

Early Ezetimibe Initiation After Myocardial Infarction Protects Against Later Cardiovascular Outcomes in the SWEDEHEART Registry



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ABSTRACT

BACKGROUND Combination lipid-lowering therapy (LLT) after myocardial infarction (MI) achieves lower low-density lipoprotein cholesterol (LDL-C) levels and better cardiovascular outcomes vs statin monotherapy. As a result, global guidelines recommend lower LDL-C but, paradoxically, advise treatment through a stepwise approach. Yet the need for combination therapy is inevitable as <20% of patients achieve goals with statins alone. Whether combining ezetimibe with a statin early vs late after MI results in better outcomes is unknown.

OBJECTIVES In this study, the authors sought to assess the impact of delayed treatment escalation on outcomes by comparing early vs late oral combination LLT (statins plus ezetimibe) in patients with MI.

METHODS LLT-naïve patients (SWEDEHEART registry) hospitalized for MI (2015–2022) and discharged on statins were included. Using clone-censor-weight and Cox proportional hazards models, we compared differences in risks of MACE (death, MI, stroke), components of MACE, and cardiovascular death between patients with ezetimibe added to statins ≤12 weeks after discharge as reference (early combination therapy), from 13 weeks to 16 months (late combination therapy), or not at all.

RESULTS Of 35,826 patients (median age 65.1 years, 26.0% women), 6,040 (16.9%) received ezetimibe early, 6,495 (18.1%) ezetimibe late, and 23,291 (65.0%) received no ezetimibe. High-intensity statin use was ≥98% in all groups. Over a median 3.96 years (Q1–Q3: 2.15–5.81 years), 2,570 patients had MACE (440 cardiovascular deaths). One-year MACE incidences were 1.79 (early), 2.58 (late), and 4.03 (none) per 100 patient-years. Compared with early combination therapy, weighted risk differences in MACE for late combination therapy at 1, 2, and 3 years were 0.6% (95% CI: 0.1%–1.1%; $P < 0.01$), 1.1% (95% CI: 0.3%–2.0%; $P < 0.01$), and 0.7% (95% CI: –0.2% to 1.3%; $P = 0.18$), and 3-year HR was 1.14 (95% CI: 0.95–1.41). For those receiving no ezetimibe, risk differences were 0.7% (95% CI: 0.2%–1.3%), 1.6% (95% CI: 0.8%–2.5%), and 1.9% (95% CI: 0.8%–3.1%; P for all <0.01; 3-year HR: 1.29 [95% CI: 1.12–1.55]). Similar differences in risk of cardiovascular death at 3 years were observed (HRs vs early: late: 1.64 [95% CI: 1.15–2.63]; none: 1.83 [95% CI: 1.35–2.69]).

CONCLUSIONS MI care pathways should implement early combination therapy with statins and ezetimibe as standard care, because delaying use of combination LLT or using high-intensity statin monotherapy is associated with avoidable harm. (JACC. 2025;85:1550–1564) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



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Observational data from registries show that at least two-thirds of patients with a myocardial infarction (MI) are statin naïve at the time of presentation.^{1,2} Thus, the first time lipid-lowering therapy (LLT) is initiated for many is after a MI. Typically, this LLT consists of a high-intensity statin before hospital discharge, based on clinical trials demonstrating that early treatment with high-intensity statins is better than moderate-intensity statins after a MI,³ with cardiovascular benefits appearing early and sustained if treatment is continued.⁴ Guidelines adopted this evidence, recommending early use of high-intensity statins and providing a quality metric of treatment effectiveness by recommending low-density lipoprotein cholesterol (LDL-C) goals of <1.8 mmol/L (<70 mg/dL).⁵ Subsequent trials have moved from statin monotherapy to combination therapies, showing first that the addition of ezetimibe to statins before hospital discharge not only lowered LDL-C levels beyond what was achievable with monotherapy, but more importantly also resulted in better cardiovascular outcomes.⁶ Trials of proprotein convertase subtilisin/kexin type-9 inhibitors (PCSK9is) showed that among patients with a recent MI if LDL-C was ≥ 1.8 mmol/L (≥ 70 mg/dL) despite high-intensity statins, the addition of PCSK9i reduced LDL-C and cardiovascular outcomes.^{7,8} The evidence that lower LDL-C levels in the post-MI setting resulted in better outcomes were adopted by both European and U.S. guidelines.⁹⁻¹¹ However, the recommendations on how to implement this consisted of a stepwise approach, starting with the initiation of high-intensity statins as close to the MI as possible, with escalation of treatment taking place after subsequent LDL-C measurements, with the addition of ezetimibe first and then PCSK9i for those failing to achieve LDL-C goals.

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However, data from the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry showed that approximately 75% to 80% of MI patients failed to achieve LDL-C goals with statin monotherapy.¹² The same study used modeling of expected LDL-C reductions from treatment escalation showing that goal attainment would double with the addition of

ezetimibe, with the remainder predicted to achieve LDL-C goals if PCSK9i were added. If the LDL-C goals currently recommended are to be stringently implemented, the use of combination therapies is unavoidable. A stepwise approach inevitably means delays in attaining recommended LDL-C goals. Whether this delay in treatment escalation is inferior to a proactive approach of early combination LLT is unknown. Given the potential ethical dilemma of using a formal randomized trial, we used the SWEDEHEART registry to provide insights into this question by using a trial emulation clone-censor-weight framework overcoming challenges with confounding and immortal time bias. We hypothesized that the delayed addition of ezetimibe to statins after a MI was associated with worse cardiovascular outcomes compared with an approach using early combination therapy with statins and ezetimibe.

METHODS

The aim of this study was to compare the incidences of major adverse cardiovascular events (MACE), the components of MACE, and cardiovascular death between patients with MI discharged on statin therapy and receiving ezetimibe add-on early, patients receiving ezetimibe add-on late, and those not receiving ezetimibe at all.

DATA SOURCES. In this observational study, prospectively collected data from four Swedish national registries were used. The SWEDEHEART registry collects data on all patients hospitalized for an MI at cardiac care units in Sweden and includes data on patient characteristics, ongoing and discharge medications, and acute coronary care.¹³ When audited against the Swedish National Inpatient Registry, SWEDEHEART captures >90% of all patients <80 years of age with MI in the country.¹⁴ Furthermore, data quality are monitored yearly in SWEDEHEART and shows completeness and accuracy of >95%.¹⁴ Data on cardiac rehabilitation interventions and outcomes, including medication and lipid measures, are also registered in SWEDEHEART during the first year after a MI, with data available in ~80% of all MI cases.¹⁵ The Prescribed Drug Registry contains data on all prescribed and filled drug prescriptions in Sweden. The National

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
LDL-C = low-density lipoprotein cholesterol
LLT = lipid-lowering therapy
MACE = major adverse cardiovascular events
MI = myocardial infarction
PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Patient Registry includes diagnoses from all non-primary care outpatient visits and hospital discharges, and the Cause of Death Registry registers causes of death for all deaths in the country. Data were linked with the use of the unique personal identity number assigned to all Swedish residents.

