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ORIGINAL ARTICLE

Association of Use and Dose of Lipid-Lowering Therapy Post Acute Myocardial Infarction With 5-Year Survival in Older Adults

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BACKGROUND: Older people are underrepresented in randomized trials. The association between lipid-lowering therapy (LLT) and its intensity after acute myocardial infarction and long-term mortality in this population deserves to be assessed.

METHODS: The FAST-MI (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) program consists of nationwide French surveys including all patients admitted for acute myocardial infarction ≤48 hours from onset over a 1- to 2-month period in 2005, 2010, and 2015, with long-term follow-up. Numerous data were collected and a centralized 10-year follow-up was organized. The present analysis focused on the association between prescription of LLT (atorvastatin ≥40 mg or equivalent, or any combination of statin and ezetimibe) and 5-year mortality in patients aged ≥80 years discharged alive. Cox multivariable analysis and propensity score matching were used to adjust for baseline differences.

RESULTS: Among the 2258 patients aged ≥80 years (mean age, 85±4 years; 51% women; 39% ST-segment elevation myocardial infarction; 58% with percutaneous coronary intervention), 415 were discharged without LLT (18%), 866 with conventional doses (38%), and 977 with high-dose LLT (43%). Five-year survival was 36%, 47.5%, and 58%, respectively. Compared with patients without LLT, high-dose LLT was significantly associated with lower 5-year mortality (adjusted hazard ratio, 0.78 [95% CI, 0.66–0.92]), whereas conventional-intensity LLT was not (adjusted hazard ratio, 0.93 [95% CI, 0.80–1.09]). In propensity score-matched cohorts (n=278 receiving high-intensity LLT and n=278 receiving no statins), 5-year survival was 52% with high-intensity LLT at discharge and 42% without statins (hazard ratio, 0.78 [95% CI, 0.62–0.98]).

CONCLUSIONS: In these observational cohorts, high-intensity LLT at discharge after acute myocardial infarction was associated with reduced all-cause mortality at 5 years in an older adult population. These results suggest that high-intensity LLT should not be denied to patients on the basis of old age.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT00673036, NCT01237418, and NCT02566200.

Key Words: atorvastatin ■ ezetimibe ■ myocardial infarction ■ outcomes ■ ST elevation myocardial infarction

Major randomized controlled trials have demonstrated the benefit of statins and lipid-lowering therapy (LLT), and particularly high-intensity lipid lowering, on both fatal and nonfatal cardiovascular events after acute myocardial infarction (AMI).[1–6] This is true for both younger and older patients included in randomized trials, but older patients in randomized trials were usually defined as over 65 years. Even in the PROSPER trial (Prospective Study of Pravastatin in the Elderly at Risk),[7,8] specifically designed to address the benefits of statin therapy in older individuals, the population included ranged from 70 to 82 years of age, with a mean age of 75 years. The

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WHAT IS KNOWN

- High-intensity lipid lowering is recommended in patients with an acute myocardial infarction.
- Although a meta-analysis of randomized trials has documented that statins have a similar efficacy in elderly people as in younger ones, very few patients over the age of 80 years have actually been included in randomized trials.
- Following myocardial infarction, the long-term mortality of elderly patients is high, which may limit the clinical benefit of lipid-lowering therapy in this population.

WHAT THE STUDY ADDS

- From 2005 to 2015, there has been a substantial increase in the use of statins and high-intensity lipid-lowering therapy in patients aged ≥80 years sustaining a myocardial infarction.
- Use of high-intensity lipid-lowering therapy in this population is associated with a reduced risk of 5-year mortality, persisting after adjustment and propensity score matching.
- Pending the results of specific randomized controlled trials in the very elderly, our data suggest that the prescription of high-intensity lipid-lowering therapy to elderly people sustaining an acute myocardial infarction should not be restrained on the sole basis of their older age.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
AMI	acute myocardial infarction
FAST-MI	French registry on Acute ST-elevation and non-ST-elevation Myocardial Infarction
HR	hazard ratio
LLT	lipid-lowering therapy
LVEF	left ventricular ejection fraction
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
STEMI	ST-segment elevation myocardial infarction

cholesterol treatment trialists collaboration meta-analysis on statin efficacy and safety in older people focused on a group >75 years of age (mean age of 79 years) and documented similar efficacy of statins on cardiovascular events in this older group. The meta-analysis was subsequently extended to nonstatin LLT (ie, ezetimibe and PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibitors) and yielded concordant results.[9] However, evidence from randomized trials in truly older patients (ie, beyond 80 years of age) is lacking; in addition, patients with comorbid conditions were frequently excluded from randomized trials. Of note, no significant reduction in all-cause mortality was observed (relative risk, 0.93 [95% CI, 0.84–1.02]).[9] Yet, older patients have the highest risk of recurrent cardiovascular and noncardiovascular events after AMI.[10] In a recent review of randomized trials cited in the American and European practice guidelines for the management of acute coronary syndromes (ACS), Mas-Llado et al[11] found that the mean age of the populations in these trials was 62 years and that 23% of the trials had older age as an exclusion criterion.

