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# Effects of statin response on cardiovascular outcomes in patients with ST-segment elevation myocardial infarction

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## SUMMARY

**OBJECTIVE:** This study aimed to evaluate the effects of statin response on cardiovascular outcomes in patients with ST-segment elevation myocardial infarction.

**METHODS:** A total of 1029 ST-segment elevation myocardial infarction patients were enrolled in the study. The patients who failed to achieve >40% reduction in baseline low-density lipoprotein cholesterol levels within 30 days to 12 months after statin initiation were defined as suboptimal statin responders. The adjusted hazard ratios for cardiovascular outcomes for low-density lipoprotein cholesterol response to statins were estimated via the Cox proportional regression model. The relationship between the statin response and cardiovascular outcomes was also evaluated in a subgroup of on-treatment low-density lipoprotein cholesterol levels below 55 mg/dL.

**RESULTS:** Among the study population, 573 (55.6%) patients demonstrated suboptimal low-density lipoprotein cholesterol response to statin therapy. These patients showed a significantly higher incidence of the composite of major adverse cardiovascular events, including cardiovascular death, reinfarction, recurrent myocardial infarction, and target vessel revascularization during the follow-up compared with optimal responders (adjusted hazard ratios 3.99; 95%CI 2.66–6.01; p<0.001). In a subgroup of patients with on-treatment low-density lipoprotein cholesterol levels below 55 mg/dL, suboptimal statin responders also showed unfavorable cardiovascular outcomes (adjusted hazard ratios 8.73; 95%CI 2.81–27.1; p<0.001).

**CONCLUSIONS:** The present study showed that over half of the patients with ST-segment elevation myocardial infarction did not exhibit optimal low-density lipoprotein cholesterol response to statin. These patients have an increased risk of future major adverse cardiovascular events.

**KEYWORDS:** Cardiovascular disease. Low-density lipoprotein cholesterol. Myocardial infarction response. Prognosis. HMG-CoA reductase inhibitors.

## INTRODUCTION

Lowering low-density lipoprotein cholesterol (LDL-C) with a 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitor (statin) has been recognized as a default strategy for preventing major adverse cardiovascular events (MACE) for both the primary and secondary care settings. Furthermore, it has been shown that more intensive LDL-C reduction with higher potency statin therapy further reduces MACE in individuals with acute coronary syndrome (ACS)[1,2]. Accordingly, the European Society of Cardiology guidelines suggested a greater reduction in LDL-C using high-intensity statin therapy in patients with ACS. However, due to the heterogeneity in individual response to statin therapy, effective LDL reduction is not achieved in most patients[3]. Numerous clinical, demographic, and genetic variables contributing to statin resistance have been reported[4,5]. However, there is limited evidence on the relationship between statin resistance and the risk of future cardiovascular (CV) events. A recent study involving primary care patients demonstrated an increased risk of future CVD in suboptimal statin responders compared to the group that responded optimally to statin therapy[6]. This study aimed to investigate the effects of statin response on CV outcomes in patients with ST-segment elevation myocardial infarction (STEMI).

## METHODS

### Patient collection data

The retrospective data of 3606 patients with STEMI were analyzed through the hospital database and the national electronic health information systems. The patients treated with fixed-dose high-intensity statin therapy for at least 12 months after the index hospitalization were selected. Patients receiving lipid-lowering treatment within 6 months before the index

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hospitalization were excluded from this study. Those who used additional lipid-modifying drugs other than statins were also excluded. A total of 1029 eligible patients were enrolled in the study. All patients underwent primary percutaneous coronary intervention and were discharged from the hospital with stable conditions. They received high-intensity statin therapy initiated within the first 24 h of admission and continued for at least 12 months. Statin adherence was evaluated through telephone calls and the patient's prescribing records. LDL-C values were obtained from hospital records and available data from the national electronic health information system. Patients had at least three LDL-C measurements (one measurement within 24 h of index hospitalization before statin administration and at least two measurements within 30 days to 12 months after statin administration). The lowest LDL level measured within 12 months after the statin therapy was used for the on-treatment response. The clinical and laboratory follow-up data were collected retrospectively from the hospital and national health database systems. Informed written consent was obtained from all patients, and the local ethical committee approved the protocol (Approval number: 71522473/050.01.04/408).

