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The Difference in Basic Risk Factors Among Genders and Simulation of Lipid-Lowering Therapy in Acute Coronary Syndrome

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Abstract

Background: Acute coronary syndrome (ACS) is a major cause of cardiovascular morbidity and mortality, with gender-related differences in cardiovascular risk factors and lipid management. Evidence regarding these differences and the potential benefit of intensified lipid-lowering therapy (LLT) in Indian patients is limited. This study evaluated gender differences in cardiovascular risk factors and simulated low-density lipoprotein cholesterol (LDL-C) target attainment with different LLT strategies.

Methods: This single-centre, retrospective observational study included 658 consecutive Indian patients with ACS undergoing percutaneous coronary intervention. Baseline demographic, clinical, and biochemical characteristics were compared between women (n=134) and men (n=524), with exploratory stratification by age (<50 and ⩾50 years). LDL-C target attainment (<50 mg/dL) was simulated with high-intensity statin monotherapy (50% LDL-C reduction), statin plus ezetimibe (60%), and triple therapy with statin, ezetimibe, and bempedoic acid (75%).

Results: Women had a higher prevalence of hypertension and diabetes, whereas smoking was more common among men (all p<0.001). Baseline LDL-C was comparable between women and men (115.2±34.7 vs. 109.4±32.1 mg/dL; p=0.071), while only 14 (2.1%) achieved LDL-C <50 mg/dL at presentation. Simulated target attainment was lower in women than men with statin monotherapy (41 (30.6%) vs. 205 (39.1%); p=0.085) and statin plus ezetimibe (87 (64.9%) vs. 371 (70.8%); p=0.225), although differences were not statistically significant. Triple therapy achieved near-universal target attainment in women and men (132 (98.5%) vs. 520 (99.2%); p=0.354). Overall attainment increased from 246 (37.4%) with statin monotherapy to 458 (69.6%) with dual therapy and 652 (99.1%) with triple therapy. Similar trends were observed across age groups.

Conclusion: Women with ACS had a greater burden of cardiovascular risk factors despite comparable LDL-C levels. Combination LLT, particularly triple therapy, markedly improved simulated LDL-C target attainment in both sexes, supporting early intensification of lipid-lowering treatment in Indian patients with ACS.

Categories: Cardiology, Emergency Medicine, Internal Medicine
Keywords: acute coronary syndrome, cardiovascular risk factors, lipid-lowering therapy, low-density lipoprotein cholesterol, percutaneous coronary intervention, sex differences

Introduction

According to the 2023 Lipid Association of India consensus statement, stringent low-density lipoprotein cholesterol (LDL-C) targets are recommended, with levels below 50 mg/dL for very high-risk patients and ⩽30 mg/dL for those in the extreme-risk category, such as individuals with a prior atherosclerotic cardiovascular disease event [1]. Emerging evidence, however, highlights that sex-based disparities significantly influence lipid management and cardiovascular outcomes. Although women are more likely to receive guideline-recommended lipid-lowering therapy (LLT) at discharge, they often achieve poorer lipid control than men [2,3] and, in high-income countries, women with acute coronary syndrome (ACS) are less likely than men to receive guideline-recommended pharmacotherapy, invasive angiography, or percutaneous coronary intervention (PCI), disparities that contribute to worse outcomes and represent opportunities for quality improvement [4-6]. In Kerala and Gujarat, India, women were found to have a higher prevalence of hypertension and diabetes, presented later, were less often treated with guideline-directed therapy, and experienced poorer in-hospital and short-term outcomes, underscoring the need to address sex disparities in cardiovascular care in low- and middle-income countries [7,8]. Despite this heightened risk, women are less frequently treated with PCI or prescribed statin therapy and consequently show smaller reductions in lipid levels over time, reflecting suboptimal intensity of lipid management compared with men [9,10].

The present study evaluated LLT outcomes among patients with ACS, with attention to gender-based differences in treatment response, and additionally examined whether these differences varied by age. We assessed the proportion of patients projected to achieve LDL-C reductions of at least 50%, 60%, and 75%, corresponding to high-intensity statin monotherapy, statin plus ezetimibe, and triple therapy with statin, ezetimibe, and bempedoic acid, respectively. This analysis provides insight into the real-world attainment of recommended LDL-C goals and the disparities between men and women overall and across age strata in achieving optimal cardiovascular risk reduction.

Materials And Methods

Study design and setting

This was a single-centre, retrospective observational study conducted at the cardiology department of a tertiary care centre in India. Consecutive patients presenting with ACS who underwent PCI were included. The study evaluated sex-based differences in baseline cardiovascular risk factors and biochemical profiles and modelled the attainment of guideline-recommended LDL-C targets using a stepwise LLT simulation, with a pre-specified secondary analysis stratifying these comparisons by age.