STUDY POPULATION. All patients aged 18 to <80 years registered with an MI diagnosis (International Classification of Disease-10th Revision [ICD-10] codes I21-I22) from January 1, 2015, to September 23, 2022, were included. Earlier data were not included, because ezetimibe use was sparse in Sweden before 2015.¹⁴ Patients on statin, ezetimibe, or PCSK9i before admission and patients not discharged on statin (defined as prescription not filled within 7 days of discharge) were excluded. Also, those with a baseline LDL-C of <1.4 mmol/L (<55 mg/dL), a truncated Dutch Lipid Clinic Network score of ≥ 6 points (using LDL-C level and age at index event only), or a diagnosis of familial hypercholesterolemia (ICD-10 F78.0A) were excluded because they were deemed likely to violate the assumption that all patients should be potential candidates for being allocated to any treatment group during the study. The age limit of <80 years was also applied for this reason, ie, to minimize treatment-allocation bias on the account of frailty, comorbidities, and high age. The study complies with the Declaration of Helsinki and was approved by the Regional Ethics Committee in Stockholm (approval no. 2012/6031/2) and the Swedish Ethical Review Authority (approval nos. 2019-04277 and 2021/00019).

EXPOSURES. Three exposure groups were defined, all with statin treatment at discharge: 1) early combination LLT with ezetimibe dispensed ≤ 12 weeks after discharge (reference group); 2) late combination LLT with ezetimibe dispensed from 13 weeks to ≤ 16 months after discharge; and 3) no ezetimibe dispensed during the first 16 months after discharge. Too few patients had in-hospital initiation of combination LLT, further restricted by limited follow-up time, to assess the effect of in-hospital initiation of combination LLT separately. Instead, the 12-week and 16-month time points were used because standard cardiac rehabilitation programs in Sweden include 2 time-fixed follow-up visits at 2 months (6-10 weeks) and 1 year (11-14 months) after discharge, aligning with information being registered in SWEDEHEART.¹⁵ During these visits, LDL-C is sampled with an accepted time window of 2 weeks before or after the 2-month visit (4-12 weeks) and 2 months before or after the 1-year visit (9-16 months). Titration of LLT is usually performed within this time frame.

Treatment with PCSK9i was rare and included in a sensitivity analysis. Use of other LLTs during the study period was negligible and not included in the analysis.

OUTCOMES. The primary outcome was major adverse cardiovascular events (MACE), consisting of all-cause death, nonfatal MI (ICD-10 I21-I22), and nonfatal stroke (ICD-10 I60-I64). Secondary outcomes were cardiovascular death (ICD-10 I00-I99), the individual components of MACE, and LDL-C target achievement. The study index date was the date of discharge from MI hospitalization. Complete follow-up was until a nonfatal event or death occurred, or at the end of data capture (December 31, 2021, for nonfatal events and cause-specific death and September 30, 2022, for all-cause death), whichever occurred first.

To minimize the effect of temporal trends in MI treatment, including use of combination LLT, and to ensure proportionality across outcomes, all outcomes are reported at 1, 2, and 3 years.

STATISTICAL ANALYSIS. Descriptive baseline data are presented as median (Q1-Q3) or n (%).

When assessing treatment effects based on observational data, there are several major challenges. First, the absence of randomization to treatment allocation introduces confounding bias due to unbalanced patient characteristics, baseline risks, and clinical choices based on those characteristics. Second, immortal time bias is introduced when timing of treatment initiation and start of study follow-up do not coincide. A strategy to overcome these challenges is the clone-censor-weight method, a methodology for emulating randomized clinical trials in observational studies.^{16,17} A visual representation of this approach, as used in the present study, is provided in [Supplemental Figure 1](#). The target trial emulation framework entails using observational data to mimic a hypothetical randomized clinical trial addressing a research question/hypothesis and includes a trial protocol with inclusion and exclusion criteria, treatments, study outcomes, and analyses used.

For each index MI discharge, 3 clones (copies) were created, corresponding to each treatment strategy. We evaluated adherence of the clones to their assigned treatment strategies at weekly intervals. If a clone deviated from its assigned strategy, ie, changed LLT, it was censored at that point. For example, if a clone assigned to the “no ezetimibe initiation within 12 weeks” strategy began treatment at 6 weeks, it was censored at that time (informative censoring). To adjust for potential selection bias due to informative censoring, we applied weight models based on the

probability of informative censoring. In cases where informative censoring occurred at a single time point, a logistic regression model was used; when it could occur at multiple time points, a pooled logistic regression model was used. We calculated the cumulative probability of remaining uncensored and derived inverse probability of censoring weights. To limit the influence of extreme weights, we truncated weights at the 99.5th percentile. Covariate balance was assessed with the use of standardized mean differences. Covariates and their definitions are listed in [Supplemental Table 1](#).

To estimate a treatment effect using the clone-censor-weight framework, risk differences were generated. Kaplan-Meier survival probability estimates were calculated for all outcomes. These analyses were stratified by treatment exposure, and weighted risk differences were evaluated at 1, 2, and 3 years of follow-up. As a complementary analysis, HRs and 95% CIs were estimated with the use of weighted Cox proportional hazards regression. CIs were calculated by means of nonparametric bootstrapping with the percentile method, and *P* values were calculated through permutation testing, in both cases with 1,000 iterations. Patients receiving add-on therapy with ezetimibe early were used as the reference group in all models.

In descriptive baseline analyses, the group with no ezetimibe dispensed during the first 16 months after discharge includes not only those not receiving ezetimibe during the first 16 months, but also patients who had an event or died before having the chance of being allocated to the ezetimibe treatment groups. Those patients contributed to event rates in the early and late treatment groups in the clone-censor-weight model, but not in descriptive data analyses, possibly causing exaggerated between-group differences in baseline data.

Sensitivity analyses were conducted by assessing between-group risk differences and HRs with the use of a negative control outcome. This was performed to identify potential bias in group allocation, using an outcome not causally influenced by the treatment under investigation. To detect unmeasured confounding and treatment bias, we used skeletal fractures (ICD-10 codes listed in [Supplemental Table 2](#)) as a “negative control outcome.” A negative control outcome is an event that shares the same potential sources of bias with the study outcome but cannot plausibly be related to the treatment of interest. Furthermore, a sensitivity analysis censoring for PCSK9i use during follow-up was performed.

