

Sex disparities in LDL-C target achievement among older adults receiving statin therapy

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ABSTRACT

Objectives To evaluate sex differences in low-density lipoprotein cholesterol (LDL-C) target achievement among older Vietnamese adults receiving statin therapy for primary cardiovascular prevention and to assess the impact of the 2025 European Society of Cardiology (ESC) guideline updates on risk stratification and goal attainment.

Methods This cross-sectional study enrolled 360 adults aged 70 years or older (median age 76 years; 47.8% female) receiving statin therapy for primary cardiovascular prevention at a tertiary hospital in Vietnam. Participants underwent comprehensive geriatric assessment, including frailty (Clinical Frailty Scale) and polypharmacy screening. Cardiovascular risk was classified using the Systematic COronary Risk Evaluation 2-Older Persons (SCORE2-OP) algorithm. LDL-C target achievement rates were compared between sexes using multivariable logistic regression, and the reclassification effects of the 2025 ESC guideline update were simulated relative to the 2021 guidelines.

Results Overall, 17.8% of participants achieved 2021 guideline-recommended LDL-C targets. Male sex was the strongest predictor of target achievement (adjusted odds ratio (aOR) = 2.64, 95% CI: 1.45–4.79, $P = 0.001$), persisting across all models. The 2025 ESC update reclassified 14.2% of participants to lower risk categories, increasing overall target achievement to 20.3% ($P = 0.004$). Frailty status was associated with differential benefit from the guideline update (interaction $P = 0.002$), with reclassification primarily benefiting non-frail adults. Neither frailty nor polypharmacy was independently associated with target non-attainment in multivariable analyses.

Conclusions Fewer than one in five older Vietnamese adults achieve LDL-C goals, with a significant disparity disadvantaging women. While the 2025 ESC guideline update improves apparent achievement rates through risk reclassification, this benefit is unevenly distributed, favoring non-frail participants. Reducing this disparity will require sex-specific management strategies and intensified therapy regardless of frailty status.

Cardiovascular disease remains the leading global cause of mortality. Lowering low-density lipoprotein cholesterol (LDL-C) by 1 mmol/L reduces major vascular events by approximately 20%, a benefit that extends to adults aged over 75 years.^[1] Yet, statin use for primary prevention remains markedly low in low- and middle-income countries such as Vietnam, revealing a persistent gap between evidence and clinical practice in ageing populations.^[2]

The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for the management of dyslipidemias established risk-tailored, treat-to-target lipid management using the Systematic COronary Risk Evaluation (SCORE) algorithm,^[3] which

was updated to SCORE2 and SCORE2-OP in the 2021 ESC Guidelines on CVD prevention in clinical practice (2021 Guidelines).^[4] External validation has raised concerns about SCORE2-OP performance in older adults, including poor discrimination and systematic risk underestimation.^[5] The 2025 Focused Update of the 2019 ESC/EAS Guidelines (2025 Update) retained these risk tools while refining very-high-risk definitions and emphasizing earlier combination therapy.^[6] However, geriatric factors including frailty, multimorbidity, and polypharmacy are not incorporated into SCORE2-OP, maintaining a gap between guideline tools and the complexity of older patients.^[7]

Sex disparities compound these challenges. Women

receive less intensive lipid-lowering therapy than men, are less likely to be prescribed high-intensity statins, and are less likely to achieve LDL-C targets.^[8,9] In Vietnamese older adults, similar disparities have been observed in secondary prevention settings.^[10] However, whether these sex differences persist in primary prevention, how the 2025 guideline update affects sex-specific outcomes, and whether geriatric syndromes modify these relationships remain unknown in ageing, resource-constrained Asian populations.

This cross-sectional study aimed to evaluate sex differences in LDL-C target achievement among older Vietnamese adults receiving statins for primary prevention, to compare risk stratification and target achievement between the 2021 ESC guidelines and the 2025 Focused Update, and to assess whether frailty and polypharmacy modify sex-specific outcomes and guideline impact. The findings are intended to inform equitable, sex-aware lipid management strategies in Vietnam and comparable clinical settings.