Study population

Patients with a confirmed diagnosis of ACS, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina, who underwent coronary angiography and PCI were enrolled. A total of 658 patients were included in the final analysis and stratified by sex (134 (20.4%) female patients and 524 (79.6%) male patients). For the secondary analysis, patients were additionally stratified by age at a 50-year cut-off (118 (17.93%) patients <50 years (12 (10.17%) female patients and 106 (89.83%) male patients); 540 (82.07%) patients ⩾50 years (122 (22.59%) female patients and 418 (77.41%) male patients)). The study flowchart is presented in Figure *1*.

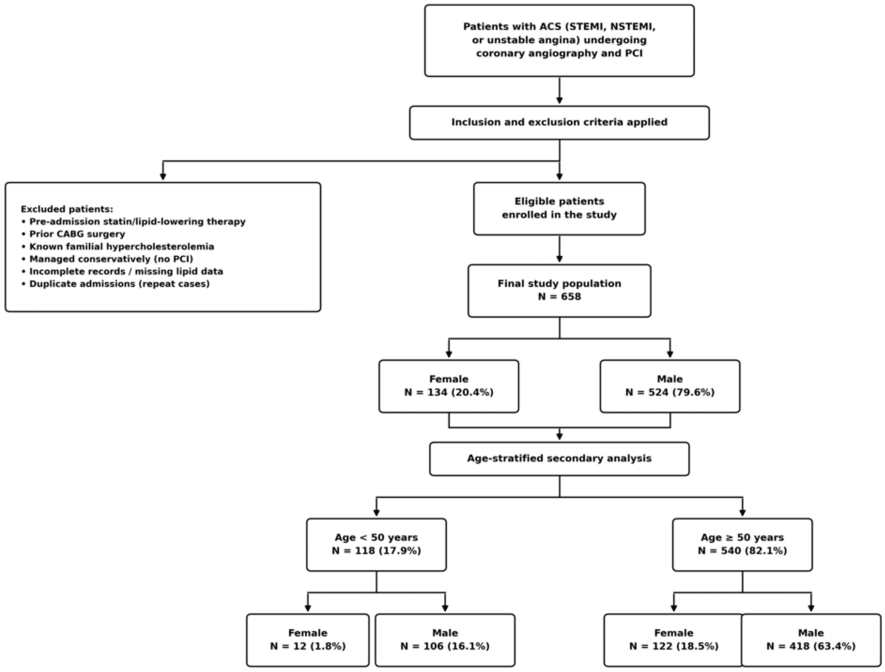


FIGURE 1: Flowchart

PCI, percutaneous coronary intervention; CABG: coronary artery bypass graft; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; ACS: acute coronary syndrome

Data collection

Demographic and clinical data were recorded for all patients, including age, sex, and cardiovascular risk factors such as hypertension, diabetes mellitus, and smoking status (current and ex-smoker). Clinical signs including xanthomas and corneal arcus, along with relevant medical history (prior myocardial infarction, prior PCI, peripheral arterial disease, stroke, and family history of cardiovascular disease), were documented, and body mass index (BMI) was recorded. Patients with ACS, including STEMI, NSTEMI, and unstable angina, who underwent coronary angiography followed by PCI were included in the study. Patients receiving statins or other LLT before admission, those with a history of coronary artery bypass graft surgery,

known familial hypercholesterolemia, patients managed conservatively without PCI, and those with incomplete clinical records or missing baseline lipid profile data were excluded from the analysis. Duplicate admissions during the study period were excluded, and only the first eligible admission for each patient was included.

The type of ACS presentation (STEMI, NSTEMI, or unstable angina) was classified according to standard diagnostic criteria [11]. Angiographic findings were categorised by extent of coronary involvement: single-vessel disease, double-vessel disease, triple-vessel disease, and left main coronary artery disease. Angiographic complexity was quantified using the SYNTAX score, and left ventricular ejection fraction (LVEF) was assessed by echocardiography.

Biochemical investigations

Venous blood samples were collected at admission. The lipid profile included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), LDL-C, triglycerides, non-HDL cholesterol, very-low-density lipoprotein cholesterol (VLDL-C), and remnant cholesterol. Additional markers comprised lipoprotein(a), apolipoprotein A, and apolipoprotein B. Glycaemic status was assessed using HbA1c, inflammatory burden by high-sensitivity C-reactive protein (hs-CRP), renal function by blood urea and serum creatinine (before and after the procedure), hepatic status by SGOT and SGPT, and serum uric acid was also measured.

