International Journal of Gerontology 16 (2022) 247–253
https://doi.org/10.6890/IJGE.202207_16(3).0015

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Original Article

The Current Status for Management of Dyslipidemia in Elderly High-Risk Patients in Taiwan: A Real-World Data in a Tertiary Medical Center

Ya-Hui Chang [a,b], Chih-Hung Liang [c], Chia-Ling Tsai [d], Jen-Yu Chuang [c], Chih-Chung Hsiao [d], Yi-Hong Zeng [e], Yi-Han Chen [f], Hung-I Yeh [a,d], Chao-Feng Lin [a,d] *

[a] *Department of Medicine, MacKay Medical College, New Taipei City, Taiwan,* [b] *Department of Pharmacy, MacKay Memorial Hospital, Taipei, Taiwan,* [c] *Department of Medical Education, MacKay Memorial Hospital, Taipei, Taiwan,* [d] *Department of Cardiology, MacKay Memorial Hospital, Taipei, Taiwan,* [e] *Department of Endocrinology, MacKay Memorial Hospital, Taipei, Taiwan,* [f] *School of Public Health, College of Public Health, Taipei Medical University, Taipei, Taiwan*

ARTICLE INFO

Accepted 16 December 2021

Keywords:
elderly,
high-intensity statin,
ezetimibe,
low-density lipoprotein cholesterol

SUMMARY

Background: The use of statin has been encouraged in elderly high-risk patients; nevertheless, the prescription rates of statin have been shown to decline with age. Despite the current Taiwan lipid guidelines has been issued, the status for management of dyslipidemia among elderly high-risk patients in Taiwan remained unclear. The present study was aimed to investigate the prescription rates of high-intensity statin (HIS)/ezetimibe and LDL-C goal attainment rates among elderly high-risk patients in a tertiary medical center.

Methods: Between July 2018 and August 2019, 208 high-risk patients with suboptimal serum LDL-C levels, including 70 elderly patients (age ≥ 65 years) and 138 non-elderly patients (age < 65 years) received lipid-lowering therapy (LLT) and observation for a 12-month follow-up. The prescription rates of any statins/HIS/ezetimibe, the percentages of LDL-C reduction, and LDL-C goal attainment rates at 12-month follow-up were compared between elderly and non-elderly high-risk patients.

Results: The serum LDL-C levels at baseline/12-month among elderly and non-elderly high-risk patients were respectively 128.8 ± 36.3/80.7 ± 46.3 and 138.5 ± 52.3/78.1 ± 37.0 mg/dL, with respectively LDL-C reductions of 34.1% and 39.6% at 12-month follow-up. The prescription rates of any statins/HIS/ezetimibe at 12-month follow-up in elderly and non-elderly high-risk patients were respectively 88.9%/68.3%/47.6% and 96.6%/72.7%/60.7%. The LDL-C goal attainment rates at 12-month follow-up in elderly and non-elderly high-risk patients were respectively 68.3% and 73.3%. All observed study outcomes were comparable between groups without significant statistical differences.

Conclusion: Our findings highlight that the elderly high-risk patients in Taiwan received similar aggressive strategy of LLT with similar LDL-C attainment rates compared with non-elderly high-risk patients.

1. Introduction

A large number of clinical evidence has demonstrated that an increased serum level of low-density lipoprotein cholesterol (LDL-C) plays an essential role in the development and progression of atherosclerotic cardiovascular disease (ASCVD).[1] In addition, clinical trials have shown that an aggressive use of statin is associated with intensive LDL-C lowering and decreased risk of ASCVD.[2,3] According to the current American[4] and European[5] guidelines for management of dyslipidemia, high-intensity statin (HIS) is recommended in high-risk patients, and ezetimibe should be added when the target LDL-C goal is not reached.[4,5] Although these aforementioned guidelines' recommendations, the attainment rates of target LDL-C levels and the prescription rates of HIS and ezetimibe in high-risk patients remain still suboptimal.[6–8]

Based on complex mechanisms with age-related decreased activity of lipoprotein lipase and impaired hepatic uptake of lipoprotein, elevation of serum LDL-C levels is prevalent[9–11] and poses a high cardiovascular risk in the elderly population.[12] According to a large-scale meta-analysis of 28 trials,[13] the use of statin has been encouraged in elderly high-risk patients to reduce major vascular events; nevertheless, the prescription rates of statin have been shown to decline with age.[13] Recently, the latest Taiwan lipid guidelines[14] has been issued and recommended the target serum LDL-C levels in high-risk patients irrespective of age. However, the current status for management of dyslipidemia in elderly high-risk patients in Taiwan, including LDL-C goal attainment rates and the prescription rates of HIS and ezetimibe, remained still unclear. To address this knowledge gap, the present study was aimed to investigate the attainment rates of target serum LDL-C levels and the prescription rates of HIS and ezetimibe among elderly high-risk patients in a tertiary medical center in Taiwan.