METHODS

Study Design, Participants, and Ethics

This cross-sectional study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines^[11] and was conducted at Outpatient Department A, Thong Nhat Hospital, a tertiary referral center in Ho Chi Minh City, Vietnam, from August 1, 2023, to February 28, 2024. Eligible participants were adults aged ≥ 70 years receiving stable statin therapy for ≥ 3 months for primary cardiovascular prevention. Exclusion criteria were established atherosclerotic cardiovascular disease (acute coronary syndrome, myocardial infarction, coronary revascularization, stroke, transient ischemic attack, or peripheral arterial disease), active malignancy with expected survival < 1 year, uncontrolled systemic infection, inability to provide informed consent due to severe sensory or cognitive impairment, familial hypercholesterolemia with prior cardiovascular events, and severe chronic kidney disease (estimated glomerular filtration rate < 30 mL/min per 1.73 m^2). Participants were enrolled consecutively. Sample size was determined using a two-sided, two-independent-proportions test (Stata version 19), assuming LDL-C target achievement rates of approximately 10% in women and 25% in men based on prior reports of sex

differences in lipid target attainment 8–10, yielding a minimum detectable absolute difference of 15 percentage points with 80% power at a two-sided $\alpha = 0.05$ and a minimum required sample of 330 participants. The study was approved by the institutional review boards of the University of Medicine and Pharmacy at Ho Chi Minh City (No. 707/HDDD-DHYD) and Thong Nhat Hospital (No. 66/2023/BVTN-HDYD), in accordance with the Declaration of Helsinki.^[12] Written informed consent was obtained from all participants prior to enrollment.

Data Collection

Each participant attended a single standardized study visit, during which trained research staff obtained demographic, clinical, and geriatric data through structured interviews and medical record review. Participants fasted for ≥ 8 h prior to venipuncture; lipid panels (total cholesterol, LDL-C, high-density lipoprotein cholesterol [HDL-C], triglycerides) and serum creatinine were measured using standardized enzymatic assays at the hospital's central laboratory under routine internal quality control. Non-HDL cholesterol was calculated as total cholesterol minus HDL-C; estimated glomerular filtration rate was calculated using the CKD-EPI creatinine equation without race adjustment. Cardiovascular risk was estimated using the Systematic COronary Risk Evaluation 2-Older Persons (SCORE2-OP) algorithm for high-risk regions, applying sex-specific linear predictors and competing-risk models.^[13] Risk categories were defined as low-to-moderate ($< 7.5\%$), high (7.5% to $< 15\%$), and very high ($\geq 15\%$) under the 2021 Guidelines,^[4] and as low-to-moderate ($< 10\%$), high (10% to $< 20\%$), and very high ($\geq 20\%$) under the 2025 Update.^[6] The primary outcome was LDL-C target achievement, defined as meeting the absolute guideline-specified LDL-C threshold for the assigned risk category: < 1.4 mmol/L for very high risk, < 1.8 mmol/L for high risk, and < 2.6 mmol/L for low-to-moderate risk;^[4,6] pre-treatment baseline values were unavailable, precluding assessment of the relative reduction criterion. The main explanatory variable was biological sex. Pre-specified effect modifiers were frailty, defined as a Clinical Frailty Scale score ≥ 5 ,^[14] and polypharmacy, defined as ≥ 5 regular medications.^[15] Additional geriatric assessments used validated instruments including the Katz Index, Lawton Instrumental Activities of Daily Living Scale, and Mini Nutritional Assessment Short Form.



Statistical Analysis

All analyses were conducted using Stata version 19 (StataCorp, College Station, TX). Categorical variables were summarized as frequency and percentage; continuous variables were reported as mean (standard deviation [SD]) or median (interquartile range), as appropriate. Bivariate comparisons used the Mann-Whitney *U* test or Welch's *t*-test for continuous variables and the chi-square or Fisher's exact test for categorical variables.

The primary analysis examined the association between sex and LDL-C target achievement under the 2021 Guidelines using multivariable logistic regression. Three pre-specified models were estimated: a clinical model (sex, statin intensity, SCORE2-OP risk category, and age); a clinical-geriatric model (sex, statin intensity, polypharmacy, and frailty); and a comprehensive model combining all six predictors. Results were expressed as adjusted odds ratios with 95% confidence intervals. Model performance was assessed using the C-statistic, pseudo- R^2 , Hosmer-Lemeshow goodness-of-fit test, Akaike information criterion, and Bayesian information criterion. For secondary analyses, changes in risk category distribution between the 2021 and 2025 guidelines were assessed using the Stuart-Maxwell test for margin-

al homogeneity; agreement was quantified using Cohen's kappa. Paired differences in LDL-C target achievement rates were compared with McNemar's test. The association between guideline version and target achievement, and its potential modification by sex, frailty, and polypharmacy, was examined using generalized estimating equations with a binomial.

No missing data were encountered; all 360 enrolled participants were included in complete-case analyses. Three pre-specified sensitivity analyses were conducted: receiver operating characteristic curve analysis of total medication count as a predictor of target achievement to evaluate the binary polypharmacy threshold; refitting the comprehensive model replacing binary polypharmacy with medication count as a continuous variable; and restriction of the comprehensive model to participants classified as very high risk under SCORE2-OP.