Simulation of stepwise lipid-lowering therapy

LDL-C target attainment was modelled using a simulation based on expected percentage reductions associated with escalating intensities of LLT. Each patient's admission LDL-C value was used as the baseline, and projected post-treatment LDL-C levels were calculated by applying fixed relative reductions corresponding to three regimens: 50% for high-intensity statin monotherapy, 60% for statin plus ezetimibe, and 75% for triple therapy (statin, ezetimibe, and bempedoic acid). These reduction magnitudes were derived from contemporary evidence and guideline-referenced efficacy estimates. The proportion of patients projected to achieve the guideline-recommended LDL-C target of <50 mg/dL was calculated for each regimen, overall, by sex, and as a secondary, exploratory analysis, by sex within age strata (<50 and ⩾50 years).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared using the independent-samples t-test; categorical variables, including regimen-specific LDL-C target attainment, were expressed as frequencies and percentages and compared between sexes using the chi-square test, or Fisher's exact test where an expected cell count was <5. A two-sided p-value of <0.05 was considered statistically significant. The primary comparison was between sexes in the overall cohort. Age-stratified (<50 vs ⩾50 years) comparisons by sex were pre-specified as a secondary, hypothesis-generating analysis; given the reduced sample size within these subgroups (particularly females <50 years, n=12), these results should be interpreted as exploratory, and no correction for multiple comparisons was applied. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26 (Released 2018; IBM Corp., Armonk, New York, United States).

Results

A total of 658 patients with ACS undergoing PCI were analysed. Of these, 134 (20.36%) were women and 524 (79.64%) were men. The primary results (Tables *1*-*4*) present sex-based comparisons in the full cohort; Tables *5*-*8* present the pre-specified secondary analysis stratifying these comparisons by age (<50 vs ⩾50 years).

Variable	Total (N=658)	Female (N=134)	Male (N=524)	P-value
Age, years	61.40±11.54	67.52±10.67	59.84±11.24	<0.0001
Hypertension	289 (43.9%)	88 (65.7%)	201 (38.4%)	<0.0001
Diabetes	182 (27.7%)	56 (41.8%)	126 (24.0%)	<0.0001
Ex-smoker	139 (21.1%)	5 (3.7%)	134 (25.6%)	<0.0001
Current smoker	261 (39.7%)	5 (3.7%)	256 (48.9%)	<0.0001
Xanthomas	19 (2.9%)	6 (4.5%)	13 (2.5%)	0.243
Corneal arcus	1 (0.2%)	1 (0.7%)	0	0.204
Past MI	18 (2.7%)	2 (1.5%)	16 (3.1%)	0.551
Past PCI	7 (1.1%)	0	7 (1.3%)	0.201
Past PAD	5 (0.8%)	0	5 (1.0%)	0.319
Past stroke	16 (2.4%)	2 (1.5%)	14 (2.7%)	0.336
Family history of CVD	38 (5.8%)	5 (3.7%)	33 (6.3%)	0.177
BMI, kg/m²	24.48±3.99	25.33±5.25	24.28±3.61	0.012
NSTEMI	122 (18.5%)	27 (20.1%)	95 (18.1%)	0.680
STEMI	487 (74.0%)	92 (68.7%)	395 (75.4%)	0.141
Unstable angina	49 (7.4%)	15 (11.2%)	34 (6.5%)	0.096
SVD	192 (29.2%)	36 (26.9%)	156 (29.8%)	0.432
DVD	237 (36.0%)	45 (33.6%)	192 (36.6%)	0.437
TVD	229 (34.8%)	53 (39.6%)	176 (33.6%)	0.251
LMCA disease	40 (6.1%)	7 (5.2%)	33 (6.3%)	0.794
Syntax score	17.27±9.18	18.54±9.11	16.94±9.18	0.079
LVEF, %	41.20±9.77	41.04±10.04	41.24±9.71	0.836

TABLE 1: Baseline characteristics between genders

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as n (%). P values represent comparisons between female and male patients. ACS, acute coronary syndrome; BMI, body mass index; CVD, cardiovascular disease; DVD, double-vessel disease; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; SVD, single-vessel disease; TVD, triple-vessel disease.