### Definitions

High-intensity statin therapy was defined as atorvastatin used at 40–80 mg or rosuvastatin used at 20–40 mg. The National Institute for Health and Care Excellence guideline adopts >40% LDL reduction to define optimal statin response in high-risk patients[7]. A recent study by Akyea used this threshold in their primary analysis. Thus, in our study, patients who failed to achieve >40% reduction in baseline LDL-C levels within 30 days to 12 months after intensive statin initiation were defined as suboptimal statin responders. We compared the patients based on their statin responses to investigate the impact of statin response on CV adverse events.

### Endpoints

The primary endpoint was the composite of MACE, such as CV death, reinfarction, recurrent myocardial infarction (MI), and target vessel revascularization (TVR) during the follow-up. The individual components of the primary endpoint were considered secondary endpoints.

### Statistical analysis

Statistical analysis was performed by SPSS (Statistical Package for Social Sciences) 21.0 for the Windows program. The Kolmogorov-Smirnov test was performed to analyze the normality of the continuous variables. Continuous variables were expressed as means (SD) or median (interquartile range) according to whether they exhibited a Gaussian distribution, and categorical variables were expressed as proportions and percentages. The independent t test was used to compare normally distributed continuous data. Continuous data, which were not normally distributed, were analyzed using the Mann-Whitney U test. The chi-square test was used to compare the dichotomous data. The Cox proportional hazard analysis, adjusting for significant covariates predictive of cardiovascular events, was used to estimate the adjusted hazard ratio and 95% confidence interval (CI) to compare the incidence of the primary endpoint in suboptimal and optimal statin responders. We calculated MACE rates (per 1000 person-years) and 95%CIs for the primary endpoint for each group. Two-sided p-values of <0.05 were considered statistically significant.

## RESULTS

### Study population and baseline characteristics

The study population included 808 men and 221 women with a median age of 61 years. Among the study population, 573 (55.6%) patients demonstrated a suboptimal LDL-C response to statin therapy at 30 days to 12 months after starting treatment. The median follow-up time was 48 and 45 months for suboptimal and optimal statin responders, respectively. The demographic variables are summarized in Table 1.

### Incidence of cardiovascular outcomes

During the follow-up, a primary endpoint event occurred in 339 patients. As shown in Table 1, the incidence of the composite MACE was significantly higher in patients with suboptimal LDL-C response to statin therapy compared to those with optimal LDL-C response (p<0.001). Among the individual components of the primary endpoint, there was a consistent pattern of favorable outcomes in patients with optimal LDL-C response to statin. CV death occurred in 29 patients (5.1%) in the suboptimal statin group and 6 patients (1.3%) in the optimal statin group (p=0.001). Patients with suboptimal statin response showed a significantly higher incidence of recurrent MI, TVR, and reinfarction than those with the optimal response (p<0.001). Outcomes for the selected secondary endpoints are also presented in Table 1. After adjustment of baseline covariates predictive of cardiovascular events (age, hypertension, prior MI, prior coronary revascularization, baseline LDL-C, baseline total cholesterol, baseline triglyceride, baseline HDL-C, on-treatment LDL-C, and high-sensitivity C-reactive protein (hs-CRP) levels), the risk of MACE remained significantly greater in patients

with suboptimal LDL-C response to statin compared with that in optimal responders (adjusted HR 3.99; 95%CI 2.66–6.01; p<0.001). The incidence rates for MACE were 17 and 102 per 1000 person-years for patients with optimal statin response and those with suboptimal statin response, respectively. We also showed that the suboptimal statin response was independently associated with reinfarction, recurrent MI, and TVR. However, no independent association was found between cardiovascular death and suboptimal statin response (adjusted HR 1.93; 95%CI 0.55–6.74; p=0.30) (Table 2).

A subgroup analysis of patients with on-treatment LDL-C levels below 55 mg/dl also showed unfavorable cardiovascular outcomes in suboptimal responders. The Cox regression analysis showed that suboptimal statin response is independently associated with the higher incidence of MACE (HR 8.73; 95%CI 2.81–27.1; p<0.001). The incidence rates for MACE were 16.9 and 61.2 per 1000 person-years for patients with optimal statin response and those with suboptimal statin response, respectively (Table 3).

## DISCUSSION

This study revealed that 55.6% of STEMI patients treated with intensive statin therapy did not exhibit optimal statin responses. An increased risk of MACE was observed in these patients.