RESULTS

Study Participants and Baseline Characteristics

The principal findings of this study are summarized in the graphical abstract (Figure 1). A total of 360 older adults (median age 76 (IQR: 72–80) years; 172 (47.8%) fe-

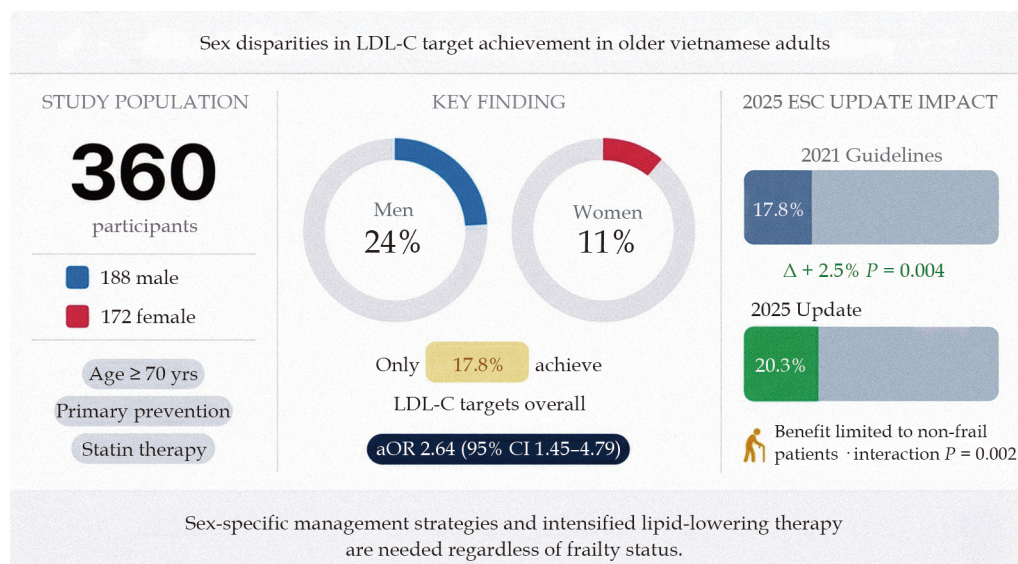


Figure 1 Graphical Abstract. This visual summary presents the key findings of a cross-sectional study examining sex disparities in target achievement among 360 older Vietnamese adults (188 male, 172 female; median age: 76 years) receiving statin therapy for primary prevention. Overall, 17.8% of participants achieved 2021 ESC-recommended LDL-C targets, with a notable sex disparity: 23.9% of men versus 11.0% of women achieved the target (adjusted odds ratio, 2.64; 95% CI: 1.45–4.79). Simulation of the 2025 ESC Focused Update increased overall target attainment to 20.3% ($P = 0.004$), a benefit confined primarily to non-frail participants (interaction $P = 0.002$). CI denotes confidence interval, ESC European Society of Cardiology, and LDL-C low-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol.

male) receiving statin therapy for primary cardiovascular prevention were included (Figure 2). Baseline characteristics by sex are presented in Table 1. Compared with women, men had significantly higher body mass index (BMI; median 23.0 vs. 21.9 kg/m²), systolic blood pressure (130 vs. 120 mmHg), and rates of diabetes (74.5% vs. 55.8%), multimorbidity (95.2% vs. 89.0%), and polypharmacy (81.4% vs. 72.7%; all $P < 0.05$). Women had higher LDL-C (2.50 vs. 1.90 mmol/L), total cholesterol (4.60 vs. 3.70 mmol/L), and triglycerides (1.70 vs. 1.50 mmol/L; all $P < 0.05$); smoking was almost exclusively prevalent in men (30.3% vs. 0.6%). Nearly all participants (90.3%) were classified as very high cardiovascular risk by SCORE2-OP under the 2021 ESC guidelines; 84.2% received moderate-intensity statins. Frailty (CFS ≥ 5) was

present in 40 participants (11.1%), with no significant sex difference ($P = 0.709$). No missing data were encountered.

Sex Disparities in LDL-C Target Achievement

Under the 2021 ESC/EAS guidelines, 64 participants (17.8%) achieved their LDL-C target, with significantly higher achievement in men than in women (45/188 [23.9%] vs. 19/172 [11.0%]; $\chi^2 = 10.21$, $P = 0.001$). This sex disparity was consistent across all prespecified subgroups, including age, cardiovascular risk category, frailty status, polypharmacy, diabetes, functional limitations, and nutritional risk; no significant sex-by-subgroup interactions (all $P > 0.05$; Table 2). Among frail participants, 4 of 40 (10.0%) achieved target; within this subgroup, 3 of the 4 achievers were women, a pattern opposite to the overall cohort (sex $\times$ frailty interaction $P = 0.039$; Table 2). In multivariable logistic regression adjusted for statin intensity, cardiovascular risk, age, polypharmacy, and frailty, male sex independently predicted target achievement in all three model specifications: Model 1 (aOR = 2.65, 95% CI: 1.47–4.79, $P = 0.001$), Model 2 (aOR = 2.56, 95% CI: 1.42–4.62, $P = 0.002$), and Model 3 (aOR = 2.64, 95% CI: 1.45–4.79, $P = 0.001$; Table 3). No other covariate reached statistical significance in any model.