2. Materials and methods

2.1. Study design, high-risk characteristics, and target serum LDL-C levels

This study was designed to conduct a retrospective analysis of

* Corresponding author.
E-mail address: thcpci@gmail.com (C.-F. Lin)

prospective enrolled high-risk patients in a tertiary medical center in Taiwan. All protocols of the present study were approved by the Institutional Review Board of our institution (Approval No. 18MMHIS 083e), and written informed consent was obtained from all participants.

High-risk characteristics were determined according to the current Taiwan lipid guidelines[14] if patients had at least one of the following medical histories: diabetes mellitus (DM), familial hypercholesterolemia (FH), ischemic stroke (IS), coronary artery disease (CAD), or peripheral artery disease (PAD). The diagnosis of CAD was made if patients had > 50% diameter stenosis of major epicardial coronary arteries confirmed by coronary angiography or coronary computed tomography (CT) angiography, or had a history of acute coronary syndrome (ACS) receiving hospitalization or coronary revascularization. The diagnosis of IS was confirmed by the neurologist's records and relevant brain CT or magnetic resonance imaging findings. Patients with PAD were defined as those who had an ankle-brachial index < 0.9 or > 1.4 and/or > 50% diameter stenosis of peripheral arteries determined by CT angiography. The patients' history of DM was based on medical records and prescribed medications. The diagnosis of FH was clinically determined when patients had a Dutch Lipid Clinic Network (DLCN) score > 8 or a confirmed genotype by gene test.[15] In addition, patients' histories of hypertension (HTN), heart failure, and uremia receiving dialysis were identified based on medical records.

The target serum LDL-C levels of high-risk patients without CAD and high-risk patients with CAD were respectively < 100 mg/dL and < 70 mg/dL irrespective of age according to the current Taiwan lipid guidelines.[14] Rosuvastatin ≥ 20 mg/day and atorvastatin 40–80 mg/day were referred as HISs.[4,5,14]

2.2. Study population, data collection, and treatment strategies

High-risk patients who did not achieve their target serum LDL-C levels were eligible to be enrolled in the present study. Thereafter we excluded patients who were under 20 years old, unable to receive regular blood tests to evaluate lipid profiles, contraindicated to statin or ezetimibe therapy, or disagreed with providing personal medical information. Finally, high-risk patients were divided into 2 groups: elderly high-risk patients and non-elderly high-risk patients (Figure 1). In the present study, the "elderly" patients were defined as those who had a chronological age of 65 years old or older, while those who had an age under 65 years old were referred to the "non-elderly" patients.[16]

The patients' baseline data, including age, sex, weight, height, smoking habit, high-risk characteristics, comorbidities, laboratory data, and prescribed medications were collected by specially-trained study nurses. Body mass index was calculated as weight in kilograms divided by the square of height in meters. The prescribed medications, including angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), antiplatelet (i.e., aspirin and $P2Y_{12}$ inhibitor), beta-blocker, calcium-channel blocker, statin, ezetimibe, fibrate, and insulin, were recorded in detail.

All patients participated in the present study received adjustment or initiation statin therapy after enrollment. Briefly, HIS therapy was encouraged, while moderate-intensity or low-intensity statin was suggested when high-risk patients did not adhere to HIS therapy. The use of ezetimibe in combination with statin therapy was suggested when high-risk patients did not attain their LDL-C goals after HIS or maximally tolerated dose of stain therapy.[4,5,14] All treatment strategies were implemented under full physician-patient discussion. The reasons of nonadherence to statins and ezetimibe therapy, including discontinuation by personal willingness, discomfort symptoms, and drug-related increase of three times the upper limit of normal in creatine kinase (CK) or alanine aminotransferase evaluated by validated diagnostic algorithm,[17] were recorded. All high-risk patients in the present study received observation and underwent blood tests for lipid profiles every 3 months for a total duration of 12 months.

An electronic checklist was integrated into medical order system and shown to assist physicians to evaluate patients' high-risk characteristics when physicians prescribed lipid-lowering therapy (LLT), thereby reminding physicians whether the patients achieved their target serum LDL-C levels and whether adjustment of LLT was needed. 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.