Because statin tolerance and pharmacokinetics differ in older populations, potentially impacting both efficacy and safety, and because higher doses of statins may have more side effects, studying all-cause mortality as the ultimate measure of both efficacy and safety seems particularly appropriate in very older adults.[12–15] In addition, one may question whether otherwise efficacious therapies for secondary prevention are really necessary when annual mortality is high, as is the case for very old patients with myocardial infarction. Currently, the American College of Cardiology/American Heart Association guidelines on the management of blood cholesterol consider that initiating high-intensity LLT in patients above 75 years old is reasonable after an individual assessment of potential benefits and risks.[16]

The current analysis from the French registry on acute ST-elevation and non-ST-elevation myocardial infarction (FAST-MI) program aimed to examine associations between LLT and intensity at hospital discharge with 5-year mortality in a population of patients aged ≥80 years who had sustained a recent AMI.

METHODS

The population and methods of the FAST-MI registry have been previously described[17,18] (Supplemental Methods). The main objective of the FAST-MI registries was to collect data on the characteristics, management, and outcome of consecutive patients admitted to intensive care units for an AMI over a 1-month period in France, during 3 different periods: 2005 (NCT00673036), 2010 (NCT01237418), and 2015 (NCT02566200).

The data used for this study may be communicated upon detailed request stating the purpose of their intended use, pending authorization of the French Society of Cardiology, and within the boundaries of French and European laws.

Patients

Patients were included in the FAST-MI registry if they were over 18 years old, were admitted within 48 hours of symptom onset in a cardiology department for an ST-segment elevation myocardial infarction (STEMI) or non-STEMI, and agreed to participate.

Patients with unstable angina were not included. Those with iatrogenic AMI were excluded, as were those initially suspected of AMI in whom this diagnosis was subsequently disproved.

In the present study, we selected patients aged ≥80 years included during the 3 different periods of the FAST-MI registry who were discharged alive with a known dose of LLT (in 6 patients, the dose of LLT was not available).

All patients gave informed consent for participation in the registry and for follow-up. The protocols of each survey were reviewed and approved by the appropriate ethics committees and received approval by the data protection commission (Commission Nationale de l'Informatique et des Libertés).

Data Collection and Definition

All data were prospectively recorded on computerized case record forms with multiple coherence checks by dedicated research technicians sent on site during the study inclusion period, who also checked consecutiveness of recruitment.

Follow-up information was obtained by dedicated research technicians at the French Society of Cardiology, who contacted both treating physicians and patients/families by mail or phone after checking the patients' vital status in municipal registers.

LLT Intensity

High-intensity LLT was defined as high-dose statins (ie, atorvastatin ≥40 mg or rosuvastatin ≥10 mg, which had a similar lipid-lowering efficacy in patients with ACS in the CENTAURUS trial [comparison of the effects noted in the ApoB/apoA-1 ratio using rosuvastatin or Atorvastatin in patients with acute coronary syndrome][19]), or any combination of ezetimibe and statins. All other statins or statin doses, as well as ezetimibe used without a statin combination, were considered conventional-dose LLT.

LLT at discharge was classified as no LLT, conventional-dose LLT, or high-intensity LLT.

Statistical Analyses

Continuous variables are reported as means with their SDs or medians and interquartile ranges, when appropriate. Discrete variables are described as counts and percentages. Groups were compared by ANOVA or nonparametric tests (Mann-Whitney or Kruskal-Wallis) for continuous variables and χ^2 or Fisher exact tests for discrete variables.

The Kaplan-Meier method was used for unadjusted survival curves, and curves were compared with log-rank tests.

We used multivariable Cox regression analysis to estimate the hazard ratios (HRs) and 95% CI evaluating the association between LLT at discharge and 5-year mortality. The multivariable model included survey year, age, sex, clinical characteristics (risk factors, comorbidity, past cardiovascular history), type of myocardial infarction (STEMI, non-STEMI type 1, and type 2), global registry of acute coronary events score, procedures performed during the index hospital stay (coronary angiography with or without percutaneous coronary intervention [PCI] and coronary artery bypass graft surgery), low density lipoprotein–cholesterol level, creatinine, hemoglobin on admission, left ventricular ejection fraction, in-hospital complications (cardiogenic shock, thrombolysis in myocardial infarction major bleeding), use of statins before the index event, and discharge medications. Continuous variables with missing values (ie, hemoglobin, creatinine, low density lipoprotein–cholesterol, left ventricular ejection fraction [LVEF], global registry of acute coronary events score) were categorized, with 1 category for missing values (eg, LVEF was categorized into 3 categories: LVEF ≤40%, LVEF >40%, and LVEF not available). No imputation was used for variables with missing values. Analyses were repeated using forward conditional logistic regression and yielded concordant results. Collinearity was verified by calculating variance inflation factors.