Risk Reclassification and Guideline-Specific Effects on Target Achievement

Application of the 2025 ESC Focused Update reclassified 51 participants (14.2%) to lower cardiovascular risk categories: 47 from very high to high risk, and 4 from high to low-to-moderate risk; no participant was reclassified upward (Supplementary Table 5). Agreement between guideline versions was moderate (Cohen's $\kappa = 0.50$, 95% CI: 0.41–0.59; observed concordance 85.8%). LDL-C target achievement increased from 17.8% (64/360) under the 2021 guidelines to 20.3% (73/360) under the 2025 guidelines, representing a net gain of 2.5 percentage points attributable exclusively to the 9 individuals reclassified to lower risk (McNemar's $\chi^2(1) = 9.00$, exact $P = 0.004$; Supplementary Table 6).

In generalized estimating equation modelling of target achievement across both guideline versions (720 person-observations), male sex remained independently associated with achievement (aOR = 2.57, 95% CI: 1.43–4.63, $P = 0.002$) after adjustment for guideline version, frailty, and polypharmacy (Table 4). The overall

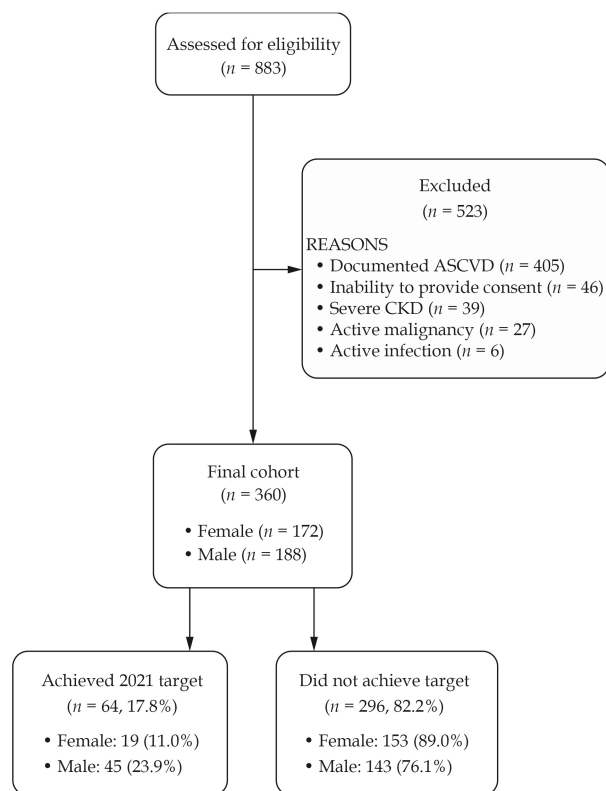


Figure 2 Study flow diagram. Of 883 participants assessed for eligibility, 523 were excluded: 405 for documented atherosclerotic cardiovascular disease, 46 for inability to provide informed consent, 39 for severe chronic kidney disease, 27 for active malignancy, and 6 for active infection. The final study cohort comprised 360 participants (172 female [47.8%] and 188 male [52.2%]). Under 2021 ESC guideline-recommended LDL-C targets, 64 participants (17.8%) achieved the target: 19 women (11.0%) and 45 men (23.9%). ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; ESC: European Society of Cardiology; LDL-C: low-density lipoprotein cholesterol.



Table 1 Baseline characteristics.