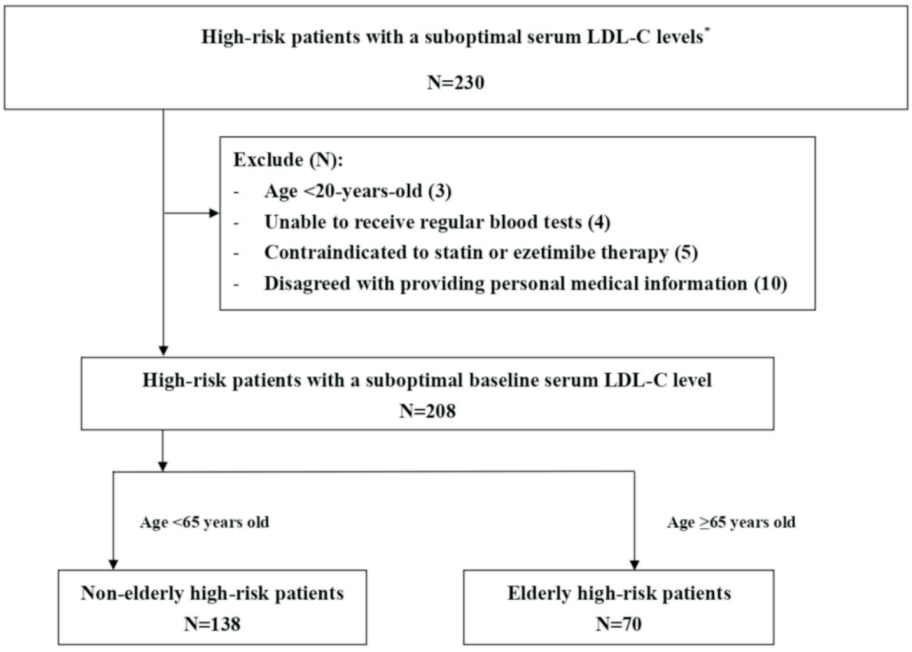

Figure 1. Diagram of patient selection.

2.3. Study outcomes

The study outcomes in the present study were the goal attainment rates of LDL-C and the prescription rates of HIS and ezetimibe in high-risk patients at 12-month follow-up.

2.4. Statistical methods

Continuous variables were presented with means (± standard deviations). Categorical variables were presented as numbers (percentages). Comparisons were performed using the unpaired Student t test, 2-sample 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 elderly high-risk patients were compared with those of non-elderly high-risk patients. The data of lipid control in patients, including serum levels of LDL-C, percentages of LDL-C reduction from baseline, goal attainment rates of LDL-C, and percentages of patients receiving any statins/HIS/ezetimibe, were recorded and analyzed at every 3-month follow-up. Finally, the aforementioned data of lipid control in elderly high-risk patients were compared with those of non-elderly high-risk patients at 12-month follow-up. Statistical significance was set at $p < 0.05$ (2-tailed). SAS statistical software (version 9.3 for Windows; SAS Institute, Cary, NC, USA) was used for all analyses.

3. Results

3.1. Demographic characteristics, lipid profiles, and LLT of patients at baseline

Of 208 high-risk patients with suboptimal serum LDL-C levels who participated in this present study, there were 70 elderly patients and 138 non-elderly patients (Figure 1). The mean age of elderly high-risk patients was 70.5 ± 4.0 years, while that of non-elderly high-risk patients was 53.1 ± 8.6 years. The elderly high-risk patients had a lower body mass index, a lower hemoglobin, a worse renal function, fewer current smokers, fewer histories of FH, more histories of hypertension, and more frequently received ACEI/ARB and insulin compared with non-elderly patients (Table 1).

The baseline serum LDL-C levels of elderly high-risk patients

Table 1
Baseline characteristics of high-risk patients.

	Total (N = 208)	Non-elderly (N = 138)	Elderly (N = 70)	*p**
Age	59.0 (11.1)	53.1 (8.6)	70.5 (4.0)	< 0.001
Male	148 (71.2)	100 (72.5)	48 (68.6)	0.558
BMI (Kg/m^2)	27.1 (4.9)	28.0 (5.3)	25.4 (3.4)	< 0.001
Medical history				
Current smoker	43 (20.7)	36 (26.1)	7 (10.0)	0.007
Hypertension	129 (62.0)	77 (55.8)	52 (74.3)	0.009
Diabetes	129 (62.0)	89 (64.5)	40 (57.1)	0.302
FH	11 (5.3)	11 (8.0)	0 (0)	0.017
Heart failure	27 (13.0)	17 (12.3)	10 (14.3)	0.690
Ischemic stroke	15 (7.2)	8 (5.8)	7 (10.0)	0.268
AF	4 (1.9)	2 (1.4)	2 (2.9)	0.604
Uremia on dialysis	3 (1.4)	3 (2.2)	0 (0)	0.552
CAD	100 (48.1)	62 (44.9)	38 (54.3)	0.202
History of ACS	59 (28.4)	39 (28.3)	20 (28.6)	0.963
PAD	16 (7.7)	12 (8.7)	4 (5.7)	0.446
Antiplatelets	107 (51.4)	68 (49.3)	39 (55.7)	0.380
Aspirin	85 (40.9)	52 (37.7)	33 (47.1)	0.190
$P2Y_{12}$ inhibitor	58 (27.9)	41 (29.7)	17 (24.3)	0.410
Prescribed medications				
Beta-blocker	115 (55.3)	72 (52.2)	43 (61.4)	0.205
Calcium channel blocker	50 (24.0)	29 (21.0)	21 (30.0)	0.152
ACEI/ARB	125 (60.1)	75 (54.3)	50 (71.4)	0.017
Insulin	23 (11.1)	10 (7.2)	13 (18.6)	0.014
Any statin	113 (54.3)	73 (52.9)	40 (57.1)	0.561
HIS	31 (14.9)	20 (14.5)	11 (15.7)	0.815
Ezetimibe	17 (8.2)	10 (7.2)	7 (10.0)	0.493
Fibrate	16 (7.7)	13 (9.4)	3 (4.3)	0.189
Laboratory and physiological data				
LVEF (%)	62.1 (7.5)	62.4 (7.1)	61.7 (8.4)	0.445
Hemoglobin (g/dL)	14.0 (1.7)	14.2 (1.7)	13.5 (1.7)	0.006
Fasting glucose (mg/dL)	123.3 (35.6)	122.0 (37.3)	125.7 (32.2)	0.218
HbA1c (%)	6.9 (1.4)	6.8 (1.2)	7.0 (1.7)	0.782
Cr (mg/dL)	1.2 (1.0)	1.1 (1.2)	1.2 (0.6)	< 0.001
eGFR (ml/min)	75.5 (24.8)	81.5 (25.3)	63.6 (19.1)	< 0.001
ALT (U/L)	25.9 (12.4)	27.3 (14.4)	23.4 (6.5)	0.143
Lipid profiles				
TC (mg/dL)	210.4 (73.5)	214.5 (85.0)	202.5 (41.9)	0.913
TG (mg/dL)	167.3 (77.2)	174.8 (81.8)	152.6 (65.2)	0.099
HDL-C (mg/dL)	44.4 (14.1)	44.6 (15.6)	44.0 (10.5)	0.705
LDL-C (mg/dL)	135.2 (47.7)	138.5 (52.3)	128.8 (36.3)	0.631
LDL-C in statin nonusers	154.0 (47.8)	159.0 (54.6)	143.0 (25.4)	0.767
LDL-C in statin users	119.5 (41.6)	120.2 (42.8)	118.1 (39.8)	0.822
% LDL-C need to reduce				
Statin nonusers	28.1 (16.2)	28.1 (15.9)	28.0 (16.9)	0.838
Statin users	37.1 (15.9)	37.5 (16.8)	36.1 (13.9)	0.844

