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ORIGINAL RESEARCH ARTICLE

Treatment Patterns of Lipid-Lowering Therapy in Patients with Coronary Artery Disease Aged Above and Below 75 Years: A Retrospective Cross-Sectional Study of 1500 Patients in a Tertiary Care Referral Center in Germany

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Abstract

Introduction Lipid-lowering therapy of elderly patients with coronary artery disease (CAD) inherits a medical challenge, as these patients experience a higher absolute risk reduction but may be more prone to side effects. We aimed to evaluate the treatment patterns in lipid-lowering therapy, comparing CAD patients above versus below 75 years of age.

Methods We retrospectively included patients with known CAD admitted to the West German Heart and Vascular Center. Low-density lipoprotein cholesterol (LDL-C) levels and intensity of statin therapy (based on dosage and type of statin) were assessed from all available hospital records.

Results We included 1500 patients (mean age 68.4 ± 11.2 years, 75.7% male) from 813 referring treating primary care physicians in 98 cities of Germany in our analysis. A total of 982 patients were < 75 years of age, whereas 518 were ≥ 75 years of age. LDL-C levels did not differ between age groups (≥ 75: 96.0 ± 35.1 mg/dl; < 75: 98.9 ± 35.8 mg/dl, $p = 0.13$). Simvastatin was most frequently prescribed in both age groups (54.9% vs. 50.7% for age ≥ 75 vs. < 75 years, $p = 0.16$), followed by atorvastatin (31.6% vs. 33.3%, $p = 0.53$). Elderly patients received slightly lower statin doses as compared to patients < 75 years of age (28.8 ± 12.8 mg vs. 31.4 ± 13.7 mg, $p = 0.0007$). Interestingly, patients ≥ 75 years of age achieved LDL-C < 70 mg/dl slightly more frequently than younger patients (24.0% vs. 20.1%, $p = 0.09$), while only a minority had LDL-C < 55 mg/dl in both age groups. Excluding patients with myocardial infarction at presentation, creatine kinase levels were not relevantly different between age groups (131.9 ± 450.0 U/l vs. 127.5 ± 111.4 U/l, $p = 0.78$).

Conclusion Patients ≥ 75 years of age receive lower doses of statin therapy and reach slightly lower LDL-C levels. However, the majority of elderly patients miss current recommendations regarding LDL-C thresholds.

1 Introduction

With increasing survival, the proportion of elderly people in the general population continues to grow. However, the elderly carry a disproportionate burden of atherosclerotic cardiovascular disease [1, 2]. Statin therapy for secondary prevention is established for risk reduction in patients with coronary artery disease (CAD) and has proven its benefit also in elderly cohorts [3, 4]. In addition to statin therapy, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors have been introduced within the last decade, lowering both low-density lipoprotein cholesterol (LDL-C) and the incidence of major cardiovascular events in secondary prevention [5, 6]. Available data suggest that given the overall higher absolute event rate in elderly cohorts, these patients show a higher risk reduction and lower number needed to treat [7].

Despite the evidence supporting its clinical benefits, statin treatment is often discontinued for various reasons, such as concomitant disease and perceptions of risk versus benefit [4, 8–10]. However, data on treatment patterns and cholesterol profiles in patients above 75 years of age are lacking. To provide information regarding the effect of aging on selection, dosing, and effects of lipid-lowering drugs,

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Key Points

Lipid-lowering therapy of elderly patients with coronary artery disease (CAD) inherits a medical challenge, as these patients experience higher absolute risk reduction but may be more prone to side effects.

In the present study, we evaluated the treatment patterns in lipid-lowering therapy, comparing CAD patients above and below 75 years of age.

While elderly patients receive lower doses of statin therapy and reach slightly lower low-density lipoprotein cholesterol (LDL-C) levels, the majority of elderly patients miss current recommendations regarding LDL-C thresholds.

we set out to evaluate treatment patterns of lipid-lowering therapy and its success in achieving LDL-C targets in a real-world, cross-sectional cohort of patients with manifest CAD, comparing those above and below 75 years of age.