The same model was used in secondary analyses according to age groups (≤85 versus >85 years), sex, use of PCI during the index hospital stay, and previous use of statins (ie, before the index AMI).

We also performed propensity score-matched analyses of patients receiving high-intensity LLT compared with those receiving no LLT (278 pairs), conventional-dose LLT compared with those receiving no LLT (371 pairs), and high-intensity LLT compared with conventional-dose LLT (586 pairs; Tables S1 through S3). Variables with a standardized difference <0.10 were considered to represent an adequate balance between the groups. Variables with a standardized difference of ≥0.10 were used for adjustment.

All statistical analyses were performed using International Business Machines Statistical Package for Social Sciences 25 with R plug-ins and Number Cruncher Statistical Systems 2022 (Number Cruncher Statistical Systems LLC) software. A $P<0.05$ was considered significant.

RESULTS

Clinical Characteristics

Among 13 130 patients included in the 3 surveys, 2496 were aged ≥80 years, among whom 2264 were discharged alive, and doses of LLT were available in 2258. Among them, 415 (18.4%) patients were discharged without LLT, 866 (38.4%) with a conventional dose of LLT, and 977 (43.2%) with high-dose LLT (Figure S1).

Clinical characteristics are detailed in Table 1. Patients without LLT were older, with a higher proportion of women, and more frequent comorbidities (such as atrial fibrillation, myocardial infarction, heart failure, or chronic kidney disease). Cardiovascular risks factors had a heterogenous distribution according to LLT intensity.

Myocardial Infarction Management and In-Hospital Complications

A higher proportion of patients with STEMI, coronary angiograms, PCI, or reperfusion therapy for STEMI received high-intensity LLT (Table 1). Thrombolysis in myocardial infarction minor bleeding during the hospital stay was less common in patients without LLT, while the other complications did not differ significantly.

Table 1. Patient Characteristics According to Lipid-Lowering Therapy at Discharge