Characteristic	Total (n = 360)	Female (n = 172)	Male (n = 188)	P-value
LDL-C target achieved	64 (17.8%)	19 (11.0%)	45 (23.9%)	0.001 ^a
Demographics, behavioural factors, and anthropometric measures				
Age, yrs	76 (72–80)	76 (72–80)	76 (72–80)	0.798 ^b
Age group				0.857 ^b
70–74 years	145 (40.3%)	70 (40.7%)	75 (39.9%)	
75–79 years	115 (31.9%)	55 (32.0%)	60 (31.9%)	
≥ 80 years	100 (27.8%)	47 (27.3%)	53 (28.2%)	
Current smoker	58 (16.1%)	1 (0.6%)	57 (30.3%)	< 0.001 ^a
BMI, kg/m ²	22.5 (21.4–24.1)	21.9 (20.6–23.5)	23 (22.0–24.2)	< 0.001 ^b
BMI stratification				< 0.001 ^b
Underweight	7 (1.9%)	4 (2.3%)	3 (1.6%)	
Normal	198 (55.0%)	113 (65.7%)	85 (45.2%)	
Overweight	140 (38.9%)	45 (26.2%)	95 (50.5%)	
Obese	15 (4.2%)	10 (5.8%)	5 (2.7%)	
Blood pressure				
SBP, mmHg	130 (120–130)	120 (120–130)	130 (120–130)	0.002 ^b
DBP, mmHg	84 (80–89)	83 (78–88)	85 (81–89)	0.015 ^b
Cardiovascular risk assessment				
SCORE2-OP	25.5 (20.3–33.4)	24.9 (19.9–35.2)	26.3 (21.3–32.3)	0.625 ^b
SCORE2-OP stratification				0.025 ^a
Low-to-moderate risk	0	0	0	
High risk	35 (9.7%)	23 (13.4%)	12 (6.4%)	
Very high risk	325 (90.3%)	149 (86.6%)	176 (93.6%)	
Geriatric assessment				
Frail	40 (11.1%)	18 (10.5%)	22 (11.7%)	0.709 ^a
ADL limitation	155 (43.1%)	75 (43.6%)	80 (42.6%)	0.841 ^a
IADL limitation	49 (13.6%)	20 (11.6%)	29 (15.4%)	0.294 ^a
Dementia	29 (8.1%)	14 (8.1%)	15 (8.0%)	0.955 ^a
Depression	92 (25.6%)	43 (25.0%)	49 (26.1%)	0.817 ^a
MNA-SF, median (IQR)	8 (6–11)	8 (5–10)	9 (7–12)	0.002 ^b
MNA-SF stratification				0.004 ^b
Malnourished	148 (41.1%)	85 (49.4%)	63 (33.5%)	
Malnutrition risk (MNA-SF ≤11)	130 (36.1%)	54 (31.4%)	76 (40.4%)	
Normal	82 (22.8%)	33 (19.2%)	49 (26.1%)	
Polypharmacy and comorbidities				
Number of drugs	5.9 ± 1.8	5.6 ± 1.8	6.1 ± 1.9	0.007 ^c
Polypharmacy	278 (77.2%)	125 (72.7%)	153 (81.4%)	0.049 ^a
Comorbidities				
Diabetes	236 (65.6%)	96 (55.8%)	140 (74.5%)	< 0.001 ^a
Hypertension	334 (92.8%)	157 (91.3%)	177 (94.1%)	0.293 ^a
CKD	99 (27.5%)	46 (26.7%)	53 (28.2%)	0.759 ^a
Multi-comorbidity	332 (92.2%)	153 (89.0%)	179 (95.2%)	0.027 ^a

Continued

Characteristic	Total (n = 360)	Female (n = 172)	Male (n = 188)	P-value
Laboratory findings				
Lipid profile, mmol/L				
LDL-C	2.1 (1.6–3.1)	2.5 (1.8–3.3)	1.9 (1.4–2.6)	< 0.001 ^b
HDL-C	1.2 (1.0–1.4)	1.2 (1.1–1.5)	1.1 (0.9–1.3)	< 0.001 ^b
Non-HDL-C	2.9 (2.3–3.9)	3.3 (2.6–4.2)	2.7 (2.0–3.5)	< 0.001 ^b
Total cholesterol	4.1 (3.4–5.3)	4.6 (3.7–5.6)	3.7 (3.2–4.8)	< 0.001 ^b
Triglyceride	1.6 (1.1–2.4)	1.7 (1.2–2.4)	1.5 (1.0–2.2)	0.006 ^b
Pharmacotherapy				
Statin intensity stratification				0.377 ^b
Low intensity	2 (0.6%)	1 (0.6%)	1 (0.5%)	
Moderate intensity	303 (84.2%)	148 (86.0%)	155 (82.4%)	
High intensity	55 (15.3%)	23 (13.4%)	32 (17.0%)	
Adjunctive ezetimibe	56 (15.6%)	31 (18.0%)	25 (13.3%)	0.217 ^a

Data are presented as *n* (%), median (IQR) or mean $\pm$ SD. ^aChi-square test; ^bMann-Whitney *U* test (exact); ^cWelch's *t*-test. ADL: activities of daily living; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; IADL: instrumental activities of daily living; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; MNA-SF: Mini Nutritional Assessment-Short Form; Non-HDL-C: non-high-density lipoprotein cholesterol; SBP: systolic blood pressure; SCORE2-OP: Systematic COronary Risk Evaluation 2-Older Persons.

Table 2 LDL-C target achievement by subgroups.