2 Methods

2.1 Study Cohort

We retrospectively enrolled patients ≥ 18 years old with known CAD (diagnosis at least 30 days prior to presentation) who received assessment of cholesterol levels and medication for clinical indications in the years between 2009 and 2016. Patients had to be on stable medical therapy for at least 30 days, including stable lipid-lowering therapy. Patients were randomly selected from hospital admissions and included both elective and emergency admissions at the West German Heart and Vascular Center, Essen. Of these patients, 24.1% were hospitalized due to an acute coronary syndrome (ACS), 37.4% due to stable CAD, and 38.5% due to a non-coronary reason. Patients at each time point were not identical. Patients with low-density lipoprotein (LDL) apheresis, end-stage renal disease, familial hypercholesterolemia, and prior medical documentation of statin intolerance were excluded from the analysis. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's human research committee (17-7458-BO).

2.2 Risk Factors and Clinical Diagnosis

Presence of known CAD manifestation was assessed from all available hospital records and defined as previous revascularization therapy, at least 30 days prior to the present admission. Cholesterol levels, demographic characteristics, cardiovascular risk factors, and medical therapy were assessed from available patient records. Statin therapy was categorized as low, moderate, and high intensity according to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) definitions [3]. Serum LDL-C levels were categorized as meeting or missing European Society of Cardiology (ESC) guidelines according to recommendations at different time points (< 100 mg/dl for 2008, < 70 mg/dl for 2012, and < 55 mg/dl for 2019 [11–13].

2.3 Statistical Analysis

The baseline characteristics are presented as mean ± standard deviation for continuous variables and as frequencies and percentages for categorical variables and are stratified by age group. A two-sided *t* test was used for normally distributed continuous variables, Wilcoxon rank-sum tests were used for non-normally distributed continuous variables, and Fisher's exact test or Chi-squared test were used for categorical variables for comparisons of baseline characteristics at first versus last time points. The frequencies of patients according to LDL-C groups and statin intensity are stratified by age group. Difference in frequency of accordance to ESC recommendations and time points were compared using Fisher's exact test, comparing the first to the last period. All analyses were performed using SAS software (version 9.2, SAS Institute Inc.). A p value of < 0.05 indicated statistical significance.

3 Results

3.1 Baseline Characteristics

A total of 1500 patients (mean age 68.4 ± 11.2 years, 75.7% male) from 813 referring primary care physicians in 98 cities of Germany were included in our analysis. Overall, 982 patients were < 75 years of age, whereas 518 were ≥ 75 years of age. Patient characteristics, stratified by age group, are shown in Table 1. Elderly patients were more likely to be hospitalized due to a non-coronary reason (47.5% vs. 33.8%, for patients ≥ 75 vs. < 75 years of age, respectively, $p < 0.001$), followed by stable CAD (32.6% vs. 39.9%, $p < 0.001$). Older patients were less likely male (68.0% vs. 79.8%, $p < 0.0001$) and had a lower body mass index (BMI) (26.8 kg/m^2 vs. 28.4 kg/m^2, $p < 0.0001$), and were less likely to be current smokers (7.3% vs. 18.8%, $p < 0.0001$, for patients ≥ 75 vs. < 75 years of age, respectively). The rate of hypertension (95.6% vs. 95.2%, $p = 0.03$) and the rate of diabetes (38.2% vs. 32.5%, $p = 0.02$) were high in both age groups, but slightly higher in elderly patients.

3.2 Lipid Profile in Patients ≥ 75 Versus < 75 Years of Age

LDL-C levels were not significantly different between age groups (≥ 75 years: 96.0 ± 35.1 mg/dl; < 75 years: 98.9 ± 35.8 mg/dl, $p = 0.13$). In contrast, elderly patients had higher HDL-cholesterol levels (49.9 ± 15.0 mg/dl vs. 46.8 ± 15.2, $p = 0.0002$) and markedly lower triglycerides (135.6 ± 89.9 mg/dl vs. 171.4 ± 124.6 mg/dl, $p < 0.0001$).

When evaluating achievement rates of LDL-C targets as set by ESC guidelines, we observed that 7.6% of the cohort had LDL-C < 55 mg/dl (2019 guidelines), 21.5% had LDL-cholesterol < 70 mg/dl (2012 guidelines), and 57.1% had LDL-C < 100 mg/dl (2008 guidelines). Interestingly, elderly patients more frequently reached the LDL-C threshold of < 55 mg/dl as recommended by current ESC guidelines (9.7% vs. 7.0% for ≥ 75 vs. < 75 years of age, $p = 0.03$). In contrast, there was a non-significant difference in achieving LDL-C goals as defined by 2012 ESC guidelines when comparing both age groups, and no relevant difference with regard to LDL-C < 100 as the threshold (Fig. 1). Patients hospitalized due to an ACS had significantly higher LDL-C levels as compared to patients without ACS at presentation (ACS: 103.5 ± 38.7 mg/dl, non-ACS 96.1 ± 34.3 mg/dl, $p = 0.001$). This effect was present for patients < 75 years of age (ACS: 106.9 ± 38.1 mg/dl, non-ACS 96.0 ± 34.5 mg/dl, $p < 0.0001$), but not for elderly patients (ACS: 95.2 ± 39.2 mg/dl, non-ACS 96.2 ± 34.1 mg/dl, $p = 0.8$).