Because participation in the National Patient and Prescribed Drug Registries is mandatory for all

Swedish residents, there are no missing data in these registries. In SWEDEHEART, a small proportion of variables had missing information, which was highest for left ventricular ejection fraction (7.5%) and LDL-C (6.5%) ([Table 1](#)). In the analyses, missing data were handled with the use of single imputation via chained equations, under the assumption that data were missing at random. All analyses were performed with the use of R software, version 3.6.0 (R Foundation).¹⁸

RESULTS

PATIENT CHARACTERISTICS. In total, 35,826 patients were included, of whom 6,040 (16.9%) received ezetimibe combination therapy early, 6,495 (18.1%) received ezetimibe combination therapy late, and 23,291 (65.0%) did not receive ezetimibe during the first 16 months after discharge ([Supplemental Figures 2 and 3](#)). The median age at the index MI was 65.1 years (Q1-Q3: 57.0-72.1 years), and 26.0% were women ([Table 1](#)). Compared with patients receiving ezetimibe combination therapy early or late, patients not receiving add-on therapy with ezetimibe during the first 16 months were older, had more comorbidities, and had a lower baseline LDL-C. Prescription of high-intensity statins at discharge was high in all groups ($\geq 98\%$). Patient characteristics stratified by sex are presented in [Supplemental Tables 3 and 4](#). The proportion of patients attending at least 1 of the 2 cardiac rehabilitation visits during the first year after MI was higher among patients receiving ezetimibe early (93.1%) or late (95.6%) than in those not receiving add-on therapy with ezetimibe (86.6%) ([Supplemental Table 5](#)). At 1 year after discharge, 85.0% had filled a prescription for statins (any intensity) during their most recent dispensing period, accounting for a 25% grace period. Differences between groups were minimal ([Supplemental Table 6](#)). Fewer than 1.0% had filled a prescription for PCSK9i, with some variation among groups, ranging from 2.0% in the early ezetimibe group to 1.3% in the late ezetimibe group and 0.3% in the no ezetimibe group. The use of other LLTs was minimal ([Table 1](#), [Supplemental Table 6](#)).

TEMPORAL TRENDS IN THE USE OF STATINS AND EZETIMIBE. The proportion of patients receiving combination therapy up to 16 months after the index event increased from approximately 14% in 2015 to almost 60% in 2021 ([Supplemental Figure 4](#)). The proportion of patients discharged from hospital after the index MI on statin plus ezetimibe was negligible before 2018. Before 2019, it was more common for patients to receive add-on therapy with ezetimibe

TABLE 1 Patient Characteristics					
	Overall (N = 35,826)	Missing	Treatment Group		
			Early Ezetimibe (n = 6,040)	Late Ezetimibe (n = 6,495)	No Ezetimibe (n = 23,291)
Admission characteristics					
Age, y	65.1 (57.0-72.1)	0	63.6 (56.0-70.6)	63.4 (55.9-70.5)	66.1 (57.7-72.8)
Female	9,302 (26.0)	0	1,395 (23.1)	1,688 (26.0)	6219 (26.7)
Body mass index, kg/m ²	26.9 (24.5-29.9)	1,471	27.0 (24.6-30.0)	27.1 (24.7-30.1)	26.8 (24.4-29.8)
Current smoker	9,683 (27.7)	895	1,647 (27.9)	1,39 (28.9)	6,197 (27.3)
Hypertension	12,519 (35.1)	179	1,835 (30.6)	2,025 (31.3)	8,659 (37.4)
Diabetes mellitus	3,543 (9.9)	0	451 (7.5)	476 (7.3)	2,616 (11.2)
Charlson comorbidity index	1.0 (1.0-2.0)	0	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)
Medical history					
Previous MI	946 (2.6)	0	125 (2.1)	152 (2.3)	669 (2.9)
Heart failure	549 (1.5)	0	58 (1.0)	64 (1.0)	427 (1.8)
Laboratory and physiological variables					
LDL-C, mmol/L	3.3 (2.7-4.0)	2,327	3.8 (3.2-4.4)	3.6 (3.0-4.2)	3.1 (2.6-3.7)
eGFR, mL/min/1.73 m ²	75.8 (66.5-85.1)	0	77.4 (68.2-86.4)	77.2 (68.1-86.2)	75.1 (65.7-84.5)
Fasting glucose, mmol/L	6.7 (5.8-8.0)	5,239	6.6 (5.8-7.8)	6.6 (5.8-7.9)	6.7 (5.8-8.1)
Systolic blood pressure, mm Hg	150 (133-170)	235	150 (132-170)	150 (133-170)	150 (133-170)
In-hospital characteristics and management					
STEMI	16,609 (46.4)	1	3,038 (50.3)	3,114 (47.9)	10,457 (44.9)
Reduced LVEF ^a	3,742 (11.3)	2,698	610 (10.7)	678 (11.2)	2,454 (11.5)
Coronary angiography	35,030 (97.8)	0	5,944 (98.4)	6,408 (98.7)	22,678 (97.4)
Multivessel disease ^b	14,067 (39.3)	0	2,659 (44.0)	2,671 (41.1)	8,737 (37.5)
Revascularized during hospitalization	30,036 (83.8)	0	5,403 (89.5)	5,673 (87.3)	18,960 (81.4)
Discharge medication					
High-intensity statin	35,285 (98.5)	0	6,015 (99.6)	6,437 (99.1)	22,833 (98.0)
Ezetimibe	1,058 (3.0)	0	1,058 (17.5)	N/A	N/A
PCSK9i	≤5	0	≤5	≤5	≤5
Other LLT ^c	8 (0.0)	0	≤5	≤5	≤5
ACE inhibitor/ARB	29,747 (83.0)	0	4,995 (82.7)	5,462 (84.1)	19,290 (82.8)
Platelet inhibitor ^d	35,561 (99.3)	0	6,019 (99.7)	6,468 (99.6)	23,074 (99.1)
Values are median (Q1-Q3), n, or n (%). ^a Left ventricular ejection fraction <40%. ^b Two or more main coronary arteries (left anterior descending artery, circumflex artery, right coronary artery, or left main) with significant (≥50%) stenoses. ^c Fibrates, resins, or nicotinic acid. ^d Acetylsalicylic acid or P2Y ₁₂ inhibitor.					
ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; STEMI = ST-segment elevation myocardial infarction.					

late (ie, ≥13 weeks after the index event), whereas toward the end of the study, initiation of combination therapy early was more common.

PROPORTION OF PATIENTS AT LDL-C GOAL. Data were available on LDL-C levels for 33,499 patients (93.5%) at baseline and for 20,351 patients (56.8%) at both cardiac rehabilitation follow-up visits (6-10 weeks and 1 year). A larger proportion of patients with early ezetimibe combination therapy had achieved the LDL-C target at 1 year compared with patients receiving ezetimibe therapy late and those not having received ezetimibe up to the 1-year visit (time frame for LDL-C sampling, 9-16 months) (**Figure 1**). Median and LDL-C changes and proportions of patients at the LDL-C target at the 6-10-week and 1-year follow-up visits for each treatment group are presented in **Supplemental Table 7**.

The proportions of patients with at least 1 measurement of LDL-C during follow-up who achieved the LDL-C target of <1.4 mmol/L (<55 mg/dL), according to the clone-censor-weight framework, are shown in **Figure 2**. Despite having the highest baseline LDL-C levels, approximately 55% of patients receiving ezetimibe combination therapy early had reached the target at 1 year after discharge. Of patients receiving ezetimibe late or not having received ezetimibe up to 1 year, fewer were at goal. Over 3 years, although the proportion at goal increased in all 3 groups, it remained better with combination therapy and was highest in the early combination therapy group (**Figure 2**).

