



Diminished response to statins predicts the occurrence of heart failure after acute myocardial infarction

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Background: Lowering low-density lipoprotein cholesterol (LDL-C) levels using a statin is a cornerstone of preventive therapeutic management following acute myocardial infarction (AMI). In addition to its anti-atherosclerotic effects, recent studies reported a lower occurrence of heart failure (HF) under statin therapy. However, there is a wide variability in statin response. The association between the response to statin and the occurrence of HF in AMI subjects remains unclear. The purpose of present study is to examine whether the variability in statin response affects HF risk after AMI.

Methods: We analyzed 505 statin-naïve AMI subjects undergoing primary percutaneous coronary intervention (PCI) who commenced atorvastatin, rosuvastatin, or pitavastatin. Statin hyporesponse was defined as a reduction in LDL-C levels <15% from baseline to 1 month after statin therapy. HF outcomes were compared between patients with and without statin hyporesponse.

Results: Statin hyporesponse was identified in 15.2% (77/505) of study subjects. During a median 4.4-year observational period, statin hyporesponse was associated with a greater likelihood of HF [hazard ratio (HR) =3.01, 95% confidence interval (CI): 1.27–6.79, P=0.01]. This increased HF risk in statin hyporesponders was consistently observed in a multivariate Cox proportional hazards model (HR =2.74, 95% CI: 1.01–6.75, P=0.04), a propensity score-matched cohort (HR =12.30, 95% CI: 1.50–100.3, P=0.01) and in an inverse probability of treatment weights analysis with average treatment effects (coefficient =7.02, 95% CI: 2.29–21.58, P=0.0006).

Conclusions: Hyporesponse to statins increases HF risk after AMI. Our findings highlight statin hyporesponse as a high-risk feature associated with HF events.

Keywords: Acute myocardial infarction (AMI); heart failure; low-density lipoprotein cholesterol (LDL-C); statin

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Introduction

Lowering low-density lipoprotein cholesterol (LDL-C) levels with a statin has become a mainstay of preventive therapeutic management in subjects with acute myocardial infarction (AMI). This is supported by randomized controlled trials (1,2) which have consistently demonstrated a significant reduction in atherosclerotic cardiovascular disease (ASCVD) in association with the degree of LDL-C control. In addition to this anti-atherosclerotic property, the potential effect of statins on heart failure (HF) events has been reported. The sub-analysis from the PROVE-IT TIMI22 study reported a lower occurrence of HF in subjects with acute coronary syndrome who achieved very low LDL-C levels under intensive statin therapy (3). One recent meta-analysis also showed that statins modestly reduced the occurrence of HF, whereas other randomized controlled trials failed to prove the reduction of HF events under statin therapy (4). These inconsistent observations suggest that the extent of HF risk reduction after statin therapy may be heterogenous due to other factors.

The degree of LDL-C reduction with statins varies across individuals. One secondary data analysis of the JUPITER trial reported that 53.6% of healthy subjects did not exhibit an expected response to 20 mg rosuvastatin (5). In another study, poor reduction in LDL-C levels (\geq change in LDL-C $<15\%$) was observed in 20% of subjects with coronary artery disease receiving statins (6). Given that an elevated LDL-C level promotes oxidative stress and endothelial dysfunction associated with HF, we hypothesized that the degree of response to statin therapy may affect HF risks after statin therapy. Therefore, the current study sought to investigate the frequency of HF events in patients with AMI according to their response to statin. We present the following study in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/cdt-20-415>).

Methods

Study sample

We retrospectively analyzed a total of 890 consecutive patients with de novo AMI who received primary percutaneous coronary intervention (PCI) from January 2007 to December 2014 at the National Cerebral and Cardiovascular Center in Suita, Japan. The diagnosis of myocardial infarction was based on the European Society of Cardiology/American College of Cardiology Foundation/

American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction (7). Of these, the following patients were excluded: patients who received a statin prior to AMI (n=128), those who did not receive statin therapy after AMI (n=166), subjects receiving a statin except atorvastatin/rosuvastatin/pitavastatin (n=50), those with in-hospital death after AMI (n=27), subjects with hemodialysis due to end-stage renal disease (n=6), and patients who did not have lipid profile data (n=8). The remaining 505 statin-naïve subjects were included into the current analysis (Figure 1). The research protocol was approved by the ethics committee of our institution (M24-055-6). The research was conducted in accordance with the Declaration of Helsinki. Informed consent was not obtained in each subject due to the observational analysis of hospitalized patients. However, the current study was posted on the website of our institution (<http://www.ncvc.go.jp/hospital/pub/clinical-research/untersuchung/untersuchung-78.html>) to inform its detail and ensure that patients could refuse inclusion into the current analysis. When we contacted with participants by a mail or telephone, we explained the study subjects and then obtained informed consent.