3.3 Trend in Statin Use and Dose in Elderly

The most common statin used was simvastatin in both age groups (50.7% vs. 54.9% for age ≥ 75 vs. < 75 years, $p = 0.16$), followed by atorvastatin (33.3% vs. 31.6%,

Table 1 Study sample characteristics

	All patients ($n = 1500$)	≥ 75 ($n = 518$)	< 75 ($n = 982$)	p value
Age, years	68.4 ± 11.2	79.8 ± 3.9	62.4 ± 8.8	< 0.0001
BMI (kg/m^2)	27.9 ± 4.9	26.8 ± 4.3	28.4 ± 5.0	< 0.0001
Sex, *n* (% male)	1136 (75.7)	352 (68.0)	784 (79.8)	< 0.0001
Total cholesterol (mg/dl)	170.0 ± 45.3	167.1 ± 41.6	171.5 ± 47.1	0.06
HDL-cholesterol (mg/dl)	47.8 ± 15.2	49.9 ± 15.0	46.8 ± 15.2	0.0002
LDL-cholesterol (mg/dl)	97.9 ± 35.6	96.0 ± 35.1	98.9 ± 35.8	0.13
Triglyceride (mg/dl)	159.0 ± 115.1	135.6 ± 89.9	171.4 ± 124.6	< 0.0001
hs-CRP	0.36 ± 1.0	0.45 ± 1.2	0.32 ± 0.86	0.1
BNP	224.3 ± 427.8	295.3 ± 527.4	186.7 ± 359.0	< 0.0001
GFR	58.4 ± 17.8	53.4 ± 17.0	61.0 ± 17.7	< 0.0001
Statins, *n* (%)	1332 (88.8)	438 (84.6)	894 (91.0)	0.0002
Non-statin, *n* (%)	60 (4.0)	44 (4.5)	16 (1.6)	0.34
Hypertension, *n* (%)	1430 (95.3)	495 (95.6)	935 (9)	0.03
Diabetes, *n* (%)	517 (34.5)	198 (38.2)	319 (32.5)	0.02
Family history of premature CHD, *n* (%)	461 (34.5)	114 (27.8)	347 (35.3)	< 0.0001
Smoking, *n* (%)				< 0.0001
Current	223 (14.9)	38 (7.3)	185 (18.8)	
Former	441 (29.4)	126 (24.3)	315 (32.1)	
Hospitalization reason, *n* (%)				< 0.0001
Non-coronary	578 (38.5)	246 (47.5)	332 (33.8)	
Stable CAD	561 (37.4)	169 (32.6)	392 (39.9)	
Unstable CAD	268 (17.9)	74 (14.3)	194 (19.8)	
NSTEMI	78 (5.2)	23 (4.4)	55 (5.6)	
STEMI	15 (1.0)	6 (1.2)	9 (0.9)	
Previous CABG, *n* (%)	522 (34.8)	210 (40.5)	312 (31.8)	0.0005
Previous STEMI, *n* (%)	399 (26.6)	113 (21.8)	286 (29.1)	0.003

Data are presented as mean and standard deviation for continuous variables and as frequency and percentages for categorical variables

BMI body mass index, *BNP* brain natriuretic peptide test, *CABG* coronary artery bypass graft, *CAD* coronary artery disease, *CHD* coronary heart disease, *GFR* glomerular filtration rate, *HDL* high-density lipoprotein, *hs-CRP* high-sensitivity C-reactive protein, *LDL* low-density lipoprotein, *NSTEMI* non-ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction

$p = 0.53$) and rosuvastatin (1.7% vs. 6.1%, $p = 0.0002$, Fig. 2a). In contrast, non-statin lipid-lowering therapy was infrequently used for both age groups (4.5% vs. 1.6%, $p = 0.21$). Elderly patients received significantly lower doses of statins (28.8 ± 12.8 mg vs. 31.4 ± 13.7 mg, $p = 0.0007$, Fig. 2b). Figure 3 depicts the frequency of no statin and low-, medium-, and high-intensity statin therapy in 2009–2010, 2012–2013, and 2015–2016, stratified by age group. While in 2009–2010, treatment regimens between patients < 75 and ≥ 75 years of age did not significantly differ, a progressive trend towards less-intensive treatment protocols in the elderly was observed at later time points. This was especially prominent in the group of coronary heart disease patients receiving no statin therapy, which reached one out of five patients ≥ 75 years of age in 2015–2016.