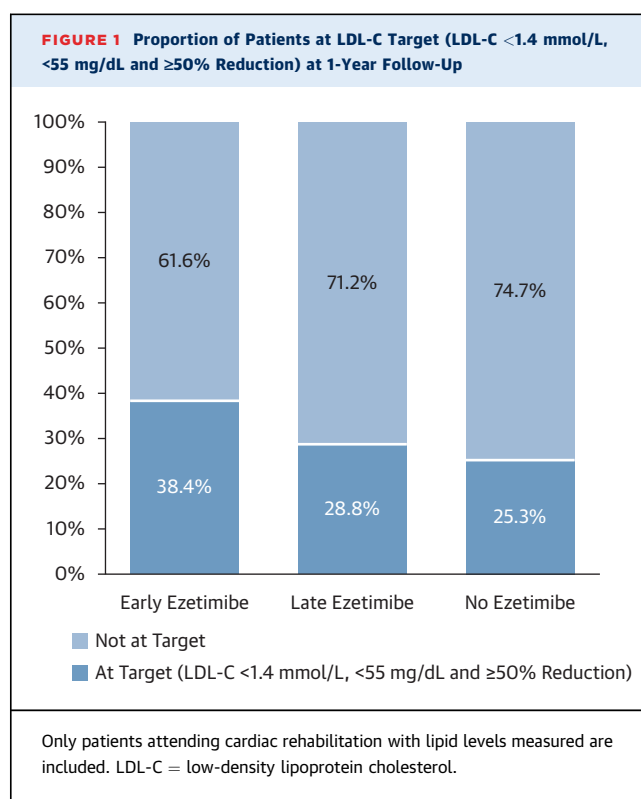
EARLY VS LATE COMBINATION LLT AND OUTCOMES. During a median follow-up of 3.96 years (Q1-Q3: 2.15-5.81 years), 2,570 patients had a MACE.

Unadjusted incidence rates at 1 year were 1.79 (early ezetimibe combination therapy), 2.58 (late ezetimibe combination therapy), and 4.03 (no ezetimibe) per 100 person-years. Covariate balance was assessed after 16 months and was within the preferred standardized mean difference of ± 0.1 for all covariates considered (Supplemental Figure 5). Compared with patients initiated on ezetimibe early, the risk of MACE for patients receiving ezetimibe add-on therapy late was higher at 1 and 2 years after MI but was not statistically significant at 3 years after MI (Figure 3). For those not receiving ezetimibe at all, the risk was higher at 1, 2, and 3 years after MI (Figure 3). The adjusted HR for MACE over 3 years for patients receiving ezetimibe late was 1.14 (95% CI: 0.95-1.41) and for patients not receiving ezetimibe was 1.29 (95% CI: 1.12-1.55) (Supplemental Figure 6).

The cumulative incidence of the 4 prespecified secondary outcomes followed a similar pattern, with patients not receiving ezetimibe at all having the highest risk for adverse outcomes compared with patients receiving add-on treatment with ezetimibe early (Figure 4). For cardiovascular death, the HRs at 3 years for patients receiving ezetimibe late or not at all were 1.64 (95% CI: 1.15-2.63) and 1.83 (95% CI: 1.35-2.69), respectively (Supplemental Figure 6).

Using the current cohort (35,826 patients and 2,570 events) and the 3-year risk differences in MACE, moving from statin monotherapy to an early combination strategy would require a number needed to treat (NNT) of 53 (95% CI: 32-125) to prevent 1 MACE. If we moved from a delayed to early combination strategy the NNT to prevent one MACE would be 143 (95% CI: 44-167). Applying these NNTs to the current study population means that instead of the observed 16.9% receiving early combination LLT, 18.1% receiving late combination LLT, and 65.0% receiving no ezetimibe, if all patients received early combination LLT then this approach could prevent an additional 477 events. Table 2 provides hypothetical scenarios of potential MACE averted through implementation of early combination therapies in populations of varying size.

SENSITIVITY ANALYSES. To evaluate potential bias or confounding related to frailty, where patients with more severe health conditions might not have been offered combination therapy, we performed a sensitivity analysis using fractures as a negative control outcome. Compared with patients receiving early combination with ezetimibe, the analysis showed no

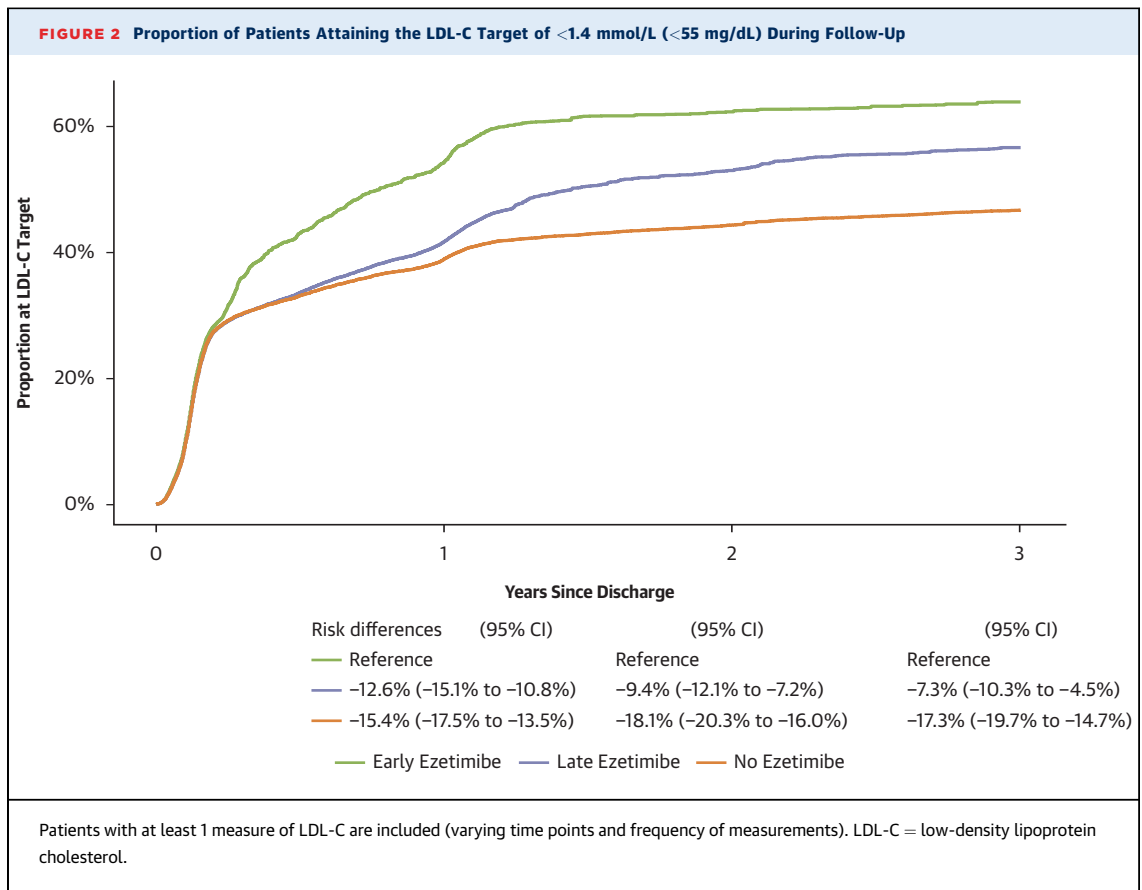


statistically significant difference in the cumulative incidence of skeletal fractures for those receiving ezetimibe late or not at all (Supplemental Figure 7).

In the sensitivity analysis censoring for PCSK9i use during follow-up, no major differences in any of the outcomes were observed (Supplemental Table 8).