Subgroup	<i>n</i>	Female	Male	P-value	P-value for interaction
By age group				0.095 ^a	0.154 ^d
70-74 years	27	5 (18.5%)	22 (81.5%)		
75-79 years	20	7 (35.0%)	13 (65.0%)		
≥ 80 years	17	7 (41.2%)	10 (58.8%)		
By risk category				1.000 ^b	0.233 ^d
High	7	2 (28.6%)	5 (71.4%)		
Very high	57	17 (29.8%)	40 (70.2%)		
By frailty				0.075 ^b	0.039 ^d
No	60	16 (26.7%)	44 (73.3%)		
Yes	4	3 (75.0%)	1 (25.0%)		
Functional limitations				0.619 ^c	0.438 ^d
No	30	8 (26.7%)	22 (73.3%)		
Yes	34	11 (32.4%)	23 (67.6%)		
Malnutrition risk (MNA-SF ≤ 11)				1.000 ^b	0.400 ^d
No	16	5 (31.2%)	11 (68.8%)		
Yes	48	14 (29.2%)	34 (70.8%)		
By polypharmacy				1.000 ^b	0.382 ^d
No	11	3 (27.3%)	8 (72.7%)		
Yes	53	16 (30.2%)	37 (69.8%)		
By diabetes				0.690 ^c	0.295 ^d
No	18	6 (33.3%)	12 (66.7%)		
Yes	46	13 (28.3%)	33 (71.7%)		
By statin intensity				1.000 ^b	0.733 ^d
Moderate	57	17 (29.8%)	40 (70.2%)		
High	7	2 (28.6%)	5 (71.4%)		

Data are presented as *n* (%). Female and Male percentages represent the sex distribution of achievers within subgroups, not achievement rates. ^aCochran-Armitage test; ^bFisher's exact test; ^cChi-square test; ^dWald chi-square test.



Table 3 Independent predictors of LDL-C target achievement.

Variable	Model 1aOR (95% CI)(n = 360)	P-value	Model 2aOR (95% CI)(n = 360)	P-value	Model 3aOR (95% CI)(n = 360)	P-value
Sex (male vs. female)	2.65 (1.47–4.79)	0.001	2.56 (1.42–4.62)	0.002	2.64 (1.45–4.79)	0.001
Statin intensity (high intensity vs. other intensities)	0.60 (0.26–1.43)	0.250	0.56 (0.24–1.32)	0.186	0.57 (0.24–1.35)	0.198
SCORE2-OP risk (very high risk vs. high risk)	0.74 (0.29–1.93)	0.540	—	—	0.64 (0.24–1.69)	0.369
Age (per 1 year increase)	1.00 (0.94–1.06)	0.888	—	—	1.01 (0.95–1.07)	0.832
Polypharmacy (yes vs. no)	—	—	1.45 (0.71–2.98)	0.308	1.55 (0.74–3.25)	0.245
Frailty (yes vs. no)	—	—	0.43 (0.15–1.28)	0.131	0.43 (0.14–1.31)	0.136
Model statistics						
C-statistic	0.641	—	0.655	—	0.662	—
Pseudo R ²	0.037	—	0.047	—	0.049	—
H-L p-value	0.877	--	0.768	--	0.650	
AIC	334	--	331	--	334	
BIC	354	--	351	--	362	

AIC: Akaike information criterion; aOR: adjusted odds ratio; BIC: Bayesian information criterion; CI: confidence interval; H-L: Hosmer-Lemeshow; LDL-C: low-density lipoprotein cholesterol; R²: R-squared; SCORE2-OP: Systematic COronary Risk Evaluation 2-Older Persons.

Table 4 Impact of guideline update and interaction with clinical factors.

Variable	OR (95% CI)	P-value
Main effects		
Guideline update (2025 vs. 2021)	1.41 (0.98–2.03)	0.067
Sex (male vs. female)	2.57 (1.43–4.63)	0.002
Frailty (yes vs. no)	0.51 (0.22–1.18)	0.117
Polypharmacy (yes vs. no)	1.37 (0.68–2.76)	0.381
Interaction effects		
Guideline update × Frailty	0.84 (0.75–0.94)	0.002
Guideline update × Sex	0.93 (0.73–1.17)	0.529
Guideline update × Polypharmacy	0.87 (0.63–1.20)	0.400

Analysis used Generalized Estimating Equations (GEE) with binomial distribution, logit link, exchangeable correlation structure, and robust standard errors.

guideline version effect was marginally non-significant (aOR = 1.41, 95% CI: 0.98–2.03, $P = 0.067$). A significant frailty × guideline interaction was identified (aOR = 0.84, 95% CI: 0.75–0.94, $P = 0.002$), indicating that the 2025 update conferred no additional achievement benefit for frail participants; among frail participants, achievement remained at 10.0% under both guideline versions, whereas non-frail participants showed a modest improvement (18.8% to 21.6%). Interactions between guideline version and sex ($P = 0.529$) or polypharmacy ($P = 0.400$) were not significant.