Definition of hyporesponse to statin

In the current study, atorvastatin, rosuvastatin or pitavastatin was commenced within 24 hours after the completion of primary PCI. The selection of statin and its dose was left to each physician's discretion. Physicians managed lipid-lowering therapy according to the Japan Atherosclerosis Society guideline for the secondary prevention of ASCVD. In brief, achieving LDL-C <100 [2007–2017] and 70 [2017–currently] mg/dl is recommended as a therapeutic goal in Japanese patients. If this goal is not achievable, escalation of the dose of a statin and/or commencement of other lipid-lowering therapy is considered (8,9). LDL-C was measured on admission and at 1 month after the completion of primary PCI in all subjects. Hyporesponse to statin was defined as a percentage of reduction in LDL-C $<15\%$ from baseline to 1 month after statin treatment (6). High-intensity statin was defined as atorvastatin ≥ 20 mg, rosuvastatin ≥ 10 mg and pitavastatin ≥ 4 mg (10).

PCI procedure

After identification of the culprit lesion on diagnostic coronary angiography, primary PCI was performed with

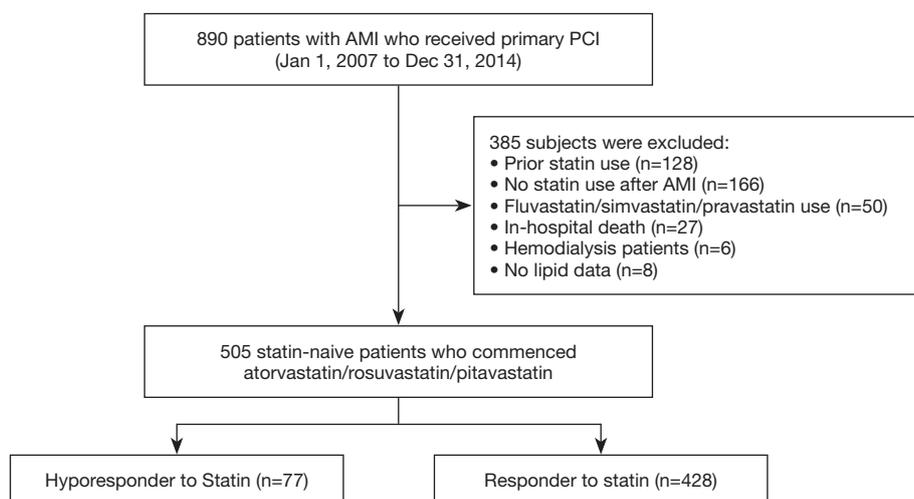


Figure 1 Patients' disposition. Hyporesponder to statin was defined as a percentage reduction of LDL-C of <15% from baseline to 1 month after the commencement of a statin. AMI, acute myocardial infarction; PCI, percutaneous coronary intervention.

the use of 6- or 7-French catheters, followed by the commencement of dual antiplatelet therapy, as previously reported (11). All procedural decisions, including device selection, the use of mechanical support, and adjunctive pharmacotherapy were made according to the discretion of the individual PCI operator.

Outcomes

The primary outcome was the occurrence of hospitalization for HF following statin therapy. The diagnosis of HF was made according to the Framingham criteria (12). The secondary outcome was a composite of cardiovascular death and hospitalization for HF after statin use. A composite of cardiovascular death, non-fatal myocardial infarction, stroke and unstable angina pectoris requiring revascularization was also analyzed. These outcomes were obtained through reviewing the medical records of each hospital visit, and, when necessary, through a questionnaire by mail and telephonic follow-up.

Statistical analysis

Descriptive statistics were summarized according to the presence or absence of hyporesponse to statin therapy. Results are presented as percentages for categorical variables and mean \pm standard deviation for continuous variables. When variables were not normally distributed, their results were described as median (interquartile range).

Clinical characteristics were compared using Student's *t*-test or Wilcoxon rank-sum test for continuous variables as appropriate. For categorical variables, the Pearson chi-square test or Fisher's exact test was used. Changes in LDL-C levels were compared by analysis of covariance, after controlling for baseline values. Wilcoxon signed rank test was used to compare changes in the CRP level between two groups.

The Kaplan-Meier method was used to estimate survival curves for primary and secondary outcomes and the log-rank test was used to assess differences between responders and hyporesponders to statins. Unadjusted hazard ratios for HF were calculated by a univariate Cox proportional hazards model. Adjusted hazard ratios were calculated by a multivariate Cox proportional hazards model with a P value of 0.10. This model included the following variables: age, gender, body mass index, type 2 diabetes mellitus, Killip class, left ventricular ejection fraction, β -blocker use, high-intensity statin use, and statin hyporesponse. A multivariate Cox proportional hazards model using stepwise selection with a P value of 0.10 was also used. This model included age, Killip class, left ventricular ejection fraction and statin hyporesponse.