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ACS = acute coronary syndrome; AF = atrial fibrillation; AST = aspartate aminotransferase; BMI = body mass index; CAD = coronary artery disease; Cr = creatinine; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; HIS = high-intensity statin; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; PAD = peripheral artery disease; TC = total cholesterol; TG = triglyceride.
* *p* value was calculated when elderly group vs. non-elderly group.

were similar to those of non-elderly high-risk patients irrespective of statin use at enrollment (Table 1). The serum LDL-C levels in statin nonusers and statin users of elderly high-risk patients were respectively 143.0 ± 25.4 mg/dL and 118.1 ± 39.8 mg/dL, while those of non-elderly high-risk patients were respectively 159.0 ± 54.6 mg/dL and 120.2 ± 42.8 mg/dL (Table 1). In addition, the percentages of LDL-C need to reduce among elderly high-risk patients were 28.0 ± 16.9% in statin nonusers and 36.1 ± 13.9% in statin users, while those among non-elderly patients were 28.1 ± 15.9% in statin nonusers and 37.5 ± 16.8% in statin users (Table 1). Other lipid profiles, including serum levels of TC, TG, and HDL-C, were comparable between elderly and non-elderly high-risk patients (Table 1). At enrollment, the prescription rates of any statins, HIS, and ezetimibe in elderly high-risk patients were respectively 57.1%, 15.7% and 10.0%, while those of non-elderly high-risk patients were respectively 52.9%, 14.5% and 7.2% (Table 1).

3.2. The percentages of reduction in LDL-C and LDL-C goal attainment rates during follow-ups

The serum LDL-C levels at 3-, 6-, 9-, and 12-month follow-ups in elderly high-risk patients were respectively 82.1 ± 39.0, 82.1 ± 37.1, 73.5 ± 25.8, and 80.7 ± 46.3 mg/dL, while those of non-elderly high-risk patients were respectively 79.2 ± 27.3, 79.9 ± 30.1, 80.1 ± 30.5, and 78.1 ± 37.0 mg/dL (Figure 2A). The percentages of reduction in serum LDL-C in elderly high-risk patients at the 3-, 6-, 9-, and 12-month follow-ups were respectively 34.4 ± 28.7%, 34.3 ± 26.1%, 39.6 ± 22.6%, and 34.1 ± 35.5%, while those of non-elderly high-risk patients were respectively 39.6 ± 19.4%, 38.2 ± 27.0%, 38.7 ± 24.7%, and 39.6 ± 27.6 (Figure 2B). The goal attainment rates of LDL-C at 3-, 6-, 9-, and 12-month follow-ups in elderly high-risk patients were respectively 62.3%, 62.9%, 70.3%, and 68.3%, while those of non-elderly high-risk patients were respectively 69.9%, 73.3%, 66.9%, and 73.3% (Figure 2C).

Generally, elderly high-risk patients had similar serum LDL-C levels (p = 0.978), LDL-C reduction following treatment (p = 0.318), and goal attainment rates of LDL-C (p = 0.477) compared with non-elderly high-risk patients at 12-month follow-up (Figure 2).