Subgroup and Sensitivity Analyses

ROC analysis of total medication count as a predictor

of LDL-C target achievement demonstrated limited discriminatory performance (area under the curve [AUC] = 0.558, 95% CI: 0.485–0.630), with an optimal cutpoint of ≥ 6 drugs (sensitivity 65.6%, specificity 44.6%, Youden index 0.10; Supplementary Tables 1–2). When Model 3 was repeated with medication count as a continuous variable ($n = 360$), the sex disparity remained unchanged (aOR = 2.61, 95% CI: 1.44–4.74, $P = 0.002$; Supplementary Table 3). In a prespecified sensitivity analysis restricted to the 325 participants classified as very high cardiovascular risk, the male sex advantage persisted (aOR = 2.34, 95% CI: 1.26–4.36, $P = 0.008$; Supplementary Table 4), confirming the robustness of the primary finding across the predominant risk stratum.

DISCUSSION

Principal Findings

This cross-sectional study evaluated LDL-C target achievement and its determinants in 360 Vietnamese adults aged 70 years or older receiving statin therapy for primary cardiovascular prevention. Fewer than one in five participants achieved guideline-recommended LDL-C targets, revealing a substantial gap between international recommendations and clinical practice. Male sex was the factor most strongly associated with target achievement, with men more than twice as likely as women to reach therapeutic goals. Simulation of the 2025 ESC Focused Update showed modest improvement in overall achievement through risk reclassification, with differential benefit favoring non-frail over frail individuals. Neither frailty nor polypharmacy was independently associated with target non-attainment, suggesting that geriatric complexity alone does not preclude successful lipid management when therapy is appropriately prescribed.

Strengths and Limitations

Strengths of this study include the use of validated geriatric assessment instruments administered through direct participant interviews, the application of the 2025 ESC Focused Update to a contemporaneous dataset before its full implementation in Vietnam, restriction to primary prevention, the clinical setting where treatment decisions are most complex, and multivariable regression with interaction testing. The principal limitation is the cross-sectional design, which precluded assessment of the dual LDL-C criterion (absolute threshold and $\geq 50\%$ reduction from untreated baseline) required by both guideline versions, potentially overestimating true target attainment. The single-center tertiary-care setting likely represents best-case performance; achievement rates in community or rural settings may be lower. Medication reconciliation without serum drug levels prevented distinction between prescribing inertia and treatment non-adherence, and the absence of apolipoprotein B and lipoprotein(a) measurements may underestimate residual cardiovascular risk in this population.

Biological Mechanisms Underlying Sex Disparities in Lipid Management

The observed sex disparity in LDL-C target achieve-

ment reflects converging biological and pharmacological mechanisms. Following menopause, women experience unfavorable shifts in lipid profiles, including elevated LDL-C and reduced HDL-C, attributable to declining endogenous estrogen.^[16] These changes in lipoprotein metabolism are mediated through sex-hormone-dependent regulation of hepatic lipase, lipoprotein lipase, and LDL receptor expression.^[17] Beyond baseline differences, women and men differ in the pharmacokinetics and pharmacodynamics of cardiovascular drugs, including statins: women generally have higher bioavailability of lipophilic statins owing to greater adipose tissue proportion, lower renal clearance, and sex-specific differences in cytochrome P450 enzyme activity, which may alter both efficacy and adverse effect profiles.^[18] In our cohort, standardized moderate-intensity statin therapy produced fixed percentage LDL-C reductions,^[19] yielding systematically unequal absolute outcomes when applied to women's higher baseline values. Furthermore, women with comorbid diabetes face a disproportionately greater relative increase in cardiovascular risk than men, potentially compounding the consequences of suboptimal lipid management.^[20]

Clinical Inertia and Prescribing Disparities Against Older Women

Despite higher baseline LDL-C and non-HDL cholesterol, women in this study were less likely to receive high-intensity statins or ezetimibe, suggesting failure to titrate therapy to biological need.^[9] This pattern is consistent with therapeutic inertia disproportionately affecting women, a phenomenon documented in European registries.^[21] Several factors may contribute: physician underestimation of cardiovascular risk in older women,^[22] heightened concern about statin-associated adverse effects in patients with lower body mass,^[23] and sex-based differences in symptom communication that may be misinterpreted as intolerance rather than undertreated risk.^[18] In the Vietnamese context, sociocultural factors may amplify these biases, as traditional family structures sometimes see older women prioritizing others' health needs over their own, with implications for adherence and willingness to pursue intensive therapy. It is important to emphasize that the observed statistical association between sex and target non-attainment likely reflects a combination of biological predisposition, pharmacological under-treatment, and behavioral or systemic factors rather than a single causal pathway.