	No lipid-lowering therapy, n=415	Conventional-dose therapy, n=866	High-intensity lipid-lowering therapy, n=977	Total, n=2258	*P* value
Survey year					0.001
2005	190 (45.8)	366 (42.3)	95 (9.7)	651 (28.8)	
2010	96 (23.1)	214 (24.7)	370 (37.9)	680 (30./1)	
2015	129 (31.1)	286 (33.0)	512 (52.4)	927 (41.1)	
Demography					
Age, y	86.4±4.4	85.1±3.7	84.8±3.4	85.2±3.8	<0.001
Women	234 (56.4)	439 (50.7)	480 (49.1)	1153 (51.1)	0.045
BMI, kg/m²	25.3±4.4	25.2±4.2	25.7±4.3	25.4±4.3	0.033
Risk factors and past medical history					
Diabetes	131 (31.6)	287 (33.1)	257 (26.3)	675 (29.9)	0.004
Hypertension	320 (77.1)	664 (76.7)	739 (75.6)	1723 (76.3)	0.793
Current smoking	27 (6.5)	42 (4.8)	39 (4.0)	108 (4.8)	0.132
Hypercholesteremia	110 (26.5)	441 (50.9)	420 (43.0)	971 (43.0)	<0.001
History of CAD	170 (41.0)	355 (41.0)	311 (31.8)	836 (37.0)	<0.001
Prior MI	105 (25.3)	213 (24.6)	212 (21.7)	530 (23.5)	0.216
Prior PCI	76 (18.3)	189 (21.8)	172 (17.6)	437 (19.3)	0.063
Prior CABG	27 (6.3)	64 (7.4)	62 (6.3)	153 (6.8)	0.658
Prior stroke/TIA	44 (11.6)	106 (12.2)	85 (8.7)	239 (10.6)	0.038
PAD	51 (12.3)	126 (14.5)	126 (12.9)	303 (13.4)	0.446
Atrial fibrillation*	48 (21.3) (n=225)	70 (14.0) (n=500)	94 (10.7) (n=882)	212(13.2) (n=1607)	<0.001
History of heart failure	75 (18.1)	89 (10.3)	89 (9.1)	253 (11.2)	<0.001
Chronic kidney disease	47 (11.3)	90 (10.4)	74 (7.6)	211 (9.4)	0.037
COPD	32 (7.7)	58 (6.7)	84 (8.6)	174 (7.7)	0.308
Previous cancer	60 (14.5)	114 (13.2)	135 (13.8)	309 (13.7)	0.804
History of infectious disease	14 (3.4)	23 (2.7)	31 (3.2)	68 (3.0)	0.719
Multiple comorbidity	117 (28.2)	225 (26.0)	213 (21.8)	550 (24.5)	0.001
Alzheimer disease*	12 (5.3) (n=225)	14 (2.8) (n=500)	36 (4.1) (n=882)	62 (3.9) (n=1607)	0.227
Statin use before index AMI	52 (12.5)	350 (40.4)	343 (35.1)	745 (33.0)	<0.001
MI characteristics, management, and in-hospital complications					
STEMI	131 (31.6)	308 (35.6)	436 (44.6)	875 (38.8)	<0.001
NSTEMI type 1	176 (42.2)	385 (44.4)	385 (39.4)	946 (41.9)	
NSTEMI type 2	108 (26.0)	173 (20.0)	156 (16.0)	437 (19.3)	
GRACE score	182±27 (n=381)	179±28 (n=806)	177±26 (n=904)	179±27 (n=2091)	0.005
LVEF	48.6±12.6 (n=296)	50.4±12.6 (n=700)	49.5±11.6 (n=875)	49.7±12.1 (n=1871)	0.088
Coronary angiography	235 (56.6)	652 (75.3)	870 (89.0)	1757 (77.8)	<0.001
PCI	150 (36.1)	476 (54.9)	684 (70.0)	1310 (58.0)	<0.001
Reperfusion therapy (STEMI)	47 (35.8) (n=131)	172 (55.8) (n=308)	315 (72.2) (n=436)	534 (61.1) (n=876)	<0.001
Recurrent MI	7 (1.7)	12 (1.4)	8 (0.8)	27 (1.2)	0.319
Stroke	6 (1.4)	6 (0.7)	4 (0.4)	16 (0.7)	0.108
Cardiogenic shock	20 (4.8)	22 (2.5)	28 (2.9)	70 (3.1)	0.092
Atrial fibrillation	61 (14.7)	96 (11.1)	116 (11.9)	273 (12.1)	0.172
Ventricular fibrillation	5 (1.0)	4 (0.5)	9 (0.9)	17 (0.8)	0.648
TIMI major bleeding	6 (1.4)	16 (1.8)	21 (2.1)	43 (1.9)	0.671
TIMI minor bleeding	7 (1.7)	29 (3.3)	51 (5.2)	87 (3.9)	0.005

AMI indicates acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GRACE, global registry of acute coronary events; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; and TIMI, thrombolysis in myocardial infarction.

*History of atrial fibrillation and history of Alzheimer disease not recorded in 2005.

Cardiovascular Pharmacotherapy at Discharge

Cardiovascular therapy at discharge is detailed in Table 2. Most concomitant medications differed among the 3 groups. Prescription rates of aspirin (77.3–95.4%), dual antiplatelet therapy (51.1–83.3%), or any antithrombotic treatment (91.3–98.5%) significantly increased according to the LLT intensity. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (54.7–74.6%) and beta-blockers (61.2–80.3%) prescription rates also significantly increased according to LLT intensity.

Conversely, oral anticoagulants, calcium channel blockers, amiodarone, or insulin were more commonly prescribed in patients without LLT.

Long-Term Survival

Five-year survival was 58% for patients discharged with high-intensity LLT, 47.5% for patients on conventional-dose LLT, and 36% for those discharged without LLT (Figure 1).

Using Cox multivariable regression analysis, high-dose LLT was associated with lower 5-year mortality (HR, 0.78 [95% CI, 0.66–0.92]; *P*=0.008), while conventional doses were not (HR, 0.93 [95% CI, 0.80–1.09]; *P*=0.39; Figure 1). Among patients receiving LLT at discharge, high-dose LLT was associated with lower long-term mortality when compared with conventional-intensity LLT (HR, 0.85 [95% CI, 0.74–0.97]; *P*=0.018).

The propensity score-matched cohorts for high-intensity LLT (n=278) and for no LLT at discharge (n=278) were well balanced for all variables (Table S1). Five-year survival was significantly higher in patients receiving high-intensity LLT at discharge (52%) than in patients without statins (42%) (HR, 0.78 [95% CI, 0.62–0.98]; *P*=0.036; Figure 2).