3.3. The prescription rates of any stains, HIS, and ezetimibe during follow-ups

The major reason of nonadherence to LLT during follow-ups was patients' personal willingness. There were no documented adverse effects, including discomfort symptoms, abnormal elevation of CK and liver enzymes following LLT, observed in elderly and non-elderly high-risk patients.

The prescription rates of any statins/HIS/ezetimibe in elderly high-risk patients at 3-, 6-, 9-, and 12-month follow-ups were respectively 98.6%/76.8%/34.8%, 94.3%/74.3%/52.9%, 93.9%/72.7%/53.0%, and 88.9%/68.3%/47.6%, while those of non-elderly high-risk patients were respectively 98.6%/73.9%/39.1%, 96.3%/69.4%/49.3%, 96.9%/73.2%/54.3%, and 96.6%/72.7%/60.7% (Figure 3). Generally, elderly high-risk patients had similar prescription rates of any statin (p = 0.052), HIS (p =0.535), and ezetimibe (p = 0.092) at 12-month follow-up compared with non-elderly high-risk patients at 12-month follow-up (Figure 3).

4. Discussion

The main findings of our present study demonstrated that the prescription rates of any statins, HIS, and ezetimibe in elderly high-risk patients were similar to those of non-elderly high-risk patients. In addition, the percentages of patients attaining their LDL-C goals were comparable between elderly and non-elderly high-risk patients. To the best of our knowledge, the present study is the first report showing the current status for management of dyslipidemia among elderly high-risk patients in Taiwan.

The use of statin exhibited clinical benefits among elderly high-risk patients in several previous landmark studies such as the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVEIT-TIMI 22),[18] Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL),[19] Heart Protection Study (HPS),[20] and Study Assessing Goals in the Elderly (SAGE)[21] trials. The recent meta-analysis[13] has further determined that statin therapy led to a significant reduction in major vascular events among elderly high-risk patients. In addition, the

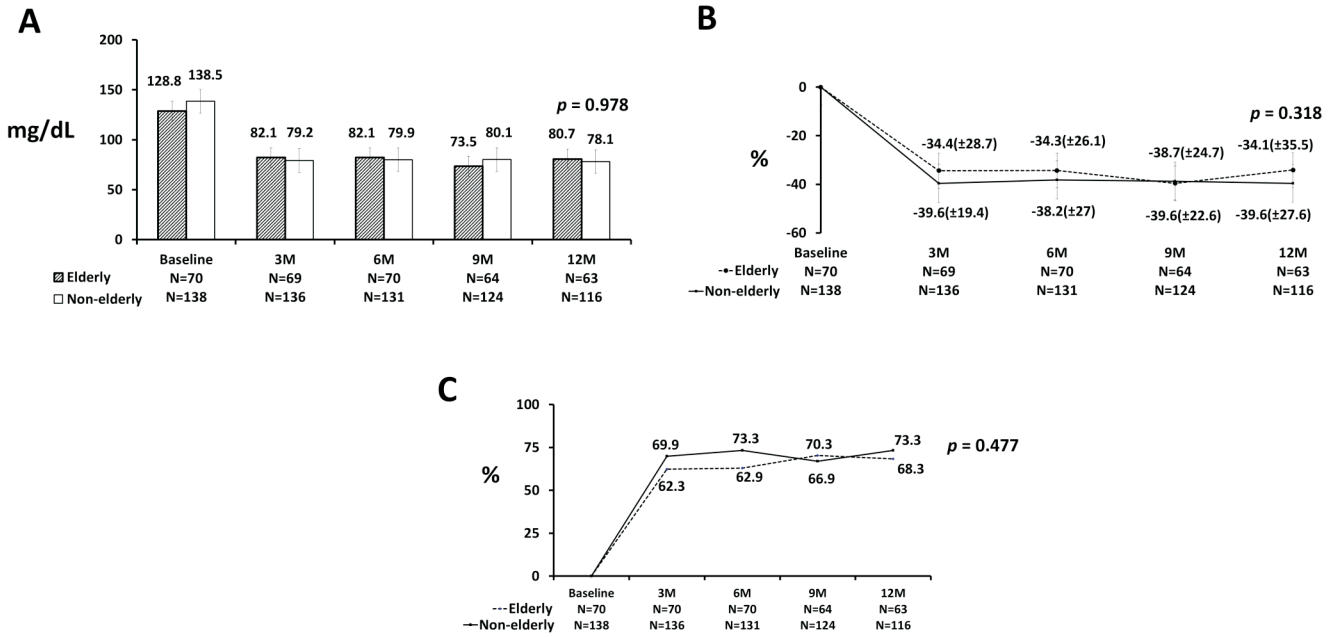

Figure 2. The serum levels of LDL-C, LDL-C reduction, and the goal attainment rates of LDL-C in elderly and non-elderly patients during follow-ups. (A) Serum LDL-C levels; (B) Percentage of LDL-C reduction; (C) The goal attainment rates of LDL-C.