To further account for significant differences in baseline clinical characteristics between statin responders and hyporesponders, a propensity score-matched analysis was performed. The propensity score was estimated using logistic regression models, with statin responders or hyporesponders as the outcome and baseline clinical

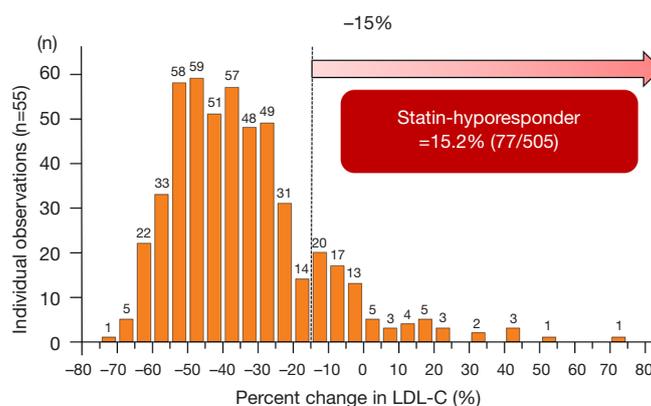


Figure 2 Distribution of percent change in LDL-C level in overall subjects. LDL-C, low-density lipoprotein cholesterol.

demographics as predictors (covariates: age, gender, body mass index, hypertension, type 2 diabetes mellitus, Killip class, left ventricular ejection fraction, baseline LDL-C and use of high-intensity statin and β -blockers). Statin responders and hyporesponders were matched by propensity score on a 2:1 basis by using the nearest-neighbour matching method the R package “Matching” using the R statistical software. In addition, inverse probability of treatment weights (IPTW) based on the calculated propensity score as mentioned above was applied to evaluate the association between statin hyporesponse and HF by estimating the average treatment effects (ATEs) (13). All P values <0.05 were considered statistically significant. All analyses were performed with JMP version 13.0.0 (SAS Institute, Cary, NC, USA), STATA version 15 (StataCorp, College Station, TX, USA) and the R statistical software.

Results

Clinical characteristics

In the current study, 15.2% (77/505) of study subjects showed hyporesponse to statins (Figure 2). Table 1 summarizes baseline clinical demographics. Statin hyporesponders were less likely to have a history of dyslipidemia (57.1% vs. 70.8%, $P=0.02$) and type 2 diabetes mellitus (22.1% vs. 36.0%, $P=0.02$). Body mass index (BMI) was lower in statin hypo-responder (23.5 ± 3.4 vs. 24.5 ± 3.6 kg/m², $P=0.04$). Clinical presentation was ST-segment elevation myocardial infarction in over 85% of each patient group ($P=0.86$). There were no significant differences in the proportion of Killip class \geq II ($P=0.43$), the number of patients who achieved final Thrombolysis In Myocardial Infarction III

flow ($P=0.84$), left ventricular ejection fraction ($P=0.08$) and the level of peak creatine phosphokinase between groups ($P=0.15$).

Regarding the use of statins and other established medical therapies (Table 1), hyporesponders to statin were more likely to receive atorvastatin (48.1% vs. 28.0%, $P=0.0008$), and less likely to be treated with rosuvastatin (16.9% vs. 40.4%, $P<0.0001$), whereas the use of pitavastatin was similar between two groups ($P=0.60$). The proportion of patients receiving ≥ 20 mg atorvastatin (0.0% vs. 0.7%, $P=1.00$), ≥ 10 mg rosuvastatin (1.3% vs. 4.9%, $P=0.23$) and ≥ 4 mg pitavastatin (1.3% vs. 4.0%, $P=0.33$) was comparable between hyporesponders and responders. While β -blocker use was less frequent in statin hyporesponders (61.0% vs. 75.9%, $P=0.01$), the use of other established medical therapies did not differ in two groups (Table 1).

Changes in LDL-C and CRP

In the current study, 98% of entire study subjects continued to receive prescription of a statin, and there was no significant difference between two groups (hypo-responder: 100% vs. responder: 96.9%, $P=1.00$). In addition, the frequency of further intensification of statin therapy (statin dose escalation and/or greater intensity statin use) was not significantly different between hyporesponders and responders (21.4% vs. 24.2%, $P=1.00$). Table 2 shows LDL-C and CRP levels on admission and at 1 month after the commencement of statin therapy. A lower LDL-C level at baseline was observed in hyporesponders to statin therapy (2.9 ± 0.7 vs. 3.6 ± 0.8 mmol/L, $P<0.001$). Predictably, these patients showed a higher LDL-C level at 1 month (2.9 ± 0.6 vs. 2.1 ± 0.5 mmol/L, $P<0.001$) accompanied by its