In the propensity score-matched cohorts of patients with conventional-dose LLT (n=371) or no LLT (n=371; Table S2), 5-year survival was 37% for those not receiving LLT and 41% for those getting conventional-dose LLT at discharge (HR, 0.96 [95% CI, 0.78–1.16]; *P*=0.66; Figure S2).

In the propensity score-matched cohorts of patients receiving high-intensity LLT (n=586) or conventional-dose LLT (n=586; Table S3), 5-year survival was 56% and 51%, respectively (HR, 0.83 [95% CI, 0.69–0.99]; *P*=0.043; Figure S3).

Subgroup Analyses

Age Groups

The interaction according to age was not significant (*P*=0.18; Figure S4). Compared with patients receiving no LLT, HRs for patients receiving high-intensity LLT were 0.65 (95% CI, 0.50–0.83) in those between 80 and 85 years of age (n=1243), and 0.89 (95% CI, 0.70–1.14) in those above 85 years of age; HRs for patients receiving conventional doses were 0.83

Table 2. Medications Prescribed at Discharge According to Lipid-Lowering Therapy

Treatments at discharge, n (%)	No lipid-lowering therapy, n=415	Conventional-dose therapy, n=866	High-intensity lipid-lowering therapy, n=977	Total, n=2258	*P* value
Aspirin	321 (77.3)	792 (91.5)	932 (95.4)	2045 (90.6)	<0.001
P2Y12 inhibitor	241 (58.1)	674 (77.8)	837 (85.7)	1752 (77.6)	<0.001
DAPT	212 (51.1)	635 (73.3)	814 (83.3)	1661 (73.6)	<0.001
Oral anticoagulant	69 (16.6)	92 (10.6)	121 (12.4)	282 (12.5)	0.010
VKA	59 (14.2)	81 (9.4)	105 (10.7)	245 (10.8)	0.032
DOAC	10 (2.4)	11 (1.3)	16 (1.6)	37 (1.6)	0.322
Any antithrombotic treatment	379 (91.3)	850 (98.0)	962 (98.5)	2191 (97.0)	<0.001
ACE inhibitors	174 (41.9)	473 (54.6)	606 (62.0)	1253 (55.5)	<0.001
ARB	54 (13.0)	97 (11.2)	126 (12.9)	277 (12.3)	0.469
ACE inhibitors or ARB	227 (54.7)	567 (65.5)	729 (74.6)	1523 (67.5)	<0.001
Beta-blockers	254 (61.2)	657 (75.9)	785 (80.3)	1696 (75.1)	<0.001
Calcium channel blockers	106 (25.5)	180 (20.8)	174 (17.8)	460 (20.4)	0.004
Nitrates	83 (20.5)	142 (16.4)	152 (15.6)	377 (17.0)	0.085
Diuretics	211 (50.8)	386 (44.6)	455 (46.6)	1053 (46.6)	0.105
Loop diuretics	175 (42.2)	316 (36.5)	379 (38.8)	870 (38.5)	0.140
Aldosterone blockers	27 (6.5)	58 (6.7)	76 (7.8)	161 (7.1)	0.571
Amiodarone	74 (17.8)	107 (12.4)	87 (8.9)	268 (11.9)	<0.001
Insulin	54 (14.2)	121 (14.0)	101 (10.3)	281 (12.4)	0.030
Proton pump inhibitors	233 (56.1)	574 (66.3)	706 (72.3)	1513 (67.0)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; P2Y12, purinergic receptor Y2 subtype 12; and VKA, vitamin K antagonist