DISCUSSION

In this study of 35,826 statin-treated patients with a recent MI, there were 3 key findings regarding timing of initiation of combination LLT by the addition of ezetimibe to high-intensity statins. First, as expected, the use of ezetimibe combination therapy early or late resulted in a greater proportion of patients achieving an LDL-C of <1.4 mmol/L (<55 mg/dL) compared with not receiving add-on therapy with ezetimibe at all. Second, early combination therapy by adding ezetimibe to background high-intensity statin was associated with greater absolute and relative benefits in terms of MACE compared with a strategy of delayed initiation of combination therapy (Central Illustration). Third, approximately two-thirds of patients had not received add-on therapy with

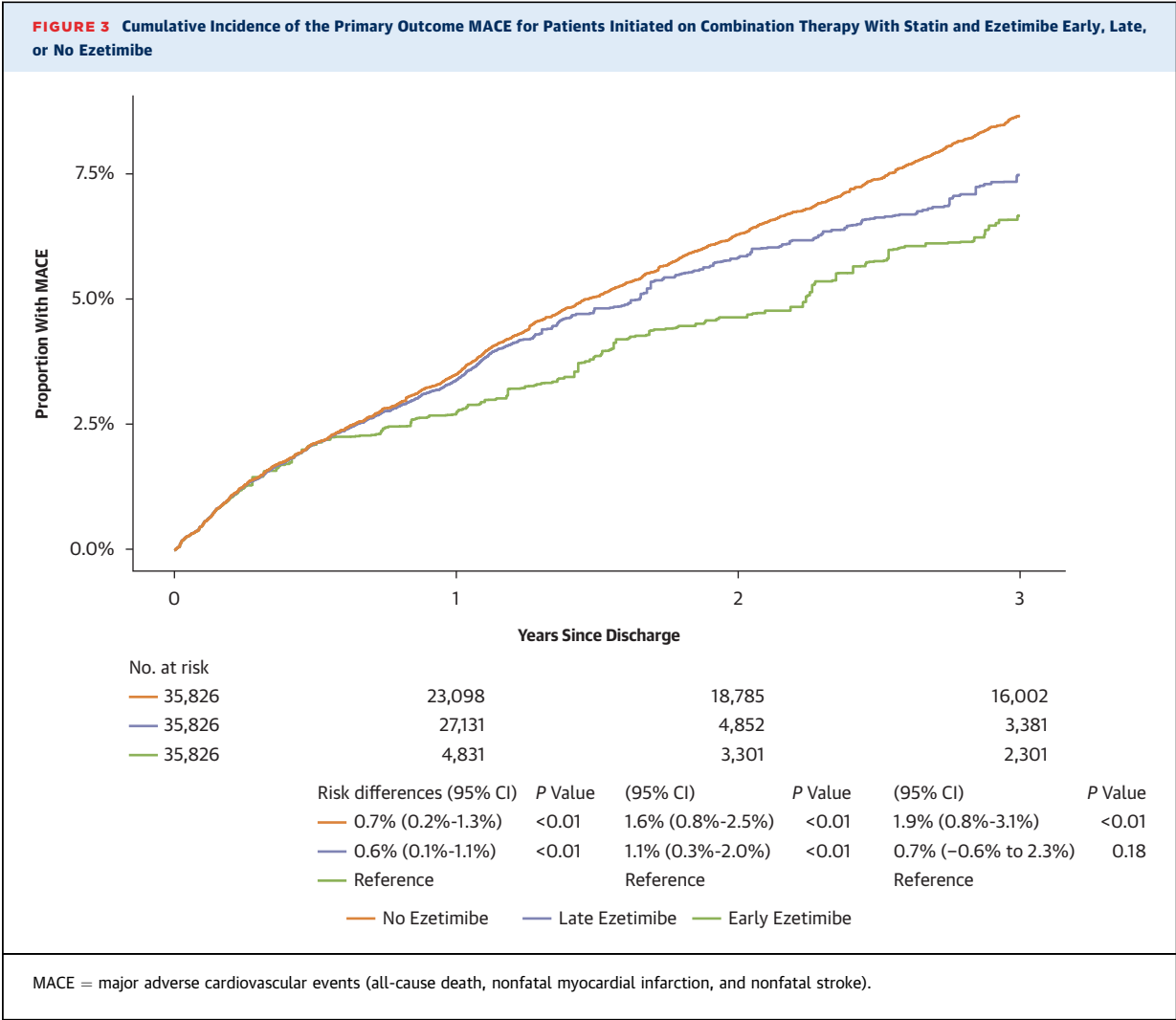


ezetimibe by 16 months after MI, and those patients experienced the highest risk of MACE and cardiovascular death.

The addition of nonstatin LLT at the time of an MI, with ezetimibe or PCSK9i, results in lower achieved LDL-C levels than possible through statin monotherapy and improves plaque morphology.^{19–21} This provided a mechanistic rationale for the reduction in atherosclerotic events observed in clinical outcome trials of combination LLTs.^{6,22} For example, in the IMPROVE-IT (Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin [Ezetimibe/Simvastatin] vs Simvastatin; [NCT00202878](#)) trial, adding ezetimibe to simvastatin in patients with acute coronary syndromes (ACS) improved cardiovascular prognosis.⁶ In that trial, ezetimibe (in addition to statins) was initiated within 10 days of the acute event, and 66% of the patients were statin naïve at study baseline. Thus, an early combination-LLT regimen was initiated in two-thirds of the patients, providing evidence for the benefit of early combination oral LLT after ACS. Subsequently, trials assessing the added value of PCSK9i after MI or ACS showed that among patients with LDL-C ≥ 1.8 mmol/L

(≥ 70 mg/dL) despite high-intensity or maximally tolerated statins, combination therapy using a PCSK9i resulted in lower achieved LDL-C levels and a lower risk of cardiovascular events.^{7,8} Collectively, those trials provide the evidence base for most global guidelines recommending lower LDL-C goals (<1.4 mmol/L, <55 mg/dL) in such patients.¹⁰

Although the “destination” of achieving lower LDL-C levels for post-MI patients seems to follow the trial evidence, the path through which the destination is reached does not. For example, guidelines such as the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society dyslipidemia guidelines paradoxically recommend the addition of ezetimibe if LDL-C goals are not achieved with the maximum-tolerated dose of statin alone.¹⁰ This was reiterated in the 2020 non-ST-segment elevation MI guidelines.²³ A review of the literature suggests that the time frame of 4 to 6 weeks was not based on evidence of prognostic superiority within that period, but rather for practical reasons, because the maximal effect of statins on LDL-C lowering occurs 2 to 4 weeks after initiating therapy. However, in real-life scenarios, it is unlikely that lipid measurements are