Table 1 Baseline clinical characteristics

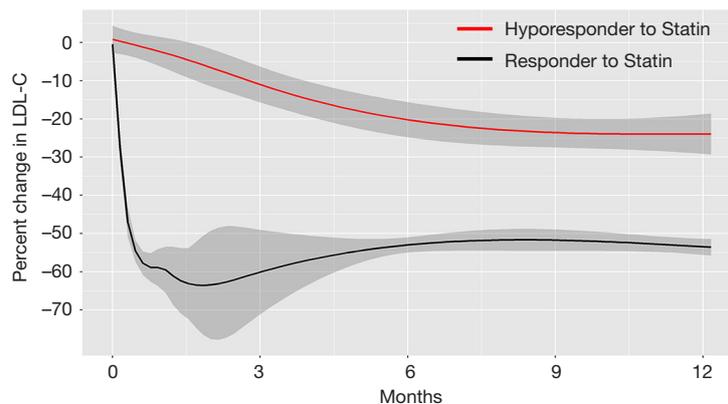
Characteristics	Hyporesponder to statin therapy (n=77)	Responder to statin therapy (n=428)	P value
Age (years)	66.3±11.4	65.9±12.7	0.78
Female, n (%)	13 (16.9)	109 (25.5)	0.11
BMI (kg/m ²)	23.5±3.4	24.5±3.6	0.04
Hypertension, n (%)	53 (68.8)	275 (64.3)	0.52
Dyslipidemia, n (%)	44 (57.1)	303 (70.8)	0.02
Type 2 diabetes mellitus, n (%)	17 (22.1)	154 (36.0)	0.02
Smoking, n (%)	60 (77.9)	288 (67.3)	0.08
CKD [‡] , n (%)	19 (24.7)	137 (32.0)	0.23
Atrial fibrillation, n (%)	4 (5.2)	32 (7.5)	0.63
Characteristics of AMI			
STEMI, n (%)	66 (85.7)	369 (86.2)	0.86
NSTEMI, n (%)	11 (14.3)	59 (13.8)	
Killip class ≥ II, n (%)	11 (14.3)	46 (10.8)	0.43
Multi-vessel disease, n (%)	35 (45.5)	209 (48.8)	0.62
Culprit lesion in LAD, n (%)	30 (39.0)	205 (47.9)	0.17
The use of MCS, n (%)	7 (9.1)	41 (9.6)	1.00
Final TIMI grade 3, n (%)	70 (90.9)	381 (89.0)	0.84
Peak CPK (IU/L) [†]	1,649 (1,018–3,241)	2,054 (1,071–3,864)	0.15
LVEF (%)	52.1±10.7	49.6±10.6	0.08
BNP [¶] (ng/L) [†]	119.5 (38.0–203.2)	119.0 (61.6–231.8)	0.09
Medication use at discharge, n (%)			
Atorvastatin	37 (48.1)	120 (28.0)	<0.01
20 mg atorvastatin	0 (0.0)	3 (0.7)	1.00
Rosuvastatin	13 (16.9)	173 (40.4)	<0.01
10 mg rosuvastatin	1 (1.3)	21 (4.9)	0.23
Pitavastatin	27 (35.1)	135 (31.5)	0.60
4 mg pitavastatin	1 (1.3)	17 (4.0)	0.33
Ezetimibe	4 (5.2)	11 (2.6)	0.26
β-blocker	47 (61.0)	325 (75.9)	0.01
ACE inhibitor or ARB	70 (90.9)	386 (90.2)	1.00
MR antagonist	6 (7.5)	32 (7.5)	1.00
Diuretics	11 (14.3)	86 (20.1)	0.27
Oral inotropic agent	2 (2.5)	6 (1.4)	0.35
Antiplatelet agents	77 (100.0)	428 (100.0)	–
DAPT	52 (67.5)	314 (73.4)	0.33
Oral anticoagulant	9 (11.7)	53 (12.4)	1.00

Data are presented as n (%) or mean ± standard deviation or median (interquartile range)[†]. [‡], CKD is defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². [¶], BNP was measured at discharge. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CK, creatine phosphokinase; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MR, mineralocorticoid receptor.

Table 2 Serial changes in LDL-C and CRP levels

Variable	Hypo-responder to statin therapy (n=77)	Responder to statin therapy (n=428)	P value
LDL-C			
Baseline (mmol/L)	2.9±0.7	3.6±0.8	<0.01
Follow-up (mmol/L)	2.9±0.6	2.1±0.5	<0.01
Percent change (%)	+2.1±17.7	-41.2±12.3	<0.01
CRP			
Baseline (mg/L) †	1.4 (0.6–5.3)	1.5 (0.7–4.8)	0.57
Follow-up (mg/L) †	1.7 (0.7–5.7)	1.7 (0.7–4.8)	0.87
Percent change (%) †	+25.0 (–74.7 to +325.0)	–1.3 (–67.4 to +175.0)	0.41

Data are presented as mean ± standard deviation or median (interquartile range)†. CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

**Figure 3** The course of percent change in LDL-C level. LDL-C, low-density lipoprotein cholesterol.

smaller reduction compared to responders (+2.1%±17.7% vs. -41.2%±12.3%, $P<0.001$). Serial change in percent reduction of LDL-C beyond 1 month was illustrated by *Figure 3*. In statin hyporesponders, a smaller percent change in LDL-C continued to exist at 6, 12 and 48 months (*Figure 3*). In addition, percent change in LDL-C was still significantly different in two groups at 6 ($P<0.0001$) and 12 months ($P<0.0001$). This comparison showed borderline significance at 48 months ($P=0.05$).