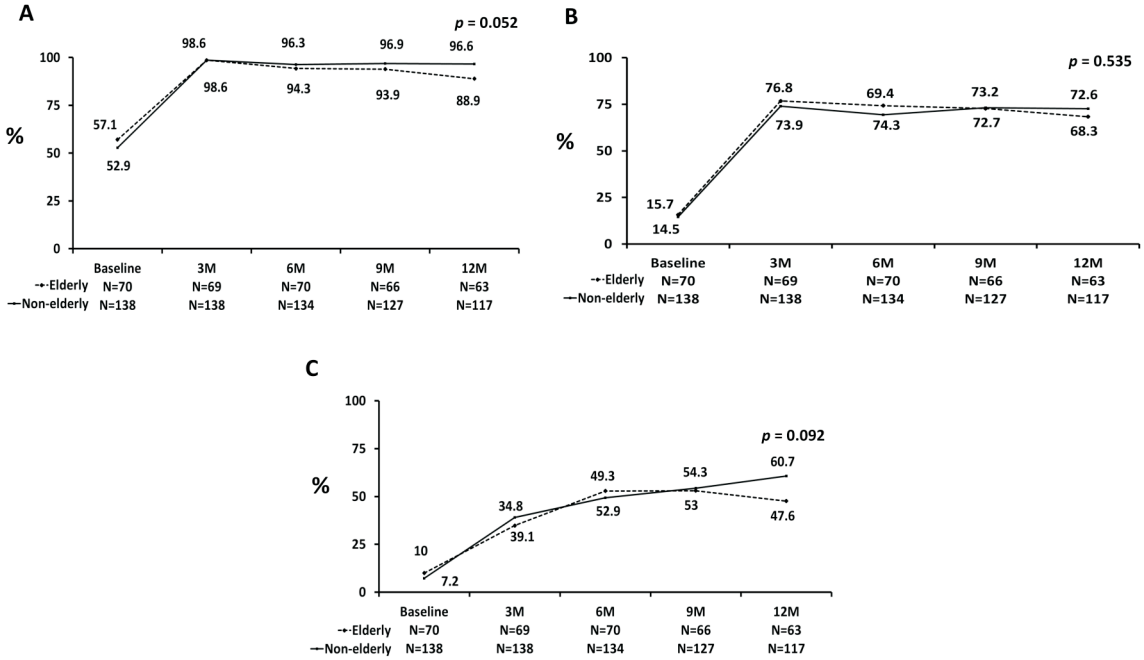

Figure 3. The prescription rates of any statin, HIS, and ezetimibe following treatment in elderly and non-elderly patients. (A) The prescription rates of any statin; (B) The prescription rates of HIS; (C) The prescription rates of ezetimibe.

SAGE[21] trial showed a favored effect of HIS over moderate- or low-intensity statin therapy in reducing all-cause mortality among elderly patients with CAD. Despite the aforementioned supportive evidence, HIS therapy has been still underutilized in elderly high-risk patients.[13,22] In Taiwan, evidence of the current prescription rates of HIS among elderly high-risk patients remained scarce. According to Taiwanese Secondary Prevention for patients with AtheRosCLErotic disease (T-SPARCLE) Registry study, most high-risk patients in Taiwan received very-low to low equipotent doses of statin therapy irrespective of age.[23] Compared with T-SPARCLE[23] and previous studies,[13,22] our present study reported a much higher prescription rate of HIS without documented HIS-associated adverse effects among elderly high-risk patients. In addition, the percentages of patients receiving HIS in the present study were comparable between elderly and non-elderly high-risk patients, implicating that we implemented an aggressive strategy of HIS therapy according to guidelines' recommendations.[4,5,14] The aggressive use of HIS therapy is especially important for patients with CAD because early use of HIS results in a reduced risk of short-term and long-term adverse coronary events.[5,24] Moreover, initiation of HIS therapy assisted to early identify high-risk patients who did not attain their LDL-C goals and need combination therapy with other drugs, such as ezetimibe.

Ezetimibe decreases cholesterol absorption in the small intestine by directly binding to Niemann-Pick C1-like 1 (NPC1L1) protein in intestinal mucosa.[25] The current American,[4] European,[5] and Taiwan[14] lipid guidelines recommended that adding ezetimibe to statin therapy results in further LDL-C lowering and reducing ASCVD risk irrespective of age based on data from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).[26] A secondary analysis of the IMPROVIT-IT study[26] determined that the use of ezetimibe showed a greater risk reduction in adverse cardiovascular events among patients above 75 years or older compared with those patients under 75 years.[27] Additionally, the incidence rates of ezetimibe-associated adverse effects in elderly patients, including myopathy, rhabdomyolysis, and abnormal elevation of liver enzymes, did not increase by combination with ezetimibe.[27] Compared with the T-SPARCLE registry study in which less than 5% of total high-risk patients received ezetimibe, the present study showed a higher prescription rate of ezetimibe in both elderly and non-elderly high-risk patients.[23] In addition, we did not observe adverse effects following ezetimibe therapy. Collectively, the increased use of ezetimibe should be encouraged to facilitate intensive LDL-C lowering and provide clinical benefits, especially for elderly high-risk patients who are potentially deemed to have risk of statin-associated adverse effects or nonadherence to HIS therapy.[4,5]