Variable	Total (N=658)	Female (N=134)	Male (N=524)	P-value
HbA1c	6.27±1.69	6.54±1.74	6.21±1.67	0.053
Total cholesterol, mg/dL	183.19±46.57	194.65±51.06	180.26±44.93	0.001
HDL-C, mg/dL	43.39±11.74	48.63±13.29	42.05±10.93	<0.001
LDL-C, mg/dL	110.60±32.72	115.15±34.69	109.43±32.13	0.071
Triglycerides, mg/dL	159.14±99.44	159.25±91.69	159.11±101.40	0.989
Non-HDL-C, mg/dL	139.74±44.12	146.03±49.60	138.13±42.52	0.065
VLDL-C, mg/dL	31.78±19.91	31.61±18.47	31.82±20.28	0.913
Remnant cholesterol, mg/dL	29.14±24.72	30.88±28.28	28.70±23.74	0.363
hs-CRP, mg/L	11.69±25.53	15.93±37.66	10.67±21.58	0.064
Lipoprotein(a), mg/dL	41.16±39.31	47.39±54.22	39.65±34.65	0.063
Apolipoprotein A, mg/dL	104.78±19.96	113.88±22.18	102.55±18.74	<0.0001
Apolipoprotein B, mg/dL	88.05±26.16	89.15±29.71	87.78±25.24	0.618
Blood urea, mg/dL	15.08±7.74	15.72±6.60	14.92±8.01	0.296
Uric acid, mg/dL	6.08±1.72	5.92±1.91	6.12±1.67	0.253
Creatinine, pre-procedure, mg/dL	1.56±7.87	2.12±12.58	1.42±6.12	0.366
Creatinine, post-procedure, mg/dL	2.15±14.16	2.22±12.17	2.13±14.62	0.951
SGOT, U/L	108.23±186.88	70.02±65.84	117.47±204.76	0.062
SGPT, U/L	63.46±145.50	40.95±31.49	68.93±161.05	0.158

TABLE 2: Blood investigations among genders at admission

Continuous variables are presented as mean ± standard deviation (SD), and p values represent comparisons between female and male patients. ApoA, apolipoprotein A; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; VLDL-C, very-low-density lipoprotein cholesterol.

LDL-C at admission	Female (N=134)	Male (N=524)	P-value
<50 mg/dL	3 (2.2%)	11 (2.1%)	0.930
≥50 mg/dL	131 (97.8%)	513 (97.9%)	
<100 mg/dL	44 (32.8%)	209 (39.9%)	0.134
≥100 mg/dL	90 (67.2%)	315 (60.1%)	

TABLE 3: Distribution of admission LDL-C categories by sex

Categorical variables are presented as n (%). P-values represent comparisons between female and male patients. ApoA, apolipoprotein A; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; VLDL-C, very-low-density lipoprotein cholesterol.

Regimen	Assumed reduction	Female <50 mg/dL (N=134)	Male <50 mg/dL (N=524)	% of cohort	P-value*
High-intensity statin	50%	41 (30.6%)	205 (39.1%)	246 (37.4%)	0.085
Statin + ezetimibe	60%	87 (64.9%)	371 (70.8%)	458 (69.6%)	0.225
Statin + ezetimibe + bempedoic acid	75%	132 (98.5%)	520 (99.2%)	652 (99.1%)	0.354

TABLE 4: Stepwise lipid-lowering therapy simulation: LDL-C target attainment (<50 mg/dL) by sex

*P-values compare female vs male attainment within each regimen (chi-square test; Fisher's exact test used for the triple-therapy row given an expected cell count <5).

Variable	<50 years			≥50 years		
	Female	Male	P-value	Female	Male	P-value
Hypertension	7 (58.3%)	23 (21.7%)	0.020	81 (66.4%)	178 (42.6%)	<0.0001
Diabetes	4 (33.3%)	28 (26.4%)	0.866	52 (42.6%)	98 (23.4%)	<0.001
Ex-smoker	0	12 (11.3%)	0.468	5 (4.1%)	122 (29.2%)	<0.0001
Current smoker	1 (8.3%)	79 (74.5%)	<0.0001	4 (3.3%)	177 (42.3%)	<0.0001
LVEF, %	38.33±12.31	41.46±8.97	0.274	41.31±9.81	41.18±9.90	0.900
Syntax score	19.55±8.01	14.71±9.20	0.098	18.45±9.23	17.50±9.10	0.328
BMI, kg/m²	27.46±2.53	24.94±3.45	0.021	25.10±5.42	24.11±3.63	0.029

TABLE 5: Baseline risk factors, ventricular function, and BMI by age and sex

Categorical variables are presented as n (%), and continuous variables are presented as mean ± standard deviation (SD). P-values represent comparisons between female and male patients within each age group (<50 years and ≥50 years). BMI, body mass index; LVEF, left ventricular ejection fraction.