With regard to CRP levels, baseline and 1-month CRP levels did not differ between the groups (*Table 2*).

Occurrence of heart failure

The incidence of HF events during the observational period [median =4.4 years, interquartile range (IQR): 2.9 to 6.8 years] in responders and hyporesponders to statin

is summarized in *Tables 3,4,5* and *Figure 4*. The frequency of β -blocker use at its maximal dose was similar in two groups (20.8% vs. 17.5%, $P=0.68$). HF and cardiac-related death occurred in 24 and 8 subjects, respectively (*Table 3*). Hyporesponse to statin was associated with a 3.01- [95% confidence interval (CI): 1.27–6.79, $P=0.01$] and 2.59-fold (95% CI: 1.16–5.47, $P=0.02$) greater likelihood of experiencing HF and a composite of HF and cardiovascular death (*Table 4, Figure 4A,B*), respectively. On multivariate Cox proportional hazard model analysis as well as the stepwise regression analysis, hyporesponse to statin continued to predict the occurrence of HF and a composite outcome (*Table 4*). The propensity score-matching analysis was conducted to further evaluate the predictive ability of hyporesponse to statin for HF events. Following the selection of 59 hyporesponders and 118 responders with matched baseline characteristics

Table 3 Summary of HF events and cardiovascular death

Variable	Overall (n=505)	Hypo-responder to statin therapy (n=77)	Responder to statin therapy (n=428)
HF, n (%)	24 (4.8)	9 (11.7)	15 (3.5)
Cardiovascular death, n (%)	8 (1.6)	2 (2.6)	6 (1.4)
Composite event (= HF + cardiovascular death), n (%)	29 (5.7)	10 (13.0)	19 (4.4)

HF, heart failure.

Table 4 Univariate and multivariate analysis of predictors for HF events and composite outcomes

Variable	Univariate analysis			Multivariate analysis			Multivariate analysis (Stepwise)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
HF events									
Age	1.03	1.00–1.07	0.08	1.05	1.00–1.09	0.04	–	–	–
Female	1.57	0.63–3.58	0.31	–	–	–	–	–	–
BMI	1.01	0.90–1.12	0.81	–	–	–	–	–	–
Type 2 DM	1.41	0.61–3.16	0.41	–	–	–	–	–	–
Killip classification	1.97	1.36–2.72	<0.01	1.29	0.85–1.88	0.21	1.39	0.91–2.03	0.11
LVEF	0.91	0.88–0.95	<0.01	0.91	0.88–0.95	<0.01	0.92	0.88–0.96	<0.01
β-blocker	0.75	0.25–1.86	0.55	–	–	–	–	–	–
High-intensity statin [†]	1.35	0.28–24.33	0.76	–	–	–	–	–	–
Statin hypo-responder	3.01	1.27–6.79	0.01	2.74	1.01–6.75	0.04	3.00	1.10–7.43	0.03
Composite outcomes									
Age	6.46	0.80–58.78	0.08	1.05	1.01–1.10	0.01	–	–	–
Female	1.41	0.33–1.64	0.41	–	–	–	–	–	–
BMI	1.00	0.89–1.10	0.93	–	–	–	–	–	–
Type 2 DM	1.22	0.56–2.54	0.61	–	–	–	–	–	–
Killip classification	2.01	1.45–2.69	<0.01	1.40	0.97–1.95	0.07	1.52	1.05–2.13	0.03
LVEF	0.92	0.89–0.95	<0.01	0.92	0.89–0.96	<0.01	0.93	0.90–0.97	<0.01
β-blocker	1.69	0.70–5.03	0.26	–	–	–	–	–	–
High-intensity statin [†]	1.34	0.21–4.55	0.71	–	–	–	–	–	–
Statin hypo-responder	2.59	1.16–5.47	0.02	2.36	0.94–5.42	0.07	2.55	1.01–5.92	0.04

[†], high-intensity statin was defined as atorvastatin ≥ 20 mg, rosuvastatin ≥ 10 mg and pitavastatin ≥ 4 mg. CI, confidence interval; HR, hazard ratio; HF, heart failure; BMI, body mass index; DM, diabetes mellitus; LVEF, left ventricular ejection fraction.

(Table S1), a greater risk for HF and composite outcome was observed in statin hypo-responders (HF: HR =12.30, 95% CI: 1.50–100.3, P=0.01, HF and cardiovascular death: HR =4.50, 95% CI: 1.19–17.06, P=0.02). Even in the IPTW analysis with ATEs, the association

between statin hypo-responders and an increased risk of HF remained (coefficient =7.02, 95% CI: 2.29–21.58, P=0.0006, Table 5 and Table S2). Additionally, statin hypo-response tended to be associated with a higher frequency of composite outcome (coefficient =3.05, 95%

Table 5 Adjusted multivariate hazard ratios for HF and composite outcome in statin hyporesponders vs. responders

Endpoint	Propensity score matching model for statin-hypo-responder		ATEs estimated by IPTW weighted multivariable adjusted model	
	HR (95% CI)	P value	Coefficient (95% CI)	P value
HF	12.30 (1.50–100.3)	0.01	7.02 (2.29–21.58)	<0.01
HF + cardiovascular death	4.50 (1.19–17.06)	0.02	10.5 (0.86–10.82)	0.08

CI, confidence interval; HR, hazard ratio; HF, heart failure; ATEs, average treatment effects; IPTW, inverse probability of treatment weights.