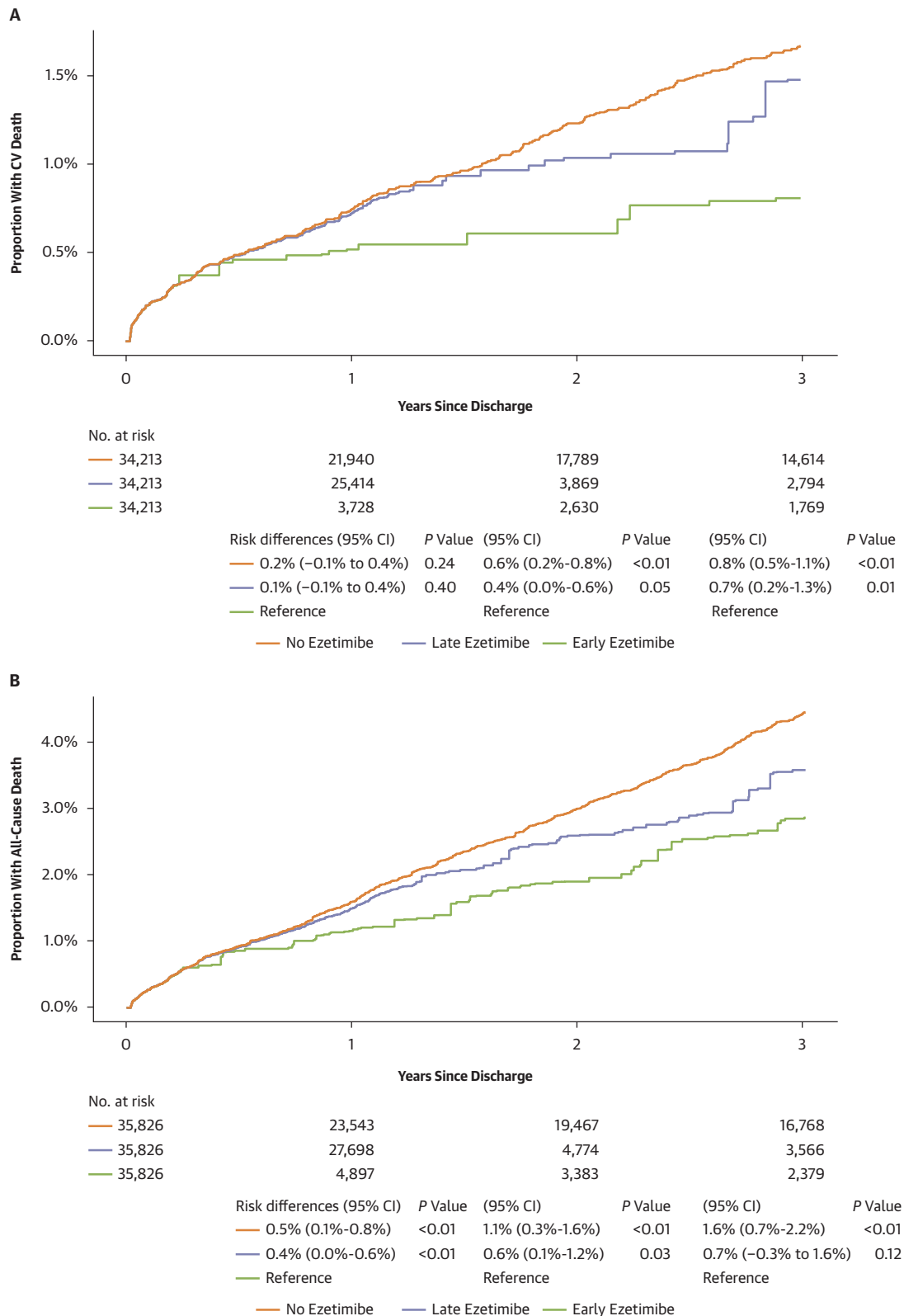
undertaken at 4 to 6 weeks, meaning that up-titration follows clinical routines such as outpatient visits during the year after an MI, so it can take much longer.^{14,24,25}

This stepwise approach of LLT escalation has been questioned in a position paper from the ESC Societies of Acute Cardiovascular Care and Preventive Cardiology.²⁶ That position paper recommends the use of a combination regimen of a high-intensity statin in conjunction with ezetimibe before discharge after ACS. This was based on the observed treatment inertia among physicians in up-titration of LLT during the post-ACS follow-up period in several surveys and consequent low rates of LDL-C target achievement, thus leaving patients at high residual risk.^{26,27} This approach has been recommended by others as well.^{28,29} In the 2023 ESC guidelines on ACS, a new Class II Level of Evidence: B recommendation on

simultaneous LLT combination therapy with high-intensity statin and ezetimibe was introduced.³⁰ The recommendation was based on IMPROVE-IT as well as the assumption that many statin-naïve patients who have LDL-C levels that make it unlikely that they would reach the LDL-C goal with statin monotherapy would benefit long term from initiation of statin and ezetimibe combination therapy during ACS hospitalization to decrease the time taken to achieve LDL-C goals.³⁰

Further support for the pragmatic use of early combination therapy before discharge was provided in a recent publication from a Polish ACS registry, where mortality was studied with the use of propensity score matching of patients initiated on combination LLT (ezetimibe plus statins) during hospitalization vs statin monotherapy (atorvastatin or rosuvastatin).³¹ Early use of combination therapy was associated

FIGURE 4 Cumulative Incidence of the 4 Prespecified Secondary Outcomes



(A) Cardiovascular (CV) death, (B) all-cause death, (C) nonfatal myocardial infarction (MI), and (D) nonfatal stroke.

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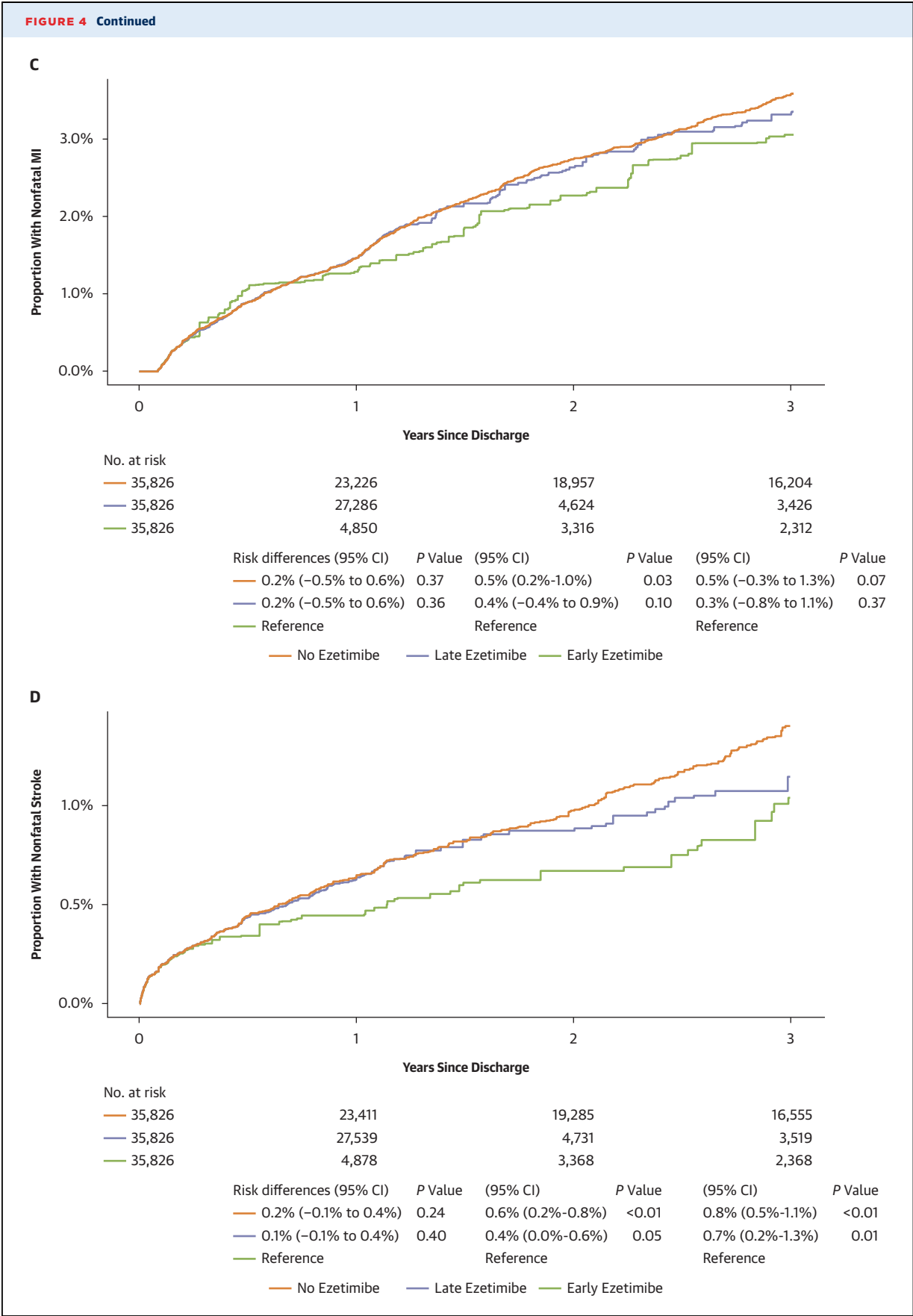