The benefits of achieving LDL goals in elderly patients have been assessed.[28,29] A secondary analysis of PROVE IT-TIMI 22 trial[18] revealed that elderly high-risk patients who achieved LDL-C goals had a 40% lower risk of composite endpoints (cardiac death, MI, and unstable angina requiring hospitalization) compared with those elderly high-risk patients who did not achieve LDL-C goals.[29] In Taiwan, the real-world data showing LDL-C goal attainment rates in elderly high-risk patients is deficient. Our present study demonstrated a better LDL-C goal attainment rate compared with previous studies.[23,28] Moreover, we also found that an increased trend of LDL-C goal attainment rates was concordant with an increased use of HIS, implicating that HIS use and treatment intensification during follow-ups may facilitate achievement of LDL-C goals.[28,29]

In the present study, the proportion of elderly high-risk patients who achieved their LDL-C goals in the present study tended to plateau after 3 months despite continuing HIS therapy and increased use of ezetimibe, which was similar to the findings of REALITY-Asia study.[30] Additionally, we observed that 31.3% of elderly high-risk patients were still nonadherence to HIS therapy despite we implemented an aggressive LLT strategy. These findings raise some real-world issues for management of dyslipidemia in high-risk patients. One important issue is that drug nonadherence remains a major challenge in efforts to improve LDL-C goal attainment. Nonadherence to HIS therapy may result in down-titration or discontinuation of HIS therapy, thereby leading to a high probability to develop adverse cardiovascular events, especially in high-risk patients.[31] A previous study showed that patients with CAD who were nonadherent to HIS therapy had a 50% higher risk of recurrent cardiac event compared with those patients who were adherent to HIS

therapy.[31] The reasons of nonadherence to HIS therapy involve misleading information from media, nonspecific discomforts or laboratory abnormalities that may be temporally associated with the recent initiation or dose escalation of statins, and beliefs that LDL-C lowering is no longer needed.[32] The decisions of down-titration or discontinuation of HIS therapy made by high-risk patients and physicians highlight the need for continued education regarding the long-term benefits and the established safety of HIS. In addition, physicians should pay attention and work with the patients' concerns of statin-associated adverse effects, including muscle symptoms and elevation of liver enzymes by using a validated diagnostic algorithm.[17,32] Another issue is that LDL-C lowering agents other than statins and ezetimibe, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and bempedoic acid, should be provided to further lower serum LDL-C levels and achieve LDL-C goals[32] in high-risk patients who are nonadherent, intolerant, or resistant to statin and ezetimibe therapy.

Our study was subjected to several limitations. First, the LDL-C goal attainment rates presented in our study might be overestimated because we did not count the data from patients who were lost to follow-ups. Moreover, we did not survey the patients' satisfaction of treatment and the patients' reasons of nonadherence in our present study. In addition, we excluded high-risk patients who were contraindicated to stains and ezetimibe therapy in this present analysis, therefore we could not observe the status of lipid control in the aforementioned patients for comparisons. Second, there were few PCSK9 inhibitor users reported in our present study because the cost of PCSK9 inhibitors was not covered by Taiwan's National Health Insurance. Moreover, bempedoic acid was not yet approved to use in Taiwan until the end of this study. Therefore, the roles of PCSK9 inhibitors and bempedoic acid could not be evaluated. Third, this was a single-center study with a small size of population, so that LLT-associated adverse effects might be underestimated. In addition, we did not observe and compare clinical cardiovascular outcomes between patients with goal attainment and those patients without attainment. A nationwide population-based investigation with longer observation periods is suggested to address this aforementioned issue. Finally, it is worthwhile to establish an artificial intelligence-based system that can actively inform both physicians and patients about suboptimal results of blood lipid tests, thereby improving LLT adherence. Despite these limitations, our data firstly demonstrate the current status for management of dyslipidemia in elderly high-risk patients in Taiwan and highlight the importance of an aggressive strategy in prescribing HIS ± ezetimibe therapy according to the current guidelines' recommendations.

5. Conclusion

The present study revealed that elderly high-risk patients had a comparable LDL-C goal attainment rate to non-elderly patients under a similar aggressive strategy in prescribing HIS and ezetimibe.

Acknowledgements

This study was supported by Amgen Inc.

Disclosure

All authors have no conflicts of interest to be disclosed.