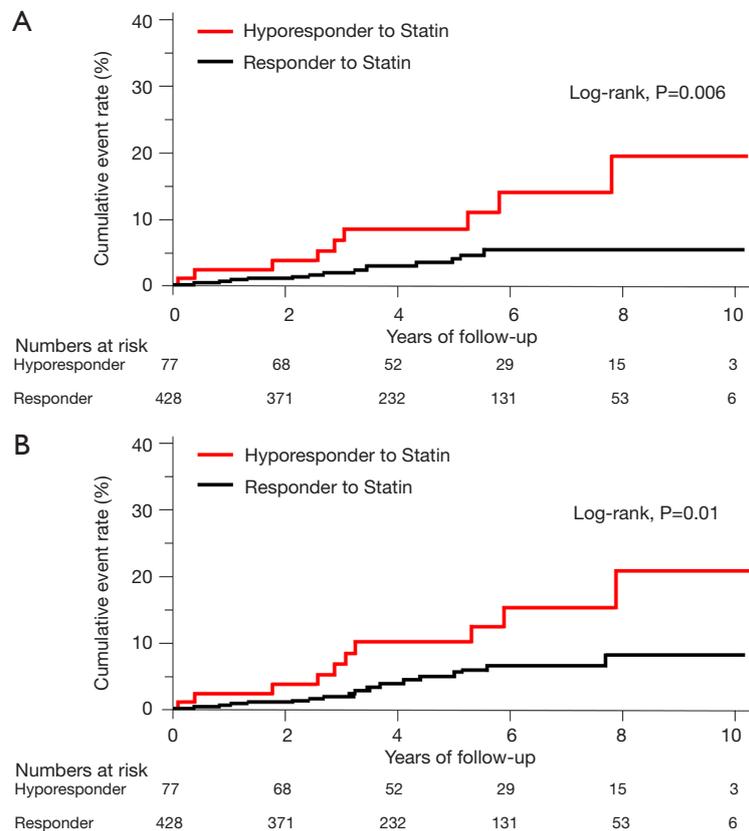


Figure 4 (A) The occurrence of HF events in responders and hyporesponders to statins. (B) The occurrence of composite outcomes in responders and hyporesponders to statins. Kaplan-Meier analysis shows a significantly higher incidence of (A) HF hospitalization and (B) a composite outcome in hypo-responder to statin (red line) than its responders (black line) (HF hospitalization: HR =3.01, 95% CI: 1.27–6.79, P=0.01, HF hospitalization + cardiovascular death: HR =2.59, 95% CI: 1.16–5.47, P=0.02). CI, confidence interval; HF, heart failure; HR, hazard ratio.

CI: 0.86–10.82, P=0.08, *Table 5*). The detailed cause of heart failure events in statin hyporesponders and responders is summarized by *Table S3*. With regard to the occurrence of atherosclerotic cardiovascular events, there was no significant difference between two groups (HR =1.33, 95% CI: 0.69–2.37, P=0.38, *Figure S1*).

Based on hazard ratio of heart failure as 7.02 obtained by IPTW analysis, the power of the analysis was calculated as 87.7% with an alpha level of 5% and 505 patients. With regard to the sample size calculation, 332 subjects were required, with an alpha level of 5% and hazard ratio of heart failure as 7.02, which gave power of 80%.

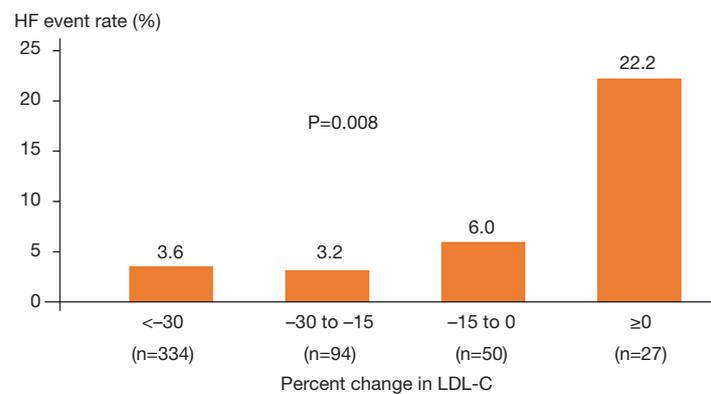


Figure 5 The risk of HF events in association with the degree of lowering LDL-C with a statin. The frequency of HF after AMI significantly increased in association with percent LDL-C reduction after commencement of a statin. HF, heart failure; AMI, acute myocardial infarction; LDL-C, low-density lipoprotein cholesterol.