Variable	<50 years			≥50 years		
	Female	Male	P-value	Female	Male	P-value
HbA1c	6.45±2.27	6.33±2.04	0.851	6.54±1.68	6.18±1.57	0.031
Total cholesterol, mg/dL	207.51±74.98	187.55±48.43	0.206	193.39±48.33	178.41±43.87	0.001
HDL-C, mg/dL	42.85±16.04	40.66±10.49	0.520	49.19±12.93	42.41±11.02	<0.001
LDL-C, mg/dL	128.89±51.97	114.40±36.07	0.211	113.80±32.50	108.18±30.97	0.082
Triglycerides, mg/dL	199.03±110.94	196.96±136.31	0.960	155.30±89.13	149.51±88.10	0.526
Non-HDL-C, mg/dL	164.66±65.18	146.89±46.71	0.234	144.19±47.75	135.91±41.15	0.060
VLDL-C, mg/dL	39.81±22.19	39.39±27.26	0.960	30.81±17.97	29.90±17.62	0.620
Remnant cholesterol, mg/dL	35.77±17.76	32.49±29.95	0.711	30.40±29.11	27.74±21.82	0.275
hs-CRP, mg/L	12.09±14.43	7.89±6.96	0.110	16.41±39.62	11.36±23.83	0.130
Lipoprotein(a), mg/dL	64.25±64.26	40.60±38.89	0.081	45.53±53.05	39.41±33.54	0.160
Apolipoprotein B, mg/dL	111.55±39.16	93.16±29.58	0.063	86.74±27.68	86.39±23.85	0.901
Apolipoprotein A, mg/dL	118.36±35.21	101.81±18.74	0.015	113.40±20.49	102.74±18.77	<0.001
Blood urea, mg/dL	11.33±3.60	13.14±5.37	0.260	16.16±6.69	15.36±8.48	0.343
Uric acid, mg/dL	4.97±1.93	5.79±1.51	0.103	6.02±1.89	6.20±1.70	0.323
Creatinine, pre-procedure, mg/dL	0.87±0.23	1.05±0.20	0.004	2.24±13.20	1.51±6.85	0.421
Creatinine, post-procedure, mg/dL	0.95±0.14	1.11±0.20	0.015	2.33±12.68	2.41±16.47	0.966
SGOT, U/L	46.29±45.53	117.12±133.58	0.172	72.79±67.56	117.56±219.10	0.120
SGPT, U/L	26.29±11.38	57.41±33.07	0.020	42.66±32.67	71.79±179.20	0.212

TABLE 6: Baseline biochemical and lipid profile by age and sex

Continuous variables are presented as mean ± standard deviation (SD). P values represent comparisons between female and male patients within each age group (<50 years and ≥50 years). HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; VLDL-C, very-low-density lipoprotein cholesterol.

LDL-C category	<50 years			≥50 years		
	Female	Male	P-value	Female	Male	P-value
<50 mg/dL	1 (8.3%)	1 (0.9%)	0.484	2 (1.6%)	10 (2.4%)	0.883
≥50 mg/dL	11 (91.7%)	105 (99.1%)		120 (98.4%)	408 (97.6%)	
<100 mg/dL	3 (25.0%)	46 (43.4%)	0.359	41 (33.6%)	163 (39.0%)	0.330
≥100 mg/dL	9 (75.0%)	60 (56.6%)		81 (66.4%)	255 (61.0%)	

TABLE 7: Admission LDL-C categories by age and sex

Categorical variables are presented as n (%). P-values represent comparisons between female and male patients within each age group (<50 years and ≥50 years). LDL-C, low-density lipoprotein cholesterol.

Regimen (assumed reduction)	<50 years			≥50 years		
	Female	Male	P-value*	Female	Male	P-value*
High-intensity statin (50%)	3 (25.0%)	46 (43.4%)	0.355	38 (31.1%)	159 (38.0%)	0.199
Statin + ezetimibe (60%)	5 (41.7%)	68 (64.2%)	0.208	82 (67.2%)	303 (72.5%)	0.308
Statin + ezetimibe + bempedoic acid (75%)	11 (91.7%)	105 (99.1%)	0.194	121 (99.2%)	415 (99.3%)	1.000

TABLE 8: Stepwise lipid-lowering therapy simulation: LDL-C target attainment (<50 mg/dL) by age and sex

*P-values compare female vs male attainment within each age stratum for each regimen (Fisher's exact test used where any expected cell count was <5, which applied throughout the <50-year stratum and the ≥50-year triple-therapy row; chi-square test otherwise).