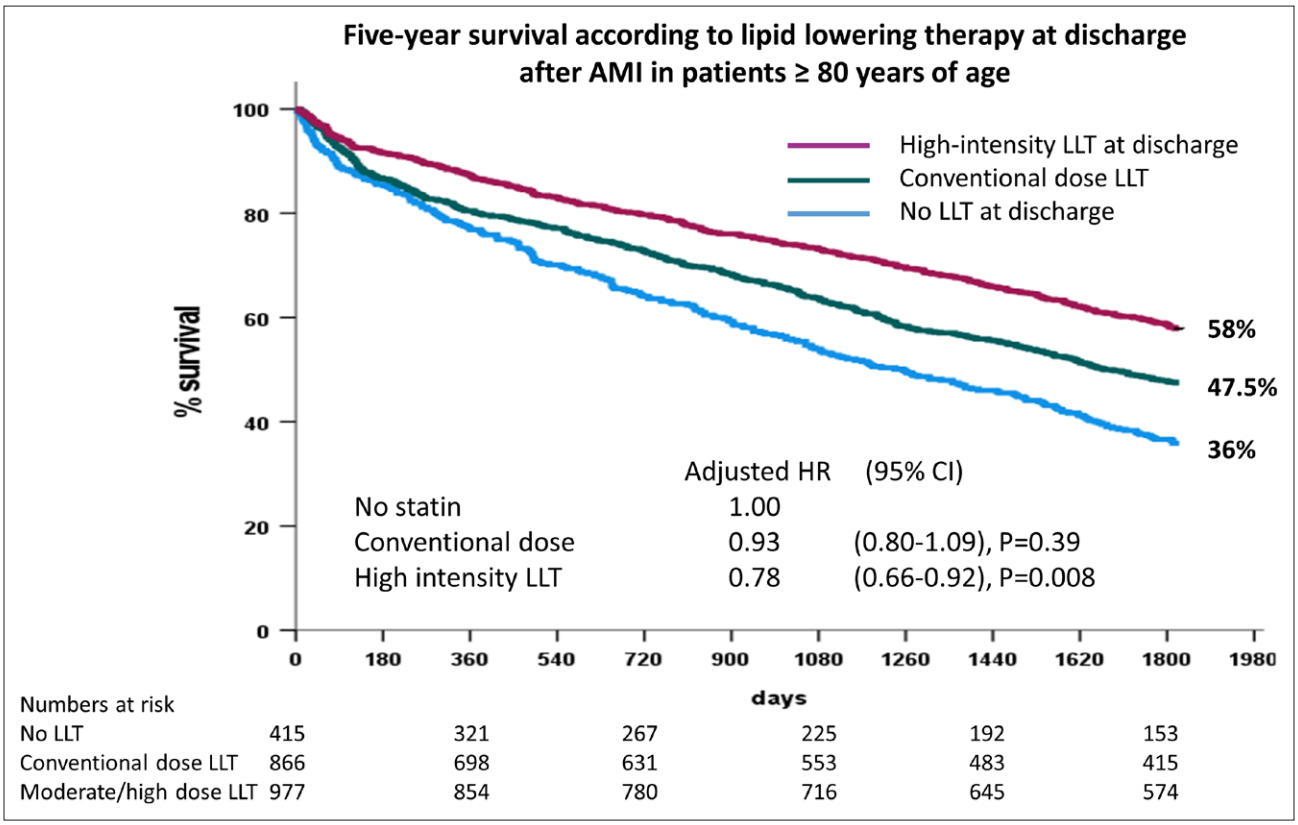

Figure 1. Five-year survival (unadjusted Kaplan-Meier survival curves) according to lipid-lowering therapy (LLT) at discharge in patients ≥80 years or age.
HR indicates hazard ratio.

(95% CI, 0.66–1.06) and 0.99 (95% CI, 0.79–1.24), respectively.

Sex

There was no significant interaction according to sex (*P*=0.155). In men, adjusted HRs for high-intensity and conventional-dose LLT were 0.79 ([95% CI, 0.62–1.02]; *P*=0.075) and 0.84 ([95% CI, 0.70–1.07]; *P*=0.157), respectively. In women, the respective figures were 0.76 ([95% CI, 0.59–0.97]; *P*=0.026) and 1.03 ([95% CI, 0.82–1.29]; *P*=0.792).

Use of PCI

Again, there was no interaction according to the use of PCI (*P*=0.817). In patients who underwent a PCI, high-intensity LLT was associated with lower 5-year mortality (HR, 0.71 [95% CI, 0.55–0.92]; *P*=0.009) and conventional-dose LLT was not (HR, 0.85 [95% CI, 0.70–1.10]; *P*=0.228; Figure S1). In patients without PCI, neither conventional-dose (HR, 1.01 [95% CI, 0.81–1.26]; *P*=0.896) nor high-intensity LLT (HR, 0.88 [95% CI, 0.68–1.13]; *P*=0.313) were associated with improved survival.

In patients with PCI over 85 years of age (n=526), high-intensity LLT yielded a HR of 0.73 ([95% CI, 0.49–1.08]; *P*=0.111).

Statin Use Before AMI

Finally, there was no interaction according to the use of statins before the AMI (*P*=0.53). The association of LLT use and intensity at discharge with 5-year mortality was of a similar magnitude according to use (HR, 0.68 [95% CI, 0.46–1.02]; *P*=0.067 for high-intensity; HR, 0.77 [95% CI, 0.52–1.13]; *P*=0.180 for conventional doses) or nonuse (HR, 0.78 [95% CI, 0.63–0.95]; *P*=0.013 for high-intensity; HR, 0.97 [95% CI, 0.80–1.17]; *P*=0.74 for conventional doses) of statins before the index AMI.