Heart failure risk and the degree of response to a statin

The occurrence of HF was compared in subjects stratified according to the percent reduction in LDL-C levels following statin therapy (Figure 5). An increased frequency of HF event was observed in association with the extent of percent reduction in LDL-C levels ($P=0.008$). In particular, the risk of HF events increased in AMI subjects who did not obtain any LDL-C reduction despite statin therapy (Figure 5).

Discussion

The current findings provide important insights into the association between the response to a statin and the occurrence of HF events. Despite statin therapy, about 15% of AMI subjects did not show an adequate lowering of LDL-C levels. Furthermore, this poor response to a statin increased the risk of HF following AMI. Our findings indicate that hyporesponse to a statin may be a potential factor associated with HF events in patients with AMI.

Statin hyporesponse causes high LDL-C levels, which is an important driver to propagate proatherogenic damage within vessel walls. Mechanistically, circulating LDL has been reported to cause eNOS uncoupling, which stimulates superoxide production and promotes endothelial dysfunction (14,15). In addition, one recent study found that LDL-C level was independently associated with oxidative markers and endothelial function (16). Given that endothelial dysfunction increases microvascular resistance and extravascular fluid accumulation (17), these LDL-C-

derived effects in statin hyporesponders may elevate a risk of HF (18,19). As shown in Figure 5, the frequency of HF varies according to the degree of LDL-C reduction under statin therapy. These observations suggest that suboptimal LDL-C lowering due to hyporesponse to a statin may negatively affect vascular tone and fluid retention, which potentially influence the ability of statins to modify HF risk following AMI.

While statins have been shown to possess anti-inflammatory properties (20,21), whether this effect is diminished in statin hyporesponders remains to be determined. In our analysis, an increase in CRP levels (25.0%) was observed in statin hyporesponders, although this difference did not meet statistical significance (Table 2). Another study identified a trend towards a smaller percentage of reduction in CRP levels in statin hyporesponders (6). These findings suggest that the property of statins to modulate inflammatory activity may be also diminished. Since a systemic inflammatory state has been considered to cause HF via increased endothelial adhesion molecules expression and reactive oxygen species production (22,23), the unfavourable control of inflammatory activity may be another driver for the occurrence of HF events in statin hyporesponders.

The precise mechanism of impaired LDL-C reduction in statin hyporesponders remains unknown. One of speculative mechanisms is the statin-mediated increase in circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) level. PCSK9 is a serine protease degrading LDL receptor, which induces an increase in circulating LDL-C (24). In addition to its property associated with LDL metabolism, PCSK9

has been shown to promote inflammation and worsen endothelial permeability, including nitric oxide production (25,26). Of note, the circulating PCSK9 level itself has been shown to be a significant predictor of a composite endpoint of all-cause death and HF hospitalization by the BIOSTAT-CHF subanalysis (27). Although the current study did not measure PCSK9 levels, a potential elevation of PCSK9 levels in statin hyporesponders may be an important substrate causing its diminished effect.

We observed that 15.2% of AMI subjects did not favorably respond to statin therapy. Given that lowering LDL-C is a mainstay of preventive management in the setting of AMI, considering additional lipid-lowering therapy is required in AMI subjects with poor response to a statin. Recent clinical trials showed clinical efficacy of ezetimibe, evolocumab and alirocumab on lipid parameters as well as cardiovascular outcomes. As such, evaluation of response to a statin could provide an opportunity to select appropriate agent for achieving optimal lipid control after AMI in each individual.

The present study has several limitations. Firstly, this was a retrospective observational study at a single center that included a relatively small number of statin hyporesponders and cardiac events. Secondly, the type and dose of statins and cardioprotective drugs were decided by each physician. Thirdly, we analyzed AMI subjects who were hospitalized from 2007 to 2014. In this study period, the guideline-recommended LDL-C goal in Japan was LDL-C <100 mg/dL, and the use of statin was not clearly recommended. This may affect a lower frequency of high-intensity statin use. Fourthly, the current study did not collect data about compliance of a statin because it is a retrospective analysis. Fifthly, serum PCSK9 and other biomarkers associated with inflammation and endothelial function have not been evaluated in this study. Lastly, β -blocker was less frequently used in statin hyporesponders, which may affect their HF outcomes. However, even after adjusting for baseline medication use, the relationship between statin hyporesponse and HF events remained.

In conclusion, the present study revealed that 15.2% of patients with AMI showed a poor response to statins. This reduced efficacy of statins caused a suboptimal control of LDL-C after AMI. Furthermore, hyporesponse to statins was associated with an increased risk of HF. Our findings highlight statin hyporesponsiveness as a phenotype with an increased risk of HF which requires additional preventive therapy.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The research protocol was approved by the ethics committee of our institution (M24-055-6). The research was conducted in accordance with the Declaration of Helsinki. Informed consent was not obtained in each subject due to the observational analysis of hospitalized patients.

