Association of adherence and treatment intensity of lipid-lowering therapy with cardiovascular outcomes and all-cause mortality in post-MI patients in Germany

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INTRODUCTION

- Elevated low-density lipoprotein cholesterol (LDL-C) is a major modifiable risk factor for the development of cardiovascular disease (CVD) [1].
- According to ESC guidelines[1], patients with history of myocardial infarction (MI) are at very-high risk of subsequent cardiovascular events (CVE).
- Both intensity and adherence to lipid lowering therapies (LLT) play an important role in effectiveness of these therapies.

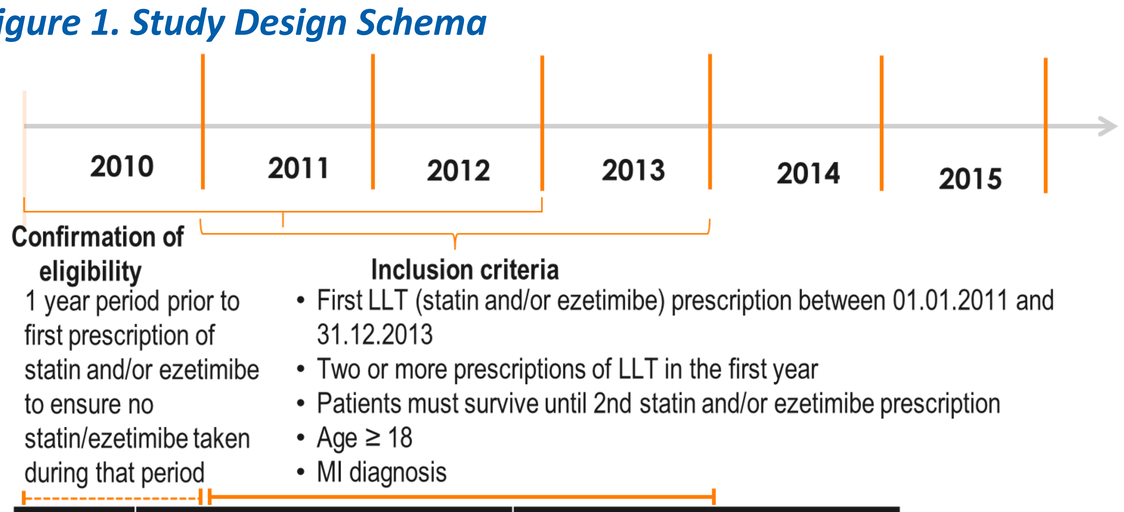
OBJECTIVE

- To evaluate the association of treatment intensity and adherence to LLT with cardiovascular outcomes and all-cause mortality in German patients with history of MI treated with a statin and/or ezetimibe.

METHODS

- Retrospective cohort study used German health claims data (2010-2015) obtained from the research institute InGef (Institut für angewandte Versorgungsforschung Berlin GmbH).
- Inclusion criteria: ≥18 years, on initial LLT (statin and/or ezetimibe) in 2011-2013, diagnosed with an MI. Patients had to have at least 2 LLT prescriptions during the first year of follow-up (Figure 1).
- Follow-up period started 1 year after the second LLT prescription and continued until a hospitalization for an MI, unstable angina, ischemic stroke, heart failure, or revascularization, all-cause death, or the end of follow-up (December 31, 2015), whichever occurred earlier.
- Treatment intensity was categorized using expected LDL-C reduction as described in the American College of Cardiology and American Heart Association (ACC/AHA) 2018 guidelines[2].
- Adherence was measured annually by the proportion of days covered (PDC) using prescription data.
- Adherence and treatment intensity were multiplied to create a combined measure of LLT intensity after accounting for adherence.
- Cox proportional hazards regression models were used to quantify the association of LLT intensity and adherence with the risk of CVE.
  - These models adjusted for age, sex, Charlson comorbidity index, type 2 diabetes, chronic kidney disease, atrial fibrillation, hypertension, and use of antithrombotic medications.
  - Intensity and adherence (separately and as a combined measure) were included as time-varying continuous covariates.
  - Individuals who received no treatment during the entire year were included in the reference group (no LLT) for that year.

Figure 1. Study Design Schema



1. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. European Heart Journal 2019.
2. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology 2018.