Table *1* presents the baseline characteristics of the study population. The mean age of participants was 61.4 years, with female patients significantly presenting later than male patients (67.5 vs 59.8 years, p<0.0001), an age gap of roughly 7.7 years suggesting later presentation in women. Hypertension and diabetes were more prevalent among female patients (88 (65.7%) vs 201 (38.4%) and 56 (41.8%) vs 126 (24.0%), both p<0.0001), while current and ex-smoking were markedly more common in male patients (256 (48.9%) vs 5 (3.7%) and 134 (25.6%) vs 05 (3.7%), both p<0.0001). BMI was higher in female patients (25.3 vs 24.3 kg/m², p=0.012). No significant sex differences were seen in xanthomas, corneal arcus, prior MI/PCI/PAD/stroke, family history, ACS type, angiographic extent of disease, syntax score, or LVEF.

The blood investigations by gender are presented in Table *2*. Female patients had significantly higher total cholesterol (194.7 vs 180.3 mg/dL, p=0.001), HDL-C (48.6 vs 42.1 mg/dL, p<0.001), and apolipoprotein A (113.9 vs 102.6 mg/dL, p<0.0001) than male patients. LDL-C was numerically but not significantly higher in female patients (115.1 vs 109.4 mg/dL, p=0.071). Triglycerides, VLDL-C, remnant cholesterol, apolipoprotein B, hs-CRP, lipoprotein(a), and renal/hepatic parameters did not differ significantly between sexes.

Only a small minority of patients of either sex already had an LDL-C <50 mg/dL at admission 03 (2.2%) female patients vs 11 (2.1%) male patients, and only about a third had LDL-C <100 mg/dL (44 (32.8%) vs 209 (39.9%), p=0.134). Most patients of both sexes therefore presented well above contemporary LDL-C targets, with no significant sex difference in admission category. The distribution of admission LDL-C categories by sex is presented in Table *3*.

With high-intensity statin monotherapy, 41 (30.6%) of female patients and 205 (39.1%) of male patients were projected to reach LDL-C <50 mg/dL (246 (37.4%) overall); this 8.5-percentage-point gap did not reach statistical significance (p=0.085). Adding ezetimibe raised attainment to 87 (64.9%) (female patients) and 371 (70.8%) (male patients), 458 (69.6% overall, p=0.225), and triple therapy with bempedoic acid produced near-universal attainment in both sexes (132 (98.5%) female patients, 520 (99.2%) male patients, p=0.354). At every step short of triple therapy, projected attainment was numerically lower in women than men, but none of these differences were statistically significant at the full-cohort level.

LDL-C target attainment by sex modelled by stepwise LLT is presented in Table *4*. With high-intensity statin monotherapy, 41 (30.6%) of female patients and 205 (39.1%) of male patients were projected to reach LDL-C <50 mg/dL 246 (37.4% overall); this 8.5-percentage-point gap did not reach statistical significance (p=0.085). Adding ezetimibe raised attainment to 87 (64.9%) (female patients), 371 (70.8%) (male patients), and 458 (69.6% overall, p=0.225), and triple therapy with bempedoic acid produced near-universal attainment in both sexes (132 (98.5%) female patients, 520 (99.2%) male patients p=0.354). At every step short of triple therapy, projected attainment was numerically lower in women than men, but none of these differences were statistically significant at the full-cohort level.

Because the risk factors and lipid profile of ACS patients change with age, and because subgroup sizes differed materially by age cut-off, a 50-year cut-off was used for this secondary analysis in preference to alternative cut-offs (e.g., 45 years), which produced very small female subgroups (6; 4.47%) and correspondingly unstable estimates. The following analysis should be regarded as exploratory and hypothesis-generating rather than confirmatory, given the modest size of the younger female subgroup (12; 8.95%).

Baseline risk factors, ventricular function, and BMI by age and sex are presented in Table *5*. In patients younger than 50 years, hypertension was significantly more common in women 07(58.3%) vs 23 (21.7%), p=0.020, and current smoking was far more common in men (79 (74.5%) vs 01 (8.3%), p<0.0001); BMI was higher in women (27.46 vs 24.94, p=0.021), while diabetes, LVEF, and syntax score were similar. The same

pattern - more hypertension, diabetes, and higher BMI in women; more smoking in men - persisted in patients ⩾50 years (hypertension 81 (66.4%) vs 178 (42.6%), p<0.0001; diabetes 52 (42.6%) vs 98 (23.4%), p<0.001; BMI 25.10 vs 24.11, p=0.029), with no significant difference in LVEF or syntax score.

Baseline biochemical and lipid profile by age and sex is shown in Table 6. Below age 50, women had higher apolipoprotein A (118.4 vs 101.8, p=0.015) and lower pre- and post-procedure creatinine (both p⩽0.02) and SGPT (26.3 vs 57.4, p=0.02) than men; LDL-C and other lipid fractions did not differ significantly, though numbers are small. At ⩾50 years, women had higher HbA1c (6.54 vs 6.18, p=0.031), total cholesterol (193.4 vs 178.4, p=0.001), HDL-C (49.2 vs 42.4, p<0.001), and apolipoprotein A (113.4 vs 102.7, p<0.001), with no significant sex difference in LDL-C, triglycerides, or renal/hepatic parameters. As in the full cohort, LDL-C, the variable driving the therapy simulation, was not significantly different between sexes in either age stratum.