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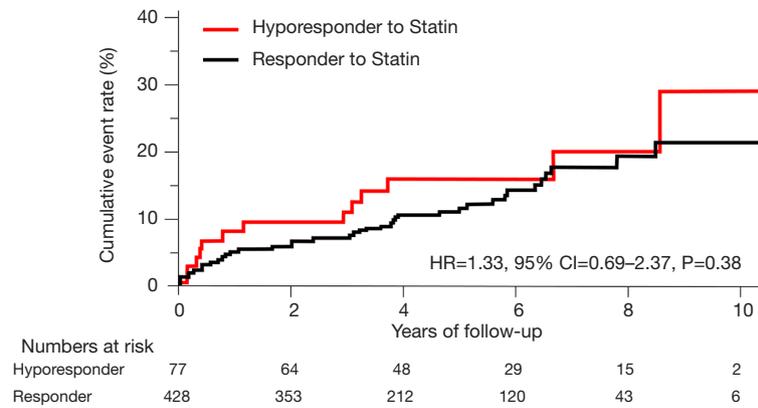


Figure S1 The occurrence of atherosclerotic cardiovascular events. Atherosclerotic cardiovascular events were defined as a composite of cardiovascular death, non-fatal myocardial infarction, stroke and unstable angina pectoris requiring revascularization.

Table S1 Clinical characteristics of propensity-score matched subjects

Characteristics	Hyporesponse to statins (n=59)	Response to statins (n=118)	P value
Age (years)	67.8±9.8	67.9±11.6	0.98
Female, n (%)	13 (22.0)	27 (22.9)	1.00
BMI (kg/m ²)	23.1±3.0	23.5±3.2	0.45
Hypertension, n (%)	41 (69.5)	81 (68.6)	1.00
Type 2 DM, n (%)	15 (25.4)	38 (32.2)	0.45
Killip class	1.3±0.8	1.3±0.8	0.89
LVEF (%)	52.5±10.3	51.5±9.4	0.48
LDL-C baseline (mmol/L)	2.8±0.6	3.0±0.5	0.05
High-intensity statin [†] use, n (%)	2 (3.4)	5 (4.2)	1.00
β-blocker use, n (%)	38 (64.4)	79 (66.9)	0.86

Data are presented as n (%) or mean ± standard deviation. [†], high-intensity statin was defined as atorvastatin ≥20 mg, rosuvastatin ≥10 mg and pitavastatin ≥4 mg. BMI, body mass index; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction.

Table S2 Clinical characteristics of IPTW matched subjects

Characteristics	Hyporesponse to statins (n=59)	Response to statins (n=353)	P value	Standardized mean difference
Age (years)	68.2±9.7	68.7±12.0	0.80	0.040
Female, n (%)	12.8 (24.0)	11.7 (22.3)	0.80	0.041
BMI (kg/m ²)	23.0±3.0	23.1±3.1	0.93	0.015
Hypertension, n (%)	36.3 (68.0)	35.6 (68.1)	0.99	0.001
Type 2 DM, n (%)	14.3 (26.8)	13.4 (25.7)	0.87	0.026
Killip class	1.3±0.8	1.3±0.8	0.79	0.044
LVEF (%)	52.3±9.9	52.4±9.4	0.93	0.013
LDL-C baseline (mmol/L)	2.9±0.6	2.9±0.5	0.79	0.043
High-intensity statin [†] use, n (%)	2.0 (3.7)	2.3 (4.5)	0.82	0.037
β-blocker use, n (%)	34.4 (64.5)	34.4 (65.9)	0.86	0.029

Data are presented as n (%) or mean ± standard deviation. [†], high-intensity statin was defined as atorvastatin ≥20 mg, rosuvastatin ≥10 mg and pitavastatin ≥4 mg. BMI, body mass index; IPTW, inverse probability of treatment weights; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction.

Table S3 The detailed causes of heart failure events in statin hyporesponders and responders

Age (years)	Sex	LVEF (%)	Factors triggering HF hospitalization
Statin hyporesponders			
79	Male	39	High blood pressure
60	Male	40	High blood pressure
81	Female	48	High blood pressure
79	Male	40	Excessive salt/fluid intake
72	Male	60	Excessive salt/fluid intake
65	Male	32	Excessive salt/fluid intake
81	Female	53	ACS
74	Male	23	Drug (NSAIDs)
53	Male	49	Infection
Statin responders			
82	Female	45	High blood pressure
69	Male	16	Excessive salt/fluid intake
45	Male	45	Excessive salt/fluid intake
80	Female	48	Excessive salt/fluid intake
57	Male	50	Excessive salt/fluid intake
82	Female	54	Arrhythmia
72	Female	30	Arrhythmia
59	Male	25	Infection
59	Male	37	Infection
79	Female	45	Anemia
71	Male	43	COPD
47	Male	45	Non-adherence of medication
66	Male	31	Sleep apnea syndrome
65	Male	30	Unknown
80	Female	34	Unknown

LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; HF, heart failure; NSAIDs, non-steroidal anti-inflammatory drugs.