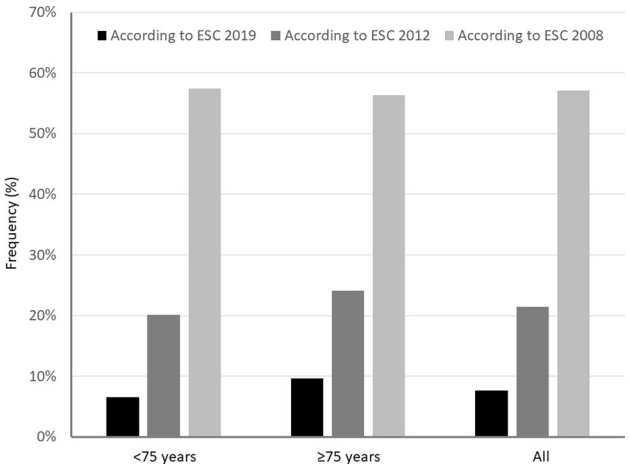

Fig. 1 Achievement of LDL-C targets according to 2019 (LDL-C < 55 mg/dl), 2012 (LDL-C < 70 mg/dl), and 2008 (LDL < 100 mg/dl) ESC guidelines, stratified by age ≥ 75 vs. < 75 years. *ESC* European Society of Cardiology, *LDL-C* low-density lipoprotein cholesterol

3.4 Creatine Kinase and High-Sensitivity C-Reactive Protein Levels Under Statin Therapy

Excluding patients with myocardial infarction at presentation, creatine kinase levels were not relevantly different between age groups (131.9 ± 450.0 U/l vs. 127.5 ± 111.4 U/l, $p = 0.78$). Likewise, excluding patients with signs of systemic inflammation, high-sensitivity C-reactive protein levels did not differ when comparing patients ≥ 75 and < 75 years of age (0.15 ± 0.12 mg/dl vs. 0.14 ± 0.12 mg/dl, $p = 0.33$).

4 Discussion

Evaluating lipid-lowering treatment in a large real-world registry with 1500 patients from 813 primary care physicians in 98 German cities, we observed that patients ≥ 75 years of age receive lower doses of statin therapy and reached slightly lower LDL-C levels. The majority of patients with known CAD miss current recommendations regarding LDL-C thresholds. But despite lower treatment intensity, elderly patients more frequently reached the strict goals regarding LDL-C as defined by current ESC guidelines. However, as a trend over time, we observed an increase in high-intensity statin therapy also in the elderly group. Interestingly, in this observational cross-sectional analysis, we observed no signs of a higher frequency of statin-induced myopathy in the elderly. While the frequency of patients without statin therapy was higher in the elderly group, we cannot rule out that therapy was discontinued due to potential statin-induced adverse events.

In 2011, the ESC guidelines changed the treatment goals for LDL-C for patients with CAD manifestation. In the present analysis, we investigated how this recommendation impacted LDL-C levels 1–2 years (2012–2013)

