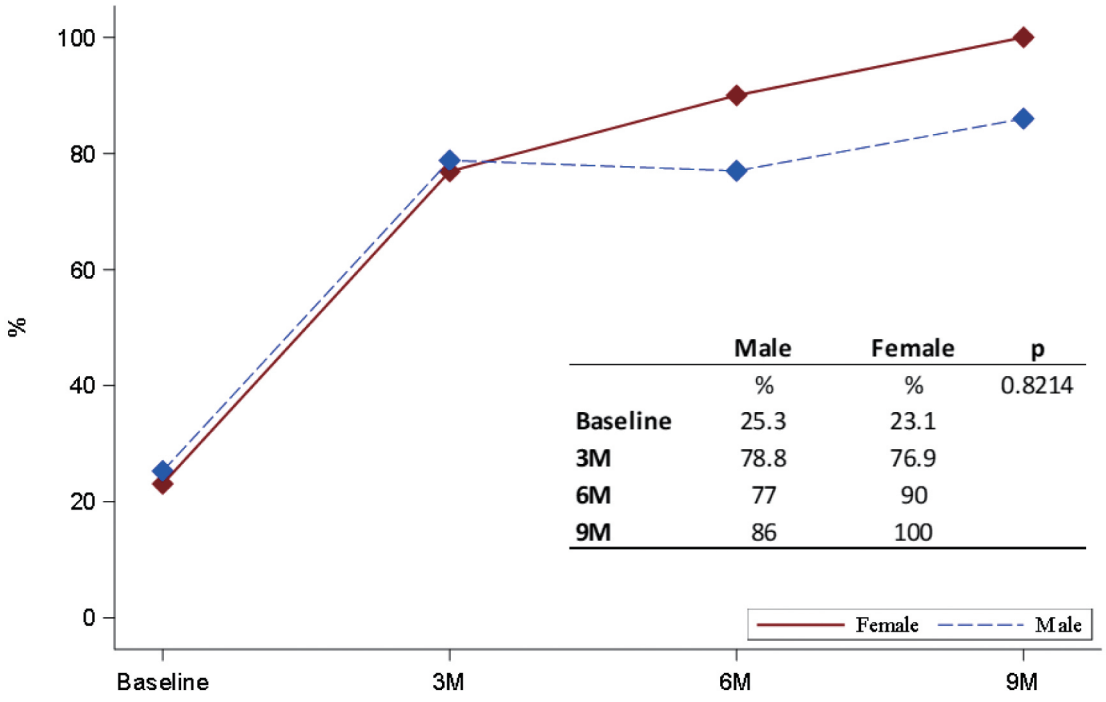
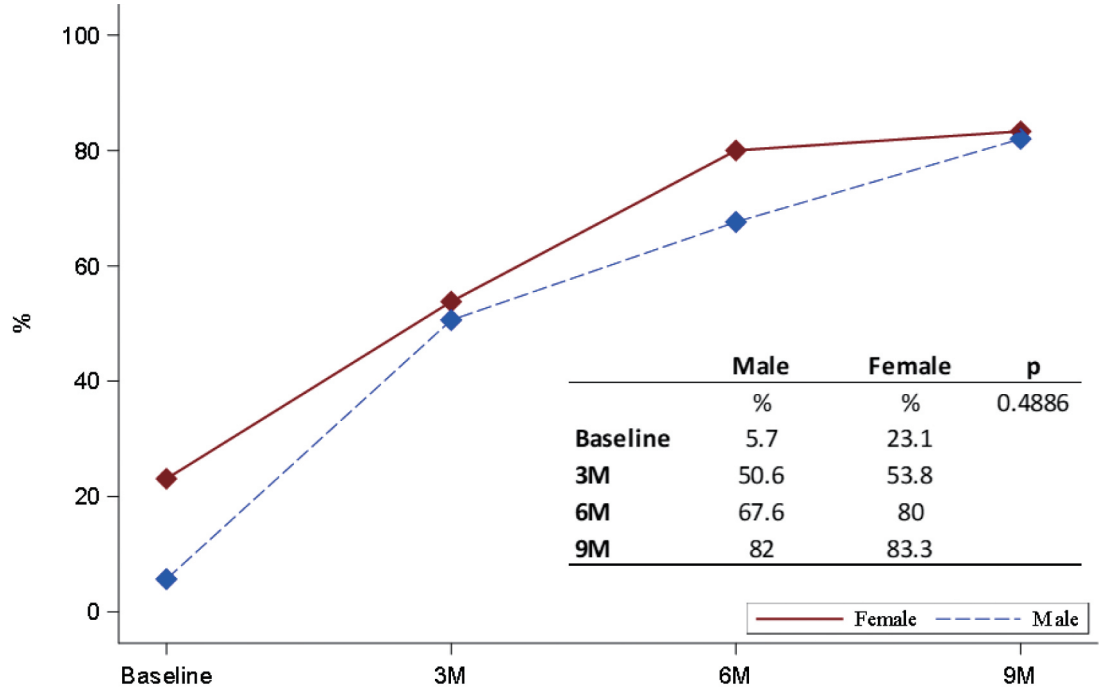


Figure 4. LDL-C goal attainment rates in both genders at 3-, 6-, and 9-month follow-ups. Abbreviations: M = month.