High variability in the percentage reduction of LDL-C may be encountered among subjects using the same dose of statin regimens. Some observational studies have investigated

**Table 1.** Baseline characteristics and outcomes by low-density lipoprotein cholesterol response to statin therapy.

| | | Total n (%) 1029 (100) | Suboptimal statin responders n (%) 573 (55.6) | Optimal statin responders n (%) 456 (44.3) | p-value |
|---|---|---|---|---|---|
| Age (median, IQR, mg/dL) | | 53/61/69 | 53/61/69 | 53/61/69 | 0.684 |
| Gender (Female, n (%)) | | 221 (21.5) | 121 (21.1) | 100 (21.9) | 0.761 |
| Hypertension, n (%) | | 655 (63.7) | 379 (66.1) | 276 (60.5) | 0.068 |
| Prior myocardial infarction, n (%) | | 56 (5.4) | 46 (8) | 10 (2.2) | **<0.001** |
| Prior coronary revascularization, n (%) | | 103 (10) | 81 (14.1) | 22 (4.8) | **<0.001** |
| Diabetes mellitus, n (%) | | 311 (30.2) | 180 (31.4) | 131 (28.7) | 0.374 |
| Smoking, n (%) | | 727 (70.7) | 415 (72.4) | 312 (68.4) | 0.169 |
| Baseline LDL-C (median, IQR, mg/dL) | | 111/133/159 | 103/124/150 | 120/145/171 | **<0.001** |
| Baseline HDL-C (median, IQR, mg/dL) | | 34/40/46 | 33/38/45 | 36/41/47 | **<0.001** |
| Baseline triglyceride (median, IQR, mg/dL) | | 72/112/176 | 74/115/179 | 71/109/171 | 0.290 |
| Baseline total cholesterol (median, IQR, mg/dL) | | 169/198/227 | 162/189/218 | 178/208/241 | **<0.001** |
| hs-CRP (median, IQR, mg/dL) | | 3/3.4/6.1 | 3/3.7/6.7 | 3/3/5.7 | **0.003** |
| Admission glucose (median, IQR, mg/dL) | | 154.6±86 | 102/125/169 | 102/125/172 | 0.821 |
| On-treatment LDL-C (median, IQR, mg/dL) | | 70/88/112 | 84/106/130 | 63/72/85 | **<0.001** |
| Follow-up times (median, IQR, months) | | 31/48/64 | 31/48/65 | 30/45/64 | 0.105 |
| Statin therapy, n | Atorvastatin 40 mg | 562 | 301 | 220 | >0.05 |
| | Atorvastatin 80 mg | 458 | 268 | 231 | |
| | Rosuvastatin 20 mg | 5 | 2 | 3 | |
| | Rosuvastatin 40 mg | 4 | 2 | 2 | |
| MACE, n (%) | | 339 (32.9) | 299 (52.2) | 40 (8.8) | **<0.001** |
| Cardiovascular death, n (%) | | 35 (3.4) | 29 (5.1) | 6 (1.3) | **0.001** |
| Reinfarction, n (%) | | 89 (8.6) | 85 (14.8) | 4 (0.9) | **<0.001** |
| Recurrent myocardial infarction n (%) | | 260 (25.3) | 235 (41) | 25 (5.5) | **<0.001** |
| Target vessel revascularization, n (%) | | 321 (31.2) | 283 (49.4) | 38 (8.3) | **<0.001** |

Data were shown as mean±standard deviation and n (%).
IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; MACE: major adverse cardiovascular events. Bold values indicate statistical significance at the p<0.05 level.

individual variability in LDL-C response to statin therapy[6,8]. Recent research by Akyea et al. on the primary prevention population showed that 51.2% of patients had a suboptimal LDL-C response to statin therapy within 24 months. A cross-sectional study consisting of 22.063 patients receiving statins in both primary and secondary care demonstrated that up to half of patients (48.2%) did not achieve optimal lipid reduction goals[3]. In our study, only 45% of patients had an optimal LDL-C response to statin therapy, which is compatible with recent literature.