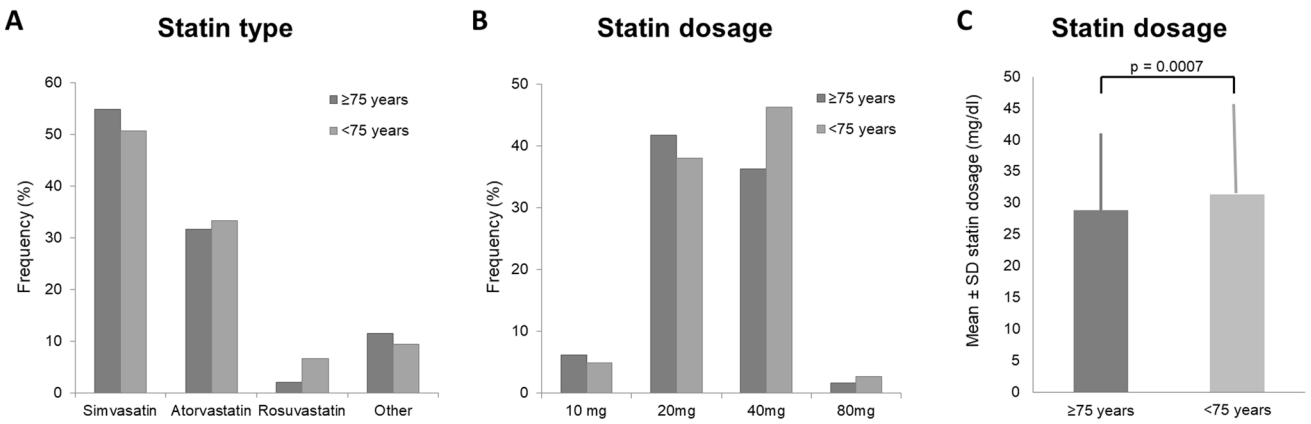

Fig. 2 Frequency of type of statin (**a**) and statin dosage (**b**), as well as mean statin dosage (± SD) (**c**) in patients with known CAD, stratified by age ≥ 75 vs. < 75 years. *CAD* coronary artery disease, *SD* standard deviation

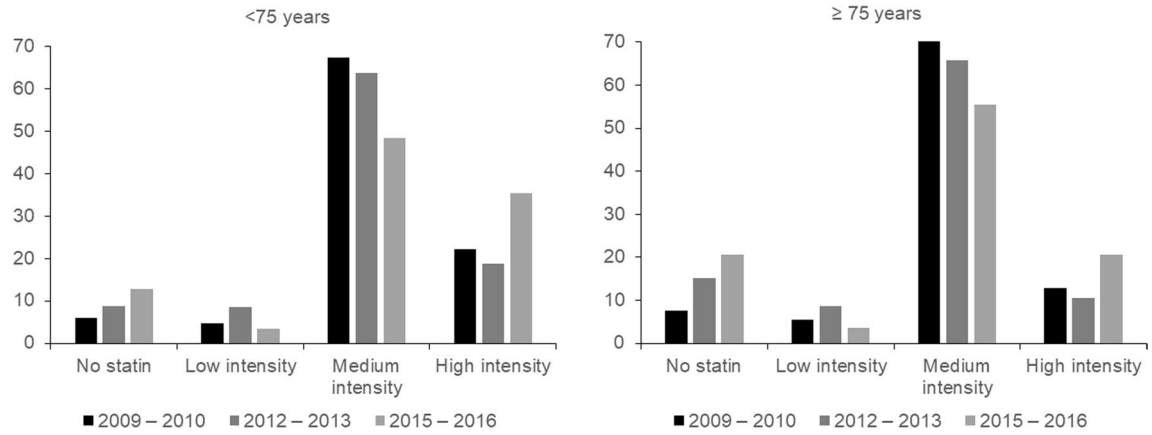

Fig. 3 Frequency (%) of low-, medium-, and high-intensity statin therapy in patients < 75 vs. ≥ 75 years of age, stratified by time point of assessment according to the 2013 ACC/AHA definition [3]. *ACC/AHA* American College of Cardiology/American Heart Association

as well as 4–5 years (2015–2016) later, as compared to LDL-C levels before the change in LDL-C goals (2009–2010). Our finding of a poor achievement in current treatment goals is in accordance with existing literature for other European cohorts, demonstrating that also in very high-risk cohorts, median LDL-C levels of > 70 mg/dl or even > 100 mg/dl frequently occur [14–16]. This finding was also reflected in the USA, where a trend analysis in the use of statins for secondary prevention showed nearly flat trends among the patients with a history of atherosclerotic cardiovascular disease during the 3 years that followed the publication of the 2013 ACC/AHA guideline. However, in this analysis, the age groups with the highest odds of statin use were 76- to 79-year-olds and 65- to 69-year-olds [17]. Also, in a Chinese population-based community analysis, the SHECHS study showed poor control of high cholesterol levels in older individuals with established cardiovascular disease using mostly low doses of statins, and a high proportion of these subjects did not achieve the LDL-C target level [18]. All these studies underline the unmet need of successful lipid control in this high-risk population.