DISCUSSION

Very limited information is available about the potential benefit of LLT over the long term after AMI in older patients.[9,12] To our knowledge, the present study is the first observational study in a truly older population with AMI, documenting the favorable association between prescription of high-intensity LLT at discharge and long-term survival: adjusted 5-year mortality was lower with high-intensity LLT, while conventional doses were not associated with significantly lower mortality.

We deliberately chose all-cause mortality as the principal outcome of interest because medications that

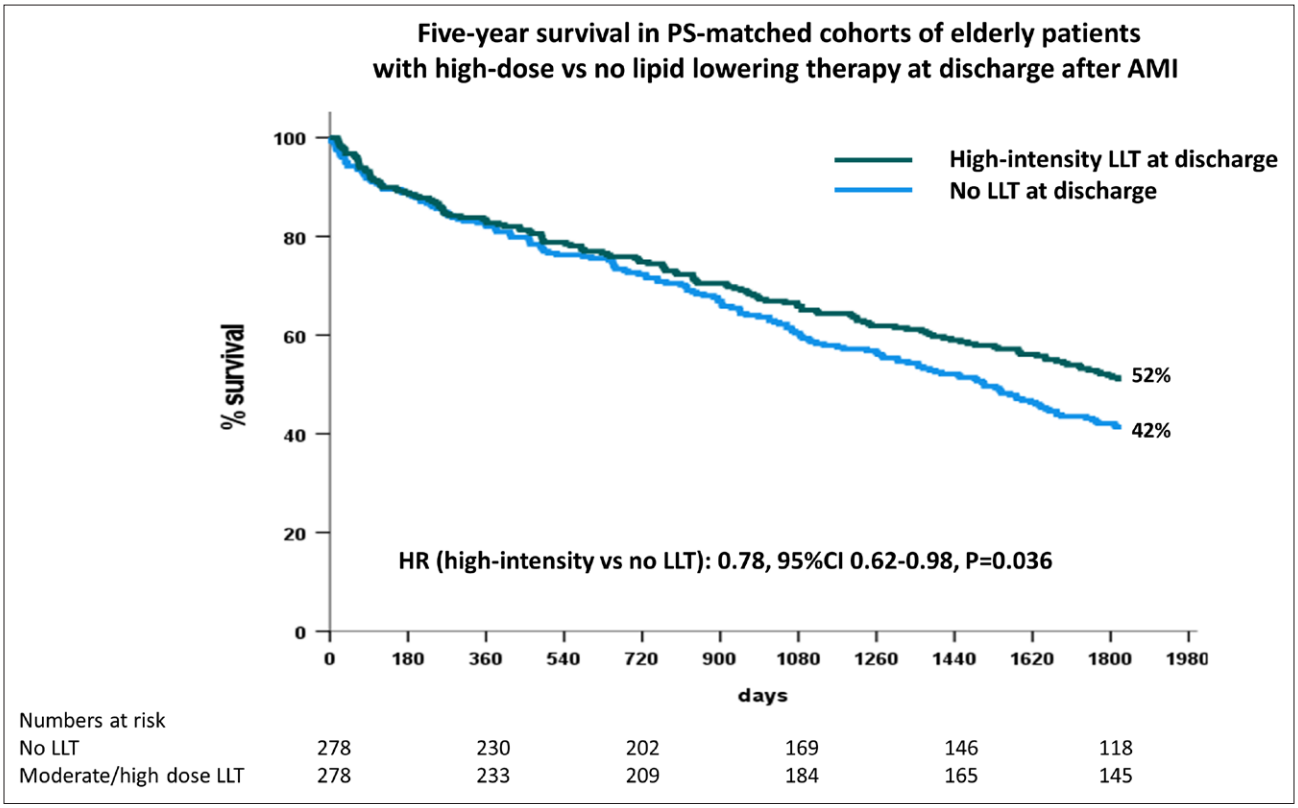

Figure 2. Five-year survival in propensity score-matched cohorts of patients with high-intensity (LLT) at discharge vs no LLT at discharge.
AMI indicates acute myocardial infarction; HR, hazard ratio; and lipid-lowering therapy.

decrease the risk of nonfatal events may be of less relevance when all-cause mortality is high. In the past, this may have explained the lack of documented efficacy of statins in populations with a poor life expectancy, such as those with advanced kidney disease or heart failure.[20–22] Also, using all-cause mortality as an end point avoids the question of competing risk.[23]

The lack of a significant effect of conventional-dose LLT on all-cause mortality is in keeping with the results of the cholesterol treatment trialists meta-analysis.[14] In contrast, the effect of high-intensity LLT appears particularly striking. Of note, the 0.78 HR for death we observed in our post-AMI population was quite similar to the effect observed with alirocumab in patients ≥75 years of age with a recent ACS.[9]