	Male	Female	p
	%	%	0.8214
Baseline	25.3	23.1	
3M	78.8	76.9	
6M	77	90	
9M	86	100	

Figure 5. Prescription rates of high-intensity statin in both genders at 3-, 6-, and 9-month follow-ups. Abbreviations: M = month.



	Male	Female	p
	%	%	0.4886
Baseline	5.7	23.1	
3M	50.6	53.8	
6M	67.6	80	
9M	82	83.3	

Figure 6. Prescription rates of ezetimibe in both genders at 3-, 6-, and 9-month follow-ups. Abbreviations: M = month

and 26.1% in China.[20] In an ICLPS study, only 32.1% of very high risk patients and 51.9% of high risk patients achieved their target LDL-C goals.[15] Real-world evidence from Germany has shown that only 35% of high risk or very high risk patients received statins, and most statin-treated patients received only low to moderate intensity statin.[18] Similarly, a recent study from China showed that most patients with CAD received moderate-intensity statin therapy, not HIS.[21] These data suggest that there is a big gap between the guidelines' recommendations and real-world practice. In our Lipid Clinic, each patient received well-organized treatment and counselling, including lipid-lowering therapy (LLT) and life-style modification, following the recommendations of the current Taiwan lipid guidelines. In addition, we aggressively prescribed HIS and ezetimibe in the Lipid Clinic, and therefore the LDL-C goal attainment rates in patients with CAD were much better than those reported in previous studies[15, 18-20] and previous reports in Taiwan.[22]

The evidence regarding differences in LDL-C goal attainment rates between both genders remains controversial. The ICLPS study[15] and the EUROASPIRE IV study[16] showed that male patients were more likely to reach target serum LDL-C levels, compared with female patients. The authors of the EUROASPIRE IV study[16] have suggested that female patients might have a lower level of education and less awareness of their disease than male patients, resulting in a lower LDL-C goal attainment rate in female patients, compared with male patients. However, the DYSIS study showed that female gender was associated with a higher chance of achieving target LDL-C levels, compared with male gender.[14] Despite these above-mentioned controversial observations, the goal attainment rates of LDL-C and the responsiveness under LLT in female patients with CAD have become important issues in the current era, because female patients with CAD tend to be older, have more comorbidities, and run a higher risk of developing further adverse cardiac events,[23,24] compared with male patients with CAD. Although female patients with CAD in our present study had a relatively higher serum LDL-C level at baseline, compared with male patients with CAD, the use of HIS and the responsiveness under LLT in female patients with CAD were greater than those of male patients with CAD, resulting in a comparable LDL-C goal attainment rate in both genders. Our present study showed that HIS use should be aggressively implemented in patients with CAD, especially in female patients who usually have more cardiovascular risk factors than male patients.

The use of HIS is associated with LDL-C goal attainment rates in high-risk patients. According to data from a large-scale database in the USA, in 2017, only 15.3% and 25.2% of patients with CAD received a HIS and achieved serum LDL-C levels <70 mg/dL, respectively.[25] The EUROASPIRE IV study[16] also showed that only 32.7% of patients with CAD were prescribed a HIS and 19.3% of these patients achieved serum LDL-C levels <70 mg/dL at 6-month follow-up. In the present study, the use of HIS and the LDL-C goal attainment rates in patients with CAD were much higher than those reported in the above-mentioned studies.[16,25] Our results were also superior to those obtained from the CEPHEUS Pan-Asian survey.[22] Notably, the present study also features aggressive prescription of ezetimibe, irrespective of gender. The results of our study provide valuable evidence to support the role of HIS and ezetimibe in facilitating LDL-C goal attainment in patients with CAD, as recommended by current guidelines.[7,26,27]

Our study has some limitations. First, this was a single-center study with a small population size. We did not evaluate and compare the differences between patients treated in the Lipid Clinic and patients treated in non-lipid clinics, and this omission may have introduced bias into the present study. Additionally, we did not observe and compare cardiovascular outcomes between genders, and further large-scale nationwide surveys are necessary to investigate this issue. Second, in this present analysis, we excluded

patients who were intolerant to statins, or for whom they were contraindicated, and therefore we could not evaluate the LDL-C goal attainment rates in such patients. Third, the number of PCSK9 inhibitor users was small because reimbursement for the cost of PCSK9 inhibitors was not yet covered by the National Health Insurance of Taiwan during the study period. Therefore, the role of PCSK9 inhibitors could not be evaluated. Despite these limitations, our data present the current status of LDL-C control in both genders in Taiwan and demonstrate the importance of an aggressive strategy when prescribing HIS ± ezetimibe therapy to improve LDL-C goal attainment rates.

In conclusion, our data suggest that female patients with CAD have relatively higher baseline LDL-C levels and also better responsiveness under LLT than male patients with CAD. The achievement of LDL-C goals was similar for both genders. Aggressive use of HIS and ezetimibe should be implemented in patients with CAD to facilitate the improvement of LDL-C goal attainment rates.

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Disclosure

All authors have no conflicts of interest to be disclosed.

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