TABLE 2 Potential Health Gains Estimated as Predicted Number of MACE Avoided Through Increasing the Proportion of Patients Receiving Early Combination Therapy vs Other Scenarios in Populations of Different Sizes

	Study Population ^a	Hypothetical Population (Predicted) ^b			
No. at risk	35,826 ^a	10,000	50,000	100,000	250,000
MACE events occurring over 3 y	2,570	717	3,587	7,174	17,934
MACE avoided over 3 y by increasing the proportion of patients receiving early ezetimibe as combination therapy vs other scenarios					
30% early, 15% late, 55% no ezetimibe	68	19	94	189	472
50% early, 15% late, 35% no ezetimibe	203	57	283	566	1415
70% early, 15% late, 15% no ezetimibe	338	94	472	943	2,358
100% receive early ezetimibe	477	133	666	1,331	3,328

^aRepresents the observed study population. ^bThis scenario reflects the status quo, ie, MACE events predicted to occur if the population at risk increased in size but the current proportion of use of different LLTs remained the same, namely, 16.9% receiving early combination LLT, 18.1% receiving late combination LLT, and 65.0% receiving no ezetimibe.
LLT = lipid-lowering therapy; MACE = major adverse cardiovascular events.

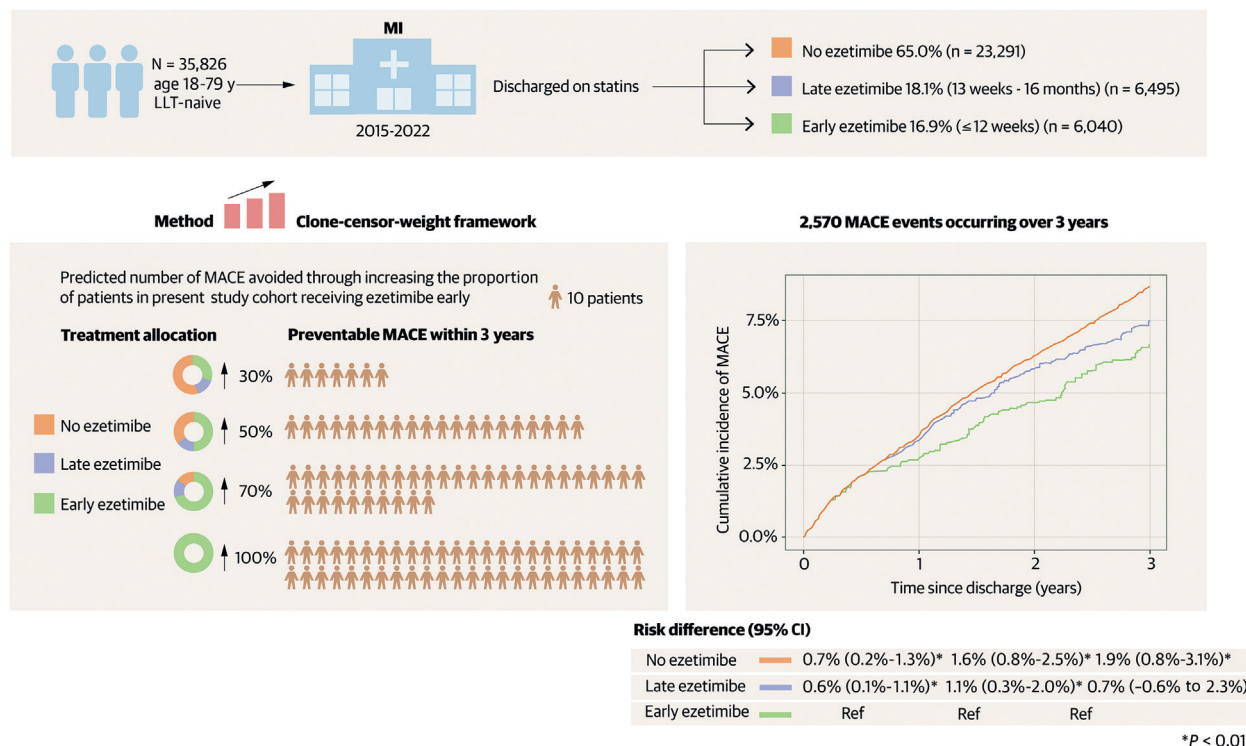
with reduced all-cause death, with an OR of 0.526 (95% CI: 0.378-0.733) and an absolute risk difference of nearly 5% after 3 years of follow-up. The Polish registry has several differences from our study in terms of design (the Polish registry study included patients on previous LLT, and subsequent up-titration or changes in statin intensity were not accounted for), but their results lend support to the present findings that early combination therapy of ezetimibe with statins after ACS is beneficial. More recently, efforts in Italy (AT TARGET IT [Evaluation of Adherence, Persistence and Efficacy of Treatment With PCSK9 Inhibitors in Italy; [NCT05430828](#)]) and Germany (Jena auf Ziel-JaZ) showed that redesigning care pathways to implement early combination therapies resulted in more patients achieving LDL-C goals and that those achieving the lowest levels had the lowest risk of adverse outcomes.^{32,33}