RESULTS

Table 1. Baseline characteristics

Patients' baseline characteristics*, N = 14,944	
Age at LLT initiation, mean (SD) years	67 (13)
Sex, n (%) male	10,267 (69%)
Follow-up time, mean (SD) years	2.9 (1.1)
Charlson Comorbidity Index (CCI) , n (%)	
1	4,731 (32%)
2+	10,213 (68%)
Type 2 Diabetes	3,844 (26%)
Chronic Kidney Disease (stage 4 and 5)	497 (3%)
Atrial fibrillation	3,071 (21%)
Hypertension	13,339 (89%)
Use of antithrombotic medications	13,981 (94%)
Initial lipid-lowering therapy, n (%)	
High intensity statin	983 (7%)
Moderate intensity statin	12,906 (86%)
Low intensity statin	666 (4%)
Statin + ezetimibe**	284 (2%)
Ezetimibe alone**	105 (1%)

Note: Laboratory data such as LDL-C levels are not reported in the InGef database

** Therapy with ezetimibe alone was considered low intensity LLT ; therapy with a statin and ezetimibe was considered high-intensity LLT*

Table 2. Treatment intensity and adherence, by year of follow-up

	Index year	Year 1	Year 2	Year 3	Year 4
LLT Intensity					
Low (%)	5%	5%	5%	6%	5%
Moderate (%)	86%	84%	82%	82%	82%
High (%)	9%	11%	13%	12%	13%
Adherence* (%)	67%	62%	63%	64%	69%

Adherence is defined as PDC ≥ 0.8

Table 3. Association of treatment intensity and/or adherence with risk of hospitalization for a cardiovascular event or all-cause death*

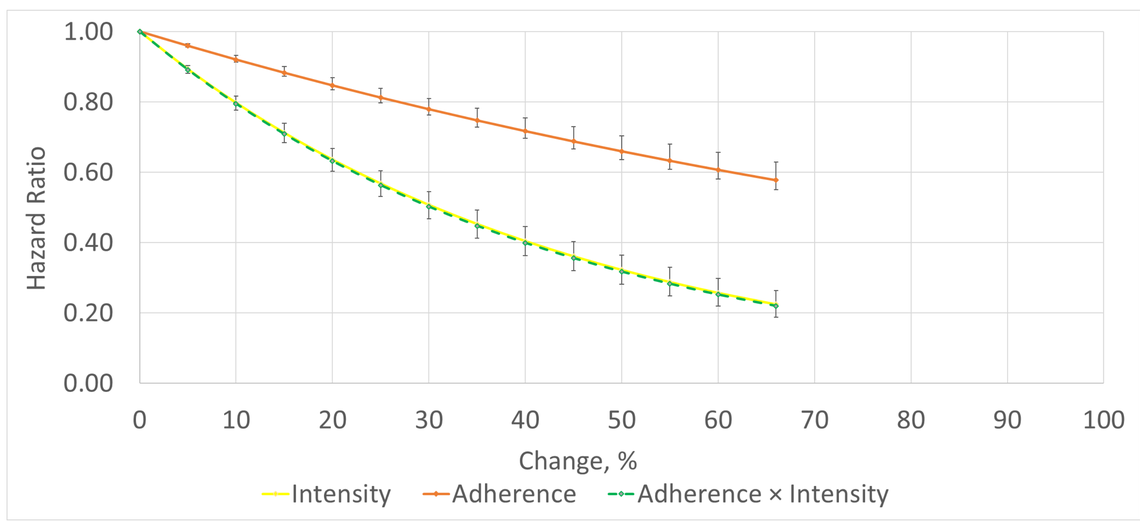
Parameter	Adjusted Hazard Ratio** (95% CI)
Intensity	0.80 (0.78-0.82)
PDC	0.92 (0.91-0.93)
Combined intensity and adherence ***	0.79 (0.78-0.82)

* Estimates are presented per 10% increase in intensity and/or adherence

** *After adjusting for age, sex, CCI score,* type 2 diabetes, chronic kidney disease, atrial fibrillation, hypertension, and use of antithrombotic medications

*** *Reflects the treatment intensity of a regimen after accounting for a patient's adherence (e.g: 10% increase in the combined measure represents 10% increase in intensity adjusted for adherence).*

Figure 2. Association of treatment intensity and/or adherence with risk of hospitalization for a cardiovascular event or all-cause death***



** The error bars represent 95% CI*

*** Treatment intensity range: 0-66%, based on expected percent LDL-C reduction. The combined measure was created by multiplying adherence (range: 0 to 100%) and treatment intensity (range: 0-66%); as a result, the combined measure ranged from 0 to 66% (i.e., 0.66 x 1.0 = 0.66).*

CONCLUSIONS

- In a German cohort of post-MI patients at very high risk of future CVE, only 9% were receiving high intensity LLT (high-intensity statin or a statin + ezetimibe) at baseline.
- Adherence to LLT was lower than 70% for the entire follow-up period.
- Higher LLT intensity and/or adherence were associated with significantly lower risk of cardiovascular outcomes or all-cause death.
- Treatment intensity was a stronger driver of overall effectiveness of LLT in post-MI patients as adherence was relatively stable during follow-up.

DISCLOSURES

This study is funded by Amgen (Europe) GmbH, and conducted independently by Certara. Certara, employer of AK, received consulting fees from Amgen (Europe) GmbH to conduct the study. Elsevier, employer of BM, received consulting fees from Certara to conduct the statistical analysis.

ES is a full time employee at Amgen (Europe) GmbH and owns Amgen stock options. MH was a full time employee at Amgen GmbH at the time of the study. IA received consulting fees from Amgen GmbH.