The exact mechanism underlying inadequate response to statins has not yet been well understood. Nevertheless, individual characteristics including age, sex, body weight, cigarette smoking, inflammatory stress, chronic kidney disease, diabetes mellitus, baseline lipid levels, and genetic variations have been identified as possible determinants of LDL-C response to

**Table 2.** Hazard ratios and incidence rates (per 1000 person-year) for the primary and secondary endpoints according to low-density lipoprotein cholesterol response to statin therapy

| | Groups (n=1029) | CVD events (n) | Rate of CVD events (per 1000 person-years) | HR (adjusted)[a] (95%CI) | p-value |
|---|---|---|---|---|---|
| MACE | Optimal | 40 | 17 | **1** | **<0.001** |
| | Suboptimal | 299 | 102 | 3.99 (2.66–6.01) | |
| Cardiovascular death | Optimal | 6 | 2.6 | 1 | **0.30** |
| | Suboptimal | 29 | 9.9 | 1.93 (0.55–6.74) | |
| Reinfarction | Optimal | 4 | 1.7 | 1 | **<0.001** |
| | Suboptimal | 89 | 30.5 | 18.17 (5.72–57.6) | |
| Recurrent myocardial infarction | Optimal | 25 | 10.7 | 1 | **<0.001** |
| | Suboptimal | 235 | 80.7 | 5.44 (3.20–9.23) | |
| Target vessel revascularization, n (%) | Optimal | 38 | 16.4 | 1 | **<0.001** |
| | Suboptimal | 283 | 97.2 | 4.04 (2.66–6.14) | |

[a]The multivariable Cox regression models for MACE, cardiovascular death, reinfarction, recurrent myocardial infarction, and target vessel revascularization were adjusted for age, hypertension, prior myocardial infarction, prior coronary revascularization, baseline LDL-C, baseline total cholesterol, baseline triglyceride, baseline HDL-C, on-treatment LDL-C, and hs-CRP levels. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; MACE: major adverse cardiovascular events. Bold values indicate statistical significance at the p<0.05 level.

**Table 3.** Estimates of hazard ratios and incidence rates (per 1000 person-year for the primary and secondary endpoints according to the statin responses in the subgroup of on-treatment low-density lipoprotein cholesterol ≤55 mg/dL).

| | Group: LDL ≤55 mg/dL (n=287) | CVD events (n) | Rate of CVD events (per 1000 person-years) | HR (adjusted)[a] (95%CI) | p-value |
|---|---|---|---|---|---|
| MACE | Optimal | 15 | 16.9 | **1** | **<0.001** |
| | Suboptimal | 19 | 61.2 | 8.73 (2.81–27.1) | |
| Cardiovascular death | Optimal | 1 | 1.1 | 1 | - |
| | Suboptimal | 3 | 9.6 | 1 | |
| Reinfarction | Optimal | 2 | 2.2 | 1 | 0.01 |
| | Suboptimal | 6 | 19.2 | 14,7 (1.72–126.3) | |
| Recurrent myocardial infarction | Optimal | 10 | 11.2 | 1 | 0.002 |
| | Suboptimal | 14 | 45.1 | 5.89 (1.89–18.3) | |
| Target vessel revascularization, n (%) | Optimal | 15 | 16.9 | 1 | 0.001 |
| | Suboptimal | 16 | 51.5 | 7.93 (2.49–25.2) | |

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; MACE: major adverse cardiovascular events. [a]The multivariable Cox regression models for MACE, cardiovascular death, reinfarction, recurrent myocardial infarction, and target vessel revascularization were adjusted for prior myocardial infarction, prior coronary revascularization, baseline LDL-C, baseline total cholesterol, baseline triglyceride, baseline HDL-C, on-treatment LDL-C, and hs-CRP levels. Bold values indicate statistical significance at the p<0.05 level.

statin therapy[4,5]. Although our study did not primarily intend to determine predictors of suboptimal statin response, patients with suboptimal response were significantly more likely to have lower baseline LDL-C and higher hs-CRP levels compared with optimal response. Likewise, data from the EUROASPIRE V study showed that the percentage of LDL-C response was significantly lower in patients with lower baseline LDL-C levels[9].

Although statins reduce the risk of CV events, the impact of diminished response to statins on future CV adverse events has not been fully elucidated. A study by Kataoka et al.[10] evaluated the natural history of atheroma burden in hyporesponders to statin therapy. They revealed that statin hyporesponders exhibited more significant atheroma progression. Recently, Akyea et al. quantified the variability in LDC response to statins and its impact on future CVD events in the primary prevention population. They showed that the risk of incident CVD was significantly greater in suboptimal responders than in optimal responders. In our study, the risk of the composite of MACE, including CV mortality, reinfarction, recurrent MI, and TVR during the follow-up, was significantly higher in patients with suboptimal LDL-C response to a statin compared with optimal statin responders. Although our study was conducted on a secondary prevention population, the abovementioned previous studies support our findings.