The potential impact on health outcomes of the timing of treatment escalation through use of combination LLTs after an MI has not been evaluated in clinical practice. An ideal scenario would be a randomized controlled trial, but to test this hypothesis may present ethical challenges where the design would consciously require offering more effective combination LLTs and thus achieve early LDL-C lowering in one group vs delaying it in another. Although observational studies can be helpful to fill in the data gaps, the lack of randomization introduces confounding because of differences in patient characteristics, risks, and treatment choices based on these characteristics. Furthermore, when the timing of a treatment initiation, in this case ezetimibe, is used to define treatment groups, immortal time bias is introduced. A strategy to overcome these challenges is to use a target trial emulation based on the

clone-censor-weight method.¹⁶ Here, for the first time using this method on secondary prevention treatments after MI, we assessed whether the timing of LLT intensification was prognostically important and, by default, whether current stepwise approaches risked harm in patients with a recent MI. Our findings indicate potential harms of the current approach to guideline implementation by way of a delayed stepwise approach. Moreover, the present findings add support for how to implement our recent observations assessing the timing of both absolute and relative changes in non-HDL-C, as well as the time to achieve target levels on cardiovascular outcomes.^{34,35} In the latter study, the best outcomes, including reduction in death, were observed when non-HDL-C targets were both achieved early (within 2 months) and sustained over 1 year compared with all other scenarios, with statistically significant benefits observed within 1 year that increased over time, supporting lower cumulative atherogenic lipid exposure.³⁴

Ezetimibe is generically available in most countries and reduces LDL-C by 20% to 25%, but it is underutilized. The reasons could reflect perceptions that ezetimibe is a “weak” LDL-C-reducing treatment, reinforced by trial evidence of a single-digit RR reduction.⁶ Such views do not take into account the fact that RR reduction in cardiovascular events with LLTs is proportional to the absolute reduction in LDL-C. In general populations, patients typically have a higher LDL-C, and thus derive a greater absolute lowering in LDL-C and would be predicted to derive greater RR reductions than observed in IMPROVE-IT. There is also little evidence of safety concerns when very low levels of LDL-C are achieved with combination therapies.³⁶⁻³⁸

CENTRAL ILLUSTRATION Early Ezetimibe Initiation After Myocardial Infarction Protects Against Later Cardiovascular Outcomes



Leosdottir M, et al. JACC. 2025;85(15):1550-1564.

LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MACE = major adverse cardiovascular events; MI = myocardial infarction; Ref = reference.

Implementing complex multistep care pathways inevitably may result in variations in care. In the latest SWEDEHEART annual report, a disturbingly wide variation in use of combination LLT at site level was observed, ranging from 10% to 65% at the 6- to 10-week follow-up and from 30% to 85% at the 1-year follow-up.¹⁴ When all evidence is considered, we think that implementation of cholesterol management after an MI, reducing variability in care, and improving prognosis are best served by moving away from a stepwise strategy, which only delays the inevitable ie the need for combination therapy for most patients to achieve guideline-recommended LDL-C goals. Public health is best served by a move toward early combination therapy, which is pragmatically achievable with a combination of high-intensity statins and ezetimibe before hospital discharge, as suggested in the ESC 2022 position paper.²⁶

Moreover, for those who fail to achieve LDL-C goals on 2 oral drugs, our proposed approach considerably reduces the time taken to assess eligibility for PCSK9i treatment, which would then be consistent with the timing of PCSK9i treatment in the ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; [NCT01663402](#)) trial, ie, ~2 months after ACS.⁸ Where cost limits use of injectable therapies, bempedoic acid could be considered as a third oral agent without necessarily increasing pill burden with the use of fixed-dose combinations with ezetimibe.^{39,40} Therefore, there seems to be little cost, biological, or safety argument against a high-intensity statin plus ezetimibe combination approach as the standard of care for all MI patients. The present study suggests that the price of delay is high and one that we can no longer afford to pay. For patients already on statins admitted with an MI, ongoing trials such as

EVOLVE-MI (EVOLocumab Very Early After Myocardial Infarction; [NCT05284747](#)) with PCSK9i added during hospitalization may provide insights into early use of PCSK9i during hospital admission in the near future, but for now their use may need to be considered on a case-by-case basis.

STUDY STRENGTHS AND LIMITATIONS. In studies where treatment effects are based on observational or registry data, there are known substantial risks of confounding by indication. The target trial emulation approach can mitigate some confounding by stating inclusion and exclusion criteria and time-zero clearly. Further bias minimization can be sought by using the novel clone-censor-weight framework, which is particularly useful when early vs late treatment strategies are compared. Such comparisons have been impossible until now, because of unsurmountable problems with immortal time bias (patients treated with a late treatment strategy need to survive until that “late” time point and are thus inherently different from early-treatment patients). The clone-censor-weight method allows for such comparisons to be unbiased. This is a unique strength of the present study. The external validity of our findings is large, because this study is based on a large unselected consecutive cohort of clinical-practice MI patients with nationwide coverage, including >90% of all MI cases in patients aged <80 years in the country during the time period, reducing the selection bias present in randomized clinical trials.⁴¹ By excluding patients likely to violate the assumption of random group allocation, the risk of selection bias inherent to observational studies was reduced, further strengthened by the adequate covariate balance obtained (including baseline LDL-C and time-varying statin intensity) and no significant differences observed in negative control noncardiac outcome analyses. Finally, the possibility of linking data between registries, with minimal missing information and virtually no loss-to-follow-up, improves the reliability and completeness of the data and enhances the overall generalizability of our findings.

There are, however, limitations. As previously stated, our real-life patient cohort, albeit large, had too few patients discharged on combination therapy with sufficient follow-up time to assess the effect on outcomes of the in-hospital initiation of combination LLT separately. Because up-titration of LLT usually takes place around the 6- to 10-week follow-up visit at Swedish cardiac rehabilitation centers, limiting the time frame of early combination treatment to the guideline-recommended 4 to 6 weeks instead of 12 weeks as used here would have resulted in the

same sample size limitation. Because the prescription of ezetimibe (both early and late) was low in the first half of the study period, the follow-up period had to be limited to 3 years in all groups. Whether the observed risk differences extend beyond 3 years is therefore unknown. Statin treatment at discharge was defined as a binary variable. Although statin intensity at baseline and time-varying statin intensity were adjusted for in the cloning models, residual confounding because of differences in type and dose of statin prescribed and filled as well as actual adherence over time, not captured by these variables, cannot be excluded. However, ~98% of patients were discharged on a high-intensity statin, reducing the impact of adding discharge statin treatment as a binary variable. Although patients being discharged from a university hospital or not was adjusted for in the models, there might have been other site-level differences in early prescription of ezetimibe not accounted for. Because this was an observational study, confounding due to nonrandom treatment allocation needs to be acknowledged. The clone-censor-weight method, however, eliminates a large part of that bias. Lack of between-group differences in the negative control outcome analysis further strengthens this assumption. Finally, as with all analyses on observational data, the risk of residual confounding needs to be acknowledged.

CONCLUSIONS

The need for combination therapy is inevitable for most patients after an MI. A delayed approach to LLT escalation is associated with avoidable harms. Care pathways can be streamlined with tangible health benefits if the standard of care for LLT after an MI consists of an early combination of high intensity statins with ezetimibe.

DATA SHARING STATEMENT SWEDEHEART does not allow individual data sharing to a third party. Access to aggregated data might be granted after review by the SWEDEHEART steering committee.

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APPENDIX For supplemental tables, figures, and references, please see the online version of this paper.