Guideline Reclassification: Administrative Gains Versus Therapeutic Improvement

The 2021 ESC Guidelines employ age-driven SCORE2-OP algorithms that classify most adults aged ≥ 70 years as very high cardiovascular risk.^[4] The 2025 Focused Update recalibrates risk thresholds by incorporating refined weighting of age-related competing mortality and updated coefficients for traditional risk factors, leading to down-classification from very high to high risk for a subset of participants.^[6] This shift permits participants with moderately elevated LDL-C to meet relaxed absolute thresholds without therapeutic modification, and the observed improvement in achievement rates therefore reflects revised categorization rather than improved biological risk control. Moderate agreement between guideline versions underscores the instability of risk prediction in this age group. In Vietnam, where stroke incidence substantially exceeds that of Western populations,^[24,25] relaxing LDL-C targets for older adults warrants particular caution. The significant interaction between guideline version and frailty status indicates that revised guidelines preferentially benefit non-frail individuals approaching target thresholds but provide minimal advantage to those receiving inadequate therapy due to frailty-related clinical hesitancy.

Frailty, Polypharmacy, and Nutritional Status in Geriatric Lipid Management

Frailty was not independently associated with LDL-C target non-attainment in multivariable analysis, suggesting that ambulatory frail participants in tertiary care, likely representing mild-to-moderate frailty phenotypes, can adhere to statin regimens as effectively as non-frail counterparts. This finding aligns with observational evidence that statin use is associated with reduced cardiovascular events and mortality in older adults in primary prevention settings,^[26] and supports the position that frailty *per se* should not preclude evidence-based lipid-lowering therapy. However, this interpretation does not extend to severely frail individuals, for whom evidence supporting continued lipid-lowering therapy is limited.^[27] Polypharmacy trended toward better achievement, likely reflecting greater healthcare system engagement: participants taking multiple medications attend more frequent reviews and are habituated to daily regimens. The coexistence of malnutrition with persistent hyperlipidemia in this cohort warrants careful interpretation. Rather than indicating metabolic dysregulation alone,

LDL-C levels are regulated substantially by genetically determined metabolic pathways,^[17] and the relationship between nutritional status and cholesterol is not simply inversely proportional in patients receiving pharmacotherapy.

Treatment Gaps Across Populations: Toward Cross-Regional Benchmarking

The low target achievement rate observed in our Vietnamese cohort parallels findings from the multinational SANTORINI study, which documented that fewer than one-third of high- and very-high-risk European patients achieved LDL-C goals between 2020 and 2021.^[28] This cross-regional consistency suggests that target non-attainment constitutes a global challenge rather than a setting-specific phenomenon. It is important to define this concept precisely: target non-attainment in our study may result from prescribing inertia (insufficient dose escalation or combination therapy), participant-level non-adherence, or intrinsic differences in pharmacological response, and our cross-sectional design cannot distinguish among these contributors. The sex disparity in target achievement remained consistent across age strata, diabetes status, and treatment intensity, indicating a systematic rather than random phenomenon.^[17,29] Even among those receiving moderate-intensity statins, men outperformed women, reinforcing the biological hypothesis that the same moderate dose is insufficient for women due to higher baseline LDL-C levels.^[18] To our knowledge, no published study has directly compared LDL-C target achievement between urban and rural settings in Asia or other resource-constrained regions, representing a critical evidence gap that future population-based registries should address.

Future Research and Remaining Gaps

Clinical trials comparing initial combination therapy with stepwise titration in Asian older adults are needed.^[30] Electronic health record alerts targeting high-risk women on suboptimal therapy may help reduce prescribing disparities. Prospective, population-based studies comparing LDL-C target achievement across geographic regions and between urban and rural settings would strengthen external validity. Developing Asia-specific cardiovascular risk algorithms, such as the SCORE2 Asia-Pacific model,^[31] represents a critical step toward reducing reclassification variability in non-European populations. Qualitative research exploring



Vietnamese women's perceptions of statin therapy could inform culturally tailored interventions.

Conclusion

Fewer than one in five older Vietnamese adults in primary prevention achieved LDL-C targets, with female sex independently associated with lower achievement, a disparity that was consistent across subgroups defined by frailty and polypharmacy status. The 2025 ESC Focused Update improved attainment rates primarily among non-frail participants through risk reclassification rather than therapeutic change, conferring no measurable benefit in frail participants. Neither frailty nor polypharmacy precluded target achievement, supporting continued evidence-based lipid management regardless of geriatric complexity. Addressing the observed sex disparity requires sex-aware prescribing practices, including intensified or combination lipid-lowering therapy where appropriate, and cross-regional benchmarking to identify modifiable treatment gaps in Vietnam and comparable clinical settings.

DISCLOSURE

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Conflict of interest

None declared.

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