Admission LDL-C categories by age and sex are presented in Table 7. Admission LDL-C category did not differ significantly by sex in either age stratum. The great majority of both men and women, at any age, presented with LDL-C above 100 mg/dL, confirming that the two sexes start from a broadly comparable and largely unfavourable baseline position.

LDL-C target attainment (<50 mg/dL) by age and sex modelled by stepwise LLT simulation is shown in Table 8. In patients younger than 50, high-intensity statin monotherapy was projected to bring three (25.0%) women and 46 (43.4%) men to target, a large absolute gap that did not reach statistical significance in this small subgroup (p=0.355); the gap narrowed numerically with ezetimibe 05(41.7%) vs 68 (64.2%), p=0.208 and with triple therapy 11 (91.7%) vs 105 (99.1%) p=0.194. In patients ⩾50 years, the same numerical pattern was present but smaller and, again, not statistically significant at any step (statin: 38 (31.1%) vs 159(38.0%), p=0.199; statin+ezetimibe: 82 (67.2%) vs 303 (72.5%), p=0.308; triple therapy: 121 (99.2%) vs 415 (99.3%), p=1.000. None of the age-stratified sex comparisons reached significance, most plausibly because subdividing an already modest female sample (134; 20.36%) by age leaves too few events per cell to detect a difference of this size. The wide absolute gaps in the youngest stratum are clinically noteworthy even though the formal test is not significant and should be read as hypothesis-generating.

Discussion

In this single-centre analysis of ACS patients undergoing PCI, women presented almost eight years later than men and carried a heavier burden of metabolic risk factors, hypertension, diabetes, and higher BMI, while smoking was predominantly a male characteristic; these baseline differences were statistically significant. Despite a higher overall lipid profile in women (higher total cholesterol, HDL-C, and apolipoprotein A), admission LDL-C was similar between the sexes, and most patients of both sexes presented well above contemporary LDL-C targets. When stepwise LLT was modelled, high-intensity statin monotherapy left most patients short of an LDL-C goal of <50 mg/dL, and only the sequential addition of ezetimibe and bempedoic acid brought attainment close to universal. Projected attainment was numerically lower in women than men at every step short of triple therapy, both overall and within each age stratum, but none of these attainment differences reached statistical significance (p=0.09-0.35 across regimens and strata), a consistent direction of effect that this sample size is underpowered to confirm rather than an absence of a sex difference. The absolute gap was largest among patients younger than 50 years on statin monotherapy (25.0% women vs 43.4% men) and narrowed with age and with treatment intensification.

The risk-factor pattern we observed older women with more hypertension and diabetes, and men who smoke more mirrors reports from Indian and other ACS cohorts, in which women also present later and experience poorer early outcomes [9,12]. Because baseline LDL-C did not differ significantly between the sexes overall or within either age stratum, the reduction required to reach target is similar for both; any sex difference in attainment therefore reflects how therapy is applied or responded to, rather than women starting from a worse LDL-C position.

Our simulation makes this treatment gap explicit: high-intensity statin monotherapy was projected to bring 37.4% of the cohort to LDL-C <50 mg/dL, increasing to 69.6% with the addition of ezetimibe and to 99.1% with triple therapy incorporating bempedoic acid. These findings are consistent with the broader literature indicating that achievement of guideline-recommended LDL-C targets after ACS remains challenging despite the availability of effective LLTs and that early combination therapy may often be required to achieve stringent LDL-C goals [13,14]. Both recent reviews emphasise the importance of intensive and early lipid lowering after ACS and highlight the substantial proportion of patients who remain above recommended LDL-C targets despite treatment [13,14]. The reduction magnitudes underlying our model are well supported: an Indian head-to-head study reported a 45% LDL-C reduction with rosuvastatin 40 mg alone versus 62% with rosuvastatin plus ezetimibe, achieving LDL-C <50 mg/dL in 28% and 75% of patients, respectively, closely matching our assumptions [15]. A German Monte Carlo simulation reached a similar conclusion by a different method, with attainment rising from about 11% at baseline to 33% with ezetimibe and 62% with bempedoic acid [16].