In a subgroup analysis of our study, we found worse CV outcomes in patients with suboptimal response to statin therapy, even with on-treatment LDL-C levels below 55 mg/dl. The current ESC/EAS guideline recommends lowering the LDL level below 55 mg/dl and more than 50% LDL reduction in patients with ACS. In contrast, it is recommended that combination therapy with statins and ezetimibe or PCSK-9 inhibitors is only reasonable in patients with clinical CVD who are deemed to be at very high risk and have an LDL-C level of 55 mg/dl or higher despite maximally tolerated statin therapy. Thus, the management of the patients with history of MI failed to achieve a 40% reduction in baseline LDL-C, while their on-treatment LDL-C below 55 mg/dl remains controversial in regard to the benefit, side effects, and cost. A study by Ridker et al. showed that the magnitude percentage of the on-treatment LDL-C reduction directly related to the magnitude of cardiovascular risk reduction was observed[11]. The importance of reducing LDL-C by at least 50% was also validated by Waters et al.[12]. Their pooled analysis of several randomized trials from the secondary prevention population suggested that percent LDL-C reduction provides incremental prognostic value over attained LDL-C levels. However, due to the relatively small number of subgroup patients, it is not our intention to suggest that percent reduction targets for statin therapy are better than absolute treatment targets for statin therapy. Further studies are needed to evaluate the effectiveness of the nonstatin cholesterol-lowering drugs in patients with on-treatment LDL-C £55 mg/dl but not achieving percent reduction targets.

Several mechanisms could be considered to induce an increased risk of CV events in suboptimal statin responders. The effect of statins on cardiovascular risk reduction is mainly attributed to declines in LDL-C. A meta-analysis of individual participant data by the Cholesterol Treatment Trialists' Collaboration[13] reported that more intensive statin-mediated LDL-C lowering by 20 mg/dl resulted in a 15% further reduction in major CV events (including a 13% reduction in coronary death or nonfatal MI, a 19% reduction in coronary revascularization, and a 16% reduction in ischemic stroke). Therefore, in patients with a suboptimal LDL-C response to a statin, relatively high on-treatment LDL-C levels may have led to increased CV risk. Another mechanism related to high CV events in suboptimal statin responders might be their diminished pleiotropic effect. Some of the pleiotropic effects of statins may be mediated through their effects on hs-CRP. Previously, it was found that statin therapy decreased hs-CRP, an independent marker for future cardiovascular events[14,15]. This anti-inflammatory property of statins has been suggested to explain their beneficial effects on cardiovascular outcomes. In our study, suboptimal statin responders were more likely to have higher hs-CRP levels than optimal statin responders. However, the data on hs-CRP levels after statin therapy were lacking. Thus, suboptimal statin responders might have lower pleiotropic effects, potentially contributing to their high risk of MACE.

### Limitations

Some limitations should be noted when interpreting our findings. First, the study sample comprised patients with statin therapy throughout the period of 12 months after the index hospitalization. After 12 months, the patterns of statin use were not taken into account in the analysis. Second, electronic drug prescribing data may not always correlate with the actual statin consumption. Although telephone visits have also checked statin adherence, the subject's self-reported adherence might be considered a limitation. Other limitations of the study include its retrospective nature, relatively short follow-up period for cardiovascular events, and the single-center patient cohort. The nonrandomized nature of the study could have resulted in selection bias.

## CONCLUSIONS

The present study showed that patients with suboptimal statin response had an increased risk for future MACE, specifically CV death, reinfarction, recurrent MI, and TVR. Unfavorable

cardiovascular outcomes are also persistent in suboptimal responders; even their on-treatment LDL-C levels are reduced below 55 mg/dL. However, further randomized trials are needed to validate these findings.

## AUTHORS' CONTRIBUTIONS

**MBV:** Methodology, Writing – original draft. **PV:** Resources, Validation. **SA:** Data curation, Formal Analysis. **HE:** Formal Analysis. **KC:** Writing – review & editing.

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