Overall, there has been intensified debate on the use of statins in the older population, related to concerns about adding another medication, consideration of nonadherence, and discussion of metabolic (diabetes mellitus) and musculoskeletal (myalgia, myositis, and the very rare rhabdomyolysis) issues, medication interactions, major organ effects (liver and kidney), and memory concerns [19]. In contrast, due to the higher absolute risk in elderly cohorts, the absolute risk reduction of preventive strategies is higher in this age group [6, 7, 20, 21]. Likewise, individual randomized trials and meta-analysis of statin therapy have reported significant cardiovascular risk reductions among elderly participants using statins as well as non-statin lipid-lowering therapy [10, 11, 22–26].

A recently published meta-analysis of 28 randomized controlled trials by the Cholesterol Treatment Trialists' Collaboration focused on age-dependent effects of statin therapy and included 14,483 (8%) of 186,854 participants older than 75 years at randomization, with a median follow-up duration of 4.9 years. The authors observed a significant reduction in major vascular events in all age groups; although proportional reductions in major vascular events diminished slightly with age, this trend was not statistically significant. There is less definitive direct evidence of benefit in the primary prevention setting among patients older than 75 years, but evidence supports the use of statin therapy in older people considered to have a sufficiently high risk of occlusive vascular events [19].

A meta-analysis from more than 3 million older statin users in 82 studies in over 40 countries showed that adherence was worse among individuals aged more than 75 years than those aged 65–75 years [27]. However, the proportion of secondary prevention subjects who were adherent at follow-up was higher compared to primary prevention subjects. Our analysis suggests that despite overall less-intensive lipid-lowering therapy regimes, elderly patients achieve comparable or even slightly better LDL-C levels than the younger cohort. This suggests that with utilization of available therapy opportunities, reaching treatment goals for LDL-C may be possible in the elderly, also with respect to the 2019 update of the dyslipidemia guidelines by the ESC, suggesting an LDL-C threshold of < 55 mg/dl for patients with CAD. Due to the limited availability of ezetimibe in the early phases of our analysis and patent protection of rosuvastatin (associated with high costs), the use of these drugs may be underestimated in our analysis. In contrast, with the current availability of generic versions of high-potency statins, including atorvastatin and rosuvastatin, more elderly patients may actually achieve desired LDL-C levels. New lipid-lowering agents, changes in pricing policy,

and omission of patent protection will lead to a broader use of more potent statin therapy and other agents for intensified lipid-lowering therapy, which will allow for tailored therapy based on the individual's risk profile.

4.1 Limitations

The limitations of our study include its retrospective study design with no information regarding previous changes to the lipid-lowering therapy of the patients. Given the retrospective design, assessing cross-sectional patient data, no information on follow-up is available. Moreover, as per the study design, we were not able to properly assess any potential side effects of statin therapy, which may have limited its use in individual patients. Further, due to the loss of patent protection for highly potent statins, including atorvastatin and rosuvastatin, changes in prescription patterns may have impacted therapy after 2016. In addition, the same patients were not evaluated over all three time points. However, long-term follow-up of identical patients would have led to a more pronounced change in patient's age over time, ultimately leading to a decrease in the generalizability of the follow-up cohorts. As admission criteria varied by referring hospital or primary care physician, this may have led to a selection bias from some institutions. However, given the high number of referring physicians and the low number of patients per referring physician in our analysis, this may not have relevantly affected our results. Lastly, our study is based on a predominantly Caucasian cohort; hence, its validity in other cohorts and ethnic groups remains uncertain.

5 Conclusions

Evaluating lipid-lowering treatment patterns in a large clinical cohort of patients with known CAD, we observed that patients ≥ 75 years of age receive lower doses of statin therapy, but reached slightly lower LDL-C levels. However, the majority of elderly patients miss current recommendations regarding LDL-C thresholds. Interestingly, no signs of a higher frequency of statin-induced myopathy in the elderly were observed in our analysis.

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Author contributions All authors contributed to the study concept and design. Material preparation and data collection and analysis were performed by ID and DW. The first draft of the manuscript was written by ID, and all authors commented on all versions of the manuscript. All authors read and approved the final manuscript. All authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Compliance with ethical standards

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Conflict of interest The authors, Iryna Dykun, Daniela Wiefhoff, Matthias Totzeck, Fadi Al-Rashid, R. Alexander Jánosi, Stefanie Hendricks, Tienush Rassaf, and Amir A. Mahabadi, declare that they have no conflict of interest.

Availability of data and material The datasets generated during and/or analyzed during the current study are not publicly available due to institutional restrictions, but are available from the corresponding author on reasonable request.

Code availability Not applicable.

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