The near-universal LDL-C target attainment observed with simulated triple therapy in our study extends beyond the findings of previous clinical studies. In the OLA study, upfront rosuvastatin plus ezetimibe

achieved LDL-C <50 mg/dL in 74.6% of statin-naïve ACS patients at four weeks [15]. Similarly, a structured stepwise approach using high-intensity statin, ezetimibe, and subsequently a PCSK9 inhibitor achieved LDL-C ⩽1.8 mmol/L in 87% of post-ACS patients [17]. Although these studies support the effectiveness of early combination and stepwise lipid-lowering strategies, their treatment regimens and LDL-C targets differed from the triple-therapy simulation evaluated in the present study. However, these projected rates should be interpreted alongside real-world experience, where some patients remain above target despite intensive therapy because of factors such as suboptimal adherence, incomplete follow-up, variable treatment response, and elevated lipoprotein(a). Lipoprotein(a), in particular, has been associated with reduced likelihood of achieving LDL-C targets and increases markedly in the early period after ACS [18]. Our simulation therefore describes the pharmacological potential of each regimen rather than guaranteed real-world performance.

The most notable sex-related finding was observed in the projected treatment response rather than at baseline. At each treatment step before triple therapy, fewer women than men were projected to achieve LDL-C <50 mg/dL, although the differences were not statistically significant. As the model applied the same percentage LDL-C reduction to both sexes, this trend likely reflects higher baseline LDL-C levels in women rather than differences in treatment efficacy. Similar observations have been reported in patients with young ACS, post-ACS, and chronic coronary syndrome, where women are less likely to achieve LDL-C targets than men [12,19]. Although our findings are in line with these reports, a larger study would be needed to confirm this association.

The age-stratified secondary analysis adds a further dimension: the absolute sex gap in projected attainment on statin monotherapy was widest in patients under 50 years (43.4% vs 25.0%) and comparatively narrow in patients ⩾50 years, even though the female subgroup under 50 also carried a markedly higher burden of hypertension, diabetes, and smoking-adjacent risk than their male counterparts. None of these age-stratified comparisons reached statistical significance, and the younger-female subgroup is very small (n=12), so this should be read as a descriptive, hypothesis-generating observation rather than a demonstrated effect. If confirmed in a larger, ideally multicentre cohort, it would suggest that younger women with ACS may derive particular benefit from early combination therapy rather than a wait-and-escalate approach; at present it is best framed as a signal worth testing rather than a finding to act on.

Together, these findings support a shift from sequential statin-first escalation toward earlier combination therapy in high-risk ACS patients, consistent with the "strike early and strike strong" approach now advocated in consensus statements and reviews, including from Indian authors [13,20,21]. Even an idealised stepwise protocol can take several weeks of reassessment to reach target, coinciding with the period of highest recurrent-event risk, and patients with high baseline LDL-C, the majority of our cohort, are precisely those in whom statin monotherapy is predictably insufficient [20,21]. In resource-limited settings, early intensification with oral combination LLT may represent a practical strategy for improving LDL-C target attainment, particularly where access to injectable therapies may be limited [13,14]. In the OLA study, upfront rosuvastatin plus ezetimibe achieved LDL-C <50 mg/dL in 74.6% of statin-naïve ACS patients at four weeks, supporting the potential value of early oral combination therapy in this setting [15]. Recent evidence from India further supports the feasibility of achieving LDL-C goals with upfront oral combination therapy in the early post-ACS period [21].

Limitations

This was a single-centre study, which may limit the generalisability of the findings. LDL-C target attainment was estimated using a simulation based on expected percentage reductions with LLTs rather than observed follow-up lipid values. Consequently, the model does not account for individual differences in treatment response, adherence, statin intolerance, dose adjustments, or changes in LDL-C after ACS, and the projected attainment rates should be viewed as expected pharmacological efficacy rather than real-world outcomes. The study also evaluated projected LDL-C target attainment instead of clinical outcomes. The relatively small number of women, particularly those younger than 50 years, limited the power to detect sex- and age-specific differences, making these analyses exploratory. In addition, multiple comparisons were not adjusted for, increasing the possibility of chance findings. Although lipoprotein(a) independently predicted failure to achieve LDL-C targets, it was not incorporated into the simulation model.

Conclusions

Men and women with ACS arrive with different risk-factor profiles; women carry significantly more hypertension, diabetes, and higher BMI, men smoke significantly more but have similar admission LDL-C, and high-intensity statin monotherapy is projected to leave most of both sexes above the recommended target. The stepwise addition of ezetimibe and bempedoic acid substantially narrows this gap and brings attainment close to universal. Overall, these findings reinforce the case for early combination LLT in high-risk ACS patients, with attention to settings where affordable oral agents are the mainstay of treatment, and support further, adequately powered study of whether women, particularly younger women, need earlier combination therapy.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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