As expected, patients receiving high-intensity LLT markedly differed from those treated with conventional doses and still more from those not receiving LLT. They were younger, more frequently had STEMI, and had less comorbidity, in particular diabetes, heart failure, and atrial fibrillation. Also, women were less likely to receive statins and high-intensity LLT than men. Invasive strategies and PCI were more frequently used at the acute stage, and they received recommended medications such as beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers more often at hospital discharge. This may reflect a more or less conscious bias that frail patients or those with multiple comorbidities might be less likely to benefit from high-intensity LLT and that it is therefore less often prescribed. There was, however, a marked improvement in the use of LLT at discharge: 14% received no LLT at discharge in 2015 versus 29% of the patients in 2005. Of note, the recent European Society of Cardiology guidelines recommend using high-intensity LLT during the index hospitalization, and preferably before PCI,[24] and one might speculate that the use of a specific quality indicator recording the prescription of high-intensity LLT might improve the actual prescription rates.[25]

Multivariable analyses are meant to take into account these differences, both as regards baseline characteristics, AMI complications, and concomitant medications at discharge. Subgroup analyses, such as those undergoing PCI, also give concordant results. It is obvious, however, that unmeasured confounders may have existed and contributed to additional bias in the prescription of LLT. In this regard, the consistent association of high-intensity LLT with improved survival in patients having undergone a PCI, even beyond the age of 85 years, may suggest that the performance of a PCI could represent a surrogate of a more favorable general health status on top of any adjustment with the other covariables used in our Cox models.

In an analysis of a large cohort of MEDICARE patients after ACS, Choudhry et al found no difference in mortality or recurrent ACS according to statin dose. The population average age, however, was 77 years (ie, 8 years younger than our population), and the definition of high doses of statins was quite liberal (eg, >10 mg for atorvastatin or 5 mg for rosuvastatin).[26] No comparison was made with patients receiving no statins. In contrast, Rodriguez et al[27] analyzed the association between statin treatment intensity and all-cause mortality at 16 months in a large cohort of patients from the Veterans Administration with known atherosclerotic cardiovascular disease; they observed a 9% reduction in mortality with high-intensity statins, compared with moderate-intensity statins, in patients aged 76 to 84 years, comparable with what was found in younger patients.

In patients over 85 years of age, there was no association of 5-year death with LLT at conventional doses; the adjusted HR for high-intensity LLT was 0.88 but was not significant. We did a further analysis in patients over the age of 85 years who had undergone PCI: high-intensity LLT was associated with reduced mortality at 5 years in this population (HR, 0.69 [95% CI, 0.48–1.00]; *P*=0.0496). These findings may suggest that the benefit of high-intensity LLT may not be apparent when overall mortality is too high, such as in patients who did not undergo PCI at the acute stage (5-year mortality in these was 68%, whereas it was 49% in those with PCI). These results, however, should be taken with caution: first, the interaction with age was not significant; second, analyzing multiple subgroups increases the risk of a so-called significant association.

The most common side effect in older adults is statin-associated muscular symptoms.[28,29] This class of side effect appears to be dose dependent and age related with more lipophilic statins carrying a higher risk.[30] Moreover, concurrent use of medications with inhibitory potential on cytochrome P450 3A4, such as calcium channel blockers or amiodarone, may increase statin concentrations and the concomitant risk of statin adverse events in older adult populations.[31] Our results therefore seem reassuring as there was no signal of any deleterious impact on survival in this older adult population post-AMI.

Our study has obvious limitations. Beside the aforementioned limitations related to any observational cohorts, we studied the relationship between discharge prescription and 5-year outcome: follow-up prescriptions were not available for all patients. Among those with follow-up prescriptions available (n=885), however, most patients had unchanged prescriptions during follow-up (76% for those with high-intensity LLT, 81% for those with conventional-intensity LLT, and 68% for those without statins at discharge). Also, as the FAST-MI program was not designed specifically for older adult populations, we did not use or record frailty scores. Finally, only 2% of our patients received ezetimibe at discharge, and none were treated with PCSK9 inhibitors. Our results therefore pertain essentially to patients receiving high doses of statins, and determining the role of an ezetimibe-statin combination or of PCSK9 inhibitors in an older adult population remains to be studied. Conversely, the FAST-MI cohorts are extremely well phenotyped, which allows much more precise medical evaluation of the patients than is usual in most administrative databases.

CONCLUSIONS

Our observational study indicates a favorable association between prescription of high-intensity LLT at discharge after AMI and 5-year survival in a truly older adult population (≥80 years, mean age 85 years). Pending specifically designed prospective trials in such very older adult populations, our results suggest that prescription of higher doses of lipid-lowering agents should not be limited on the basis of older age only.

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