References

1. Packard C, Chapman MJ, Sibartie M, et al. Intensive low-density lipoprotein cholesterol lowering in cardiovascular disease prevention: opportunities and challenges. *Heart.* 2021;107:1369–1375.
2. Mills EJ, O'Regan C, Eyawo O, et al. Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of > 40,000 patients. *Eur Heart J.* 2011;32:1409–1415.
3. Cannon CP, Steinberg BA, Murphy SA, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol.* 2006;48:438–445.
4. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;73:3168–3209.
5. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020;41:111–188.
6. Kajinami K, Ozaki A, Tajima Y, et al. Real-world data to identify hypercholesterolemia patients on suboptimal statin therapy. *J Atheroscler Thromb.* 2019;26:408–431.
7. Cannon CP, Khan I, Klimchak AC, et a. Simulation of lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease. *JAMA Cardiol.* 2017;2:959–966.
8. Reiner Ž, De Backer G, Fras Z, et al. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries—Findings from the EUROASPIRE IV survey. *Atherosclerosis.* 2016;246:243–250.
9. Shanmugasundaram M, Rough SJ, Alpert JS. Dyslipidemia in the elderly: Should it be treated? *Clin Cardiol.* 2010;33:4–9.
10. Lin CF, Chien SC, Yeh HI. Epidemiology of dyslipidemias in Asia Pacific countries: Differences between general population and the elderly. *Int J Gerontol.* 2019;13:100–102
11. Liu HH, Li JJ. Aging and dyslipidemia: a review of potential mechanisms. *Ageing Res Rev.* 2015;19:43–52.
12. Mortensen MB, Falk E. Primary prevention with statins in the elderly. *J Am Coll Cardiol.* 2018;71(1):85–94.
13. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet.* 2019;393:407–415.
14. Li YH, Ueng KC, Jeng JS, et al. 2017 Taiwan lipid guidelines for high risk patients. *J Formos Med Assoc.* 2017;116:217–248.
15. Defesche JC, Lansberg PJ, Umans-Eckenhausen MA, et al. Advanced method for the identification of patients with inherited hypercholesterolemia. *Semin Vasc Med.* 2004;4:59–65.
16. Laws & Regulations Database of The Republic of China (Taiwan). *Senior Citizens Welfare Act*. Taipei, Taiwan: Ministry of Health and Welfare; 2020. Available at https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=D0050037.
17. Chien SC, Chen PS, Huang YH, et al. 2019 Taiwan Society of Lipids and Atherosclerosis expert consensus statement on statin intolerance. *J Formos Med Assoc.* 2019;118:1385–1392.
18. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350:1495–1504.
19. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* 2006;355:549–559.
20. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg.* 2007;45:645–654.
21. Deedwania P, Stone PH, Bairey Merz CN, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). *Circulation.* 2007;115:700–707.
22. Musich S, Wang SS, Schwebke K, et al. Underutilization of statin therapy for secondary prevention of cardiovascular disease among older adults. *Popul Health Manag.* 2019;22:74–82.
23. Ho LT, Yin WH, Chuang SY, et al. Determinants for achieving the LDL-C target of lipid control for secondary prevention of cardiovascular events in Taiwan. *PLoS One.* 2015;10:e0116513.
24. Schwartz GG, Fayyad R, Szarek M, et al. Early, intensive statin treatment reduces 'hard' cardiovascular outcomes after acute coronary syndrome. *Eur J Prev Cardiol.* 2017;24:1294–1296.

25. Morgan AE, Mooney KM, Wilkinson SJ, et al. Cholesterol metabolism: A review of how ageing disrupts the biological mechanisms responsible for its regulation. *Ageing Res Rev.* 2016;27:108–124.
26. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med.* 2015;372:2387–2397.
27. Bach RG, Cannon CP, Giugliano RP, et al. Effect of Simvastatin-ezetimibe compared with simvastatin monotherapy after acute coronary syndrome among patients 75 years or older: A secondary analysis of a Randomized Clinical Trial. *JAMA Cardiol.* 2019;4:846–854.
28. Nichols GA, Nag S, Chan W. Intensity of lipid-lowering therapy and low-density lipoprotein cholesterol goal attainment among the elderly before and after the 2004 National Cholesterol Education Program Adult Treatment Panel III update. *Am Heart J.* 2007;154:554–560.
29. Ray KK, Bach RG, Cannon CP, et al. Benefits of achieving the NCEP optional LDL-C goal among elderly patients with ACS. *Eur Heart J.* 2006; 27:2310–2316.
30. Kim HS, Wu Y, Lin SJ, et al. Current status of cholesterol goal attainment after statin therapy among patients with hypercholesterolemia in Asian countries and region: the Return on Expenditure Achieved for Lipid Therapy in Asia (REALITY-Asia) study. *Curr Med Res Opin.* 2008;24:1951–1963.
31. Serban MC, Colantonio LD, Manthripragada AD, et al. Statin intolerance and risk of coronary heart events and all-cause mortality following myocardial infarction. *J Am Coll Cardiol.* 2017;69:1386–1395.
32. Rosenson RS, Colantonio LD, Goonewardena SN. Optimizing cholesterol management improves the benefits of percutaneous coronary intervention. *J Am Coll Cardiol.* 2020;76:1451–1454.