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Utilization of lipid-modifying therapy and low-density lipoprotein cholesterol goal attainment in patients at high and very-high cardiovascular risk: Real-world evidence from Germany

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ABSTRACT

Background and aims: Elevated low-density lipoprotein cholesterol (LDL-C) is a causal risk factor for cardiovascular (CV) events. European guidelines recommend reducing LDL-C as the primary lipid target to reduce CV risk, using lifestyle modifications and lipid-lowering therapy (LLT). Many European patients do not achieve guideline-recommended LDL-C levels. The present database analysis aimed to assess LLT treatment patterns and LDL-C threshold attainment in Germany in a large, real-world cohort of patients.

Methods: Patients from the Cegedim Longitudinal Practice Database in Germany who met selection criteria were included: (a) LDL-C measurement in 2013; (b) ≥20 years of age; (c) high or very-high CV risk conditions: recent acute coronary syndrome (ACS), other coronary heart disease (CHD), ischemic stroke, peripheral arterial disease (PAD) (atherosclerotic cardiovascular disease [ASCVD]) or diabetes mellitus (DM) (non-ASCVD). LDL-C threshold attainment was assessed based on LDL-C targets from 2011 European guidelines.

Results: 42,767 patients met the inclusion criteria; 35% received current statin treatment, and 30% achieved guideline-recommended LDL-C targets. Attainment of LDL-C goals among ASCVD hierarchical categories was 46.7% for recent ACS, 35.8% for ischemic stroke, 34.9% for other CHD, and 26.9% for PAD. Among patients in the non-ASCVD group with DM, 23.6% achieved LDL-C goals. Similar results were observed when patients were grouped by prevalence (patients assigned to every risk group for which they qualified).

Conclusions: In this high/very-high CV risk population in Germany, statin utilization was low; suggesting that LLTs are not prescribed as per European guidelines. These results highlight the need to increase LLT use among high-risk patients.

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1. Introduction

Despite substantial decreases in cardiovascular (CV) disease (CVD) death rates since 2003, CVD remains the main cause of death in Europe, accounting for 31.5% of overall deaths [1]. In Germany, CVD accounts for approximately 40% of deaths [2], or 148,538 deaths per year [3]. In 2014, the age-standardized death rates for coronary heart disease (CHD) in Germany were 204.1 per 100,000 for men and 111.2 per 100,000 for women. Decreasing low-density lipoprotein cholesterol (LDL-C) with statins has been shown to reduce all-cause and CV mortality.
among patients with atherosclerotic CV disease (ASCVD), and without ASCVD, including those with diabetes mellitus (DM) [4–9]. A meta-analysis conducted by the Cholesterol Treatment Trialsists’ (CTT) Collaboration demonstrated that for each 1 mmol/L (38.7 mg/dL) reduction in LDL-C, a 22% relative reduction in major CV events over a wide range of starting LDL-C levels was achieved [6,7].

Despite the safety and tolerability of statins being well established [6], appropriate statin use and LDL-C reduction may remain suboptimal within clinical practice in Europe. A study in the Netherlands found that lipid-lowering therapy (LLT) was used in 67% of patients at high CV risk, and overall, 55% of patients achieved an LDL-C goal <2.6 mmol/L (<100 mg/dL) [10]. Similarly, among > 180,000 high CV risk patients in the UK in 2014, 79% and 62% of ASCVD and non-ASCVD received statins, but only 31% and 26%, respectively, reached the LDL-C goal of <1.8 mmol/L (70 mg/dL) [11]. In Germany, the proportions of patients with CVD achieving risk-based LDL-C goals with statins has ranged from 14% to 27% [12,13], and the proportion of German patients with CHD receiving lipid-lowering therapy has been reported to be less than 35% [14].

In Germany, lipid treatment targets are aligned with the European guidelines (European Atherosclerosis Society (EAS) and European Society of Cardiology (ESC)) [15–18], whereby LDL-C targets are based on the patient’s CV risk. When data extraction for the present study was conducted, the 2011 EAS/ESC guidelines were in place, which recommended LDL-C as the primary lipid target to reduce CV risk [15]. When the guidelines were updated in 2016, the strategy to reduce CV risk remained unchanged [4,18]. To reduce LDL-C levels, a combination of lifestyle modifications and LLT, including statins and non–statin therapies, was advised within the 2011 EAS/ESC guidelines; however, statins were recommended as first-line pharmacological treatment of hypercholesterolemia [15]. The 2011 guidelines recommended that patients with very high CV risk (defined as having CVD, including previous myocardial infarction [MI], acute coronary syndrome [ACS], coronary vasoconstriction, coronary artery bypass surgery and other arterial revascularization procedures, stroke and peripheral artery disease [PAD]; type 1 or 2 DM with target organ damage; severe chronic kidney disease [CKD]; or a calculated SCORE [Systemic Coronary Risk Estimation] ≥10% for 10-year risk of fatal CVD) should achieve an LDL-C treatment goal of <1.8 mmol/L (<70 mg/dL) and/or a ≥50% reduction from baseline LDL-C. For patients designated to have high CV risk (defined as having markedly elevated single risk factors, including familial dyslipidemias and severe hypertension; type I or II DM, but without CV risk factors or target organ damage; moderate CKD; or a calculated SCORE of ≥5% and <10% for 10-year risk of fatal CVD), an LDL-C treatment goal of <2.6 mmol/L (<100 mg/dL) was recommended [15].

The present database analysis assessed LLT treatment patterns and LDL-C goal attainment relative to the EAS/ESC 2011 guidelines within a general practice setting in Germany in 2013. In a large cohort of patients with established CVD and/or DM, we assessed real-world LLT usage overall, and among patients with ASCVD stratified by CV conditions (recent ACS, CHD, ischemic stroke, and PAD), and non-ASCVD patients with DM. This study provides critical updates to extend literature documenting that in Germany, as well as more broadly, many patients do not achieve the guideline-recommended LDL-C goals, even with long-term LLT use. We contribute to this literature by providing estimates of LLT usage and lipid goal attainment in Germany.

2. Materials and methods

2.1. Database and cohort selection

A retrospective, observational, cross-sectional database analysis of German patients at high or very-high CV risk was conducted using data from the Cegedim Longitudinal Patient Database (LPD). The database consisted of anonymized electronic medical records (EMR) of 600,813 patients in Germany from office-based practices of approximately 500 German general practitioners (GPs), from January 1, 2011 through December 31, 2013. The general practice database is a large primary care database of GPs, consisting of anonymized patient-level medical, prescription, sociodemographic and laboratory results data and hospitalizations details. The study was conducted in accordance with applicable laws and regulations in Germany, and guidelines for the performance and evaluation of secondary data were considered [19]. Since the study was a retrospective analysis, there was no requirement to obtain specific Ethics Committee approval.

The following inclusion criteria were used: (a) presence of ≥1 lipid profile in 2013 (the last LDL-C measurement in 2013 was considered the index date); (b) ≥20 years of age as of the index date; and (c) evidence of at least one high or very-high CV risk condition at baseline, for which statins would be recommended as per the EAS/ESC 2011 guidelines. At least 2 years of continuous representation in the database prior to the index date (defined as the baseline period) were required to examine prior statin use.

2.2. Determination of ASCVD and non-ASCVD categories

Using the EAS/ESC 2011 guidelines as guidance, five high/very-high CV risk mutually exclusive groups were defined in the baseline period, in the following decreasing order of relative importance: (a) recent ACS (MI or unstable angina requiring hospitalization within the 12 months before the index date); (b) other CHD (history of MI or unstable angina >12 months prior to the index date and within the baseline period, stable angina, coronary revascularization, or other chronic ischemic heart disease); (c) ischemic stroke (a history of ischemic stroke); (d) PAD (peripheral vascular disease from non-coronary atherosclerotic disease, abdominal aortic aneurysm, and carotid artery stenosis; and (e) DM (type I and type II DM). High/very-high CV risk groups were identified per the International Classification of Diseases, Tenth Revision (ICD–10) diagnosis or procedure codes (Supplementary Table 1).

Patients were also categorized by overlapping prevalent conditions, in which each patient was placed in every disease profile for which they qualified. For example, a patient with evidence of both ischemic stroke and a prior PAD diagnosis would be categorized into the ischemic stroke and PAD groups. Patients with recent ACS, other CHD, ischemic stroke, and PAD were collectively referred to as ‘ASCVD’, while patients with DM without ASCVD were referred to as non-ASCVD, and are presented separately. Per EAS/ESC definitions, ASCVD patients were all considered very-high risk, while DM patients could have been high or very-high risk, depending on the presence of additional risk factors.

2.3. Determination of LLT treatment

Current LLT treatment was assumed if, for a recorded prescription of any days' supply, there was evidence of medication coverage on or within 30 days before the index date. These patients were designated as “currently treated” with LLT (Supplementary Fig. 1).
Patients with evidence of a prescription for LLT over 30 days before the index date but not “currently treated” were considered to have a history of LLT treatment. Patients with no evidence of a prescription for LLT on the index date or during the 2 years before the index date were considered to have no evidence of LLT treatment.

LLTs included in the any LLT category were: statins, ezetimibe, fibrates (gemfibrozil, fenofibrate, fenofibric acid, ciprofibrate and bezafibrate), bile acid sequestrants (cholestyramine, colesvelam and colestipol) and niacin (nicotinic acid). The any LLT group was further divided into statin or non-statin LLT.

Statin use was grouped per a) overall statin therapy, b) high-intensity statin therapy and c) low-to-moderate intensity statin therapy, all either alone or in combination with other non-statin LLT. High- and low-to-moderate intensity was defined in accordance with US American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, as EAS/ESC guidelines do not define intensity [5]). High-intensity statin therapy included atorvastatin 40 and 80 mg, rosuvastatin 20 and 40 mg and simvastatin 80 mg daily. Low-to-moderate intensity statin therapy included all other statin types and doses.

2.4. Achievement of LDL-C thresholds on the index date

For ASCVD patients, we assessed the LDL-C threshold achievement as defined in the EAS/ESC guidelines as per the target for very-high CV risk (<1.8 mmol/L [<70 mg/dL]). We also assessed achievement of the threshold for high-risk (1.8 to <2.6 mmol/L [70 to <100 mg/dL]) to determine whether ASCVD patients who did not reach their risk-based threshold could achieve this less stringent target. As DM patients without ASCVD could be considered high or very-high risk, depending on the presence of additional risk factors, we assessed the proportions of DM patients without ASCVD who reached both thresholds.

The current LLT and LDL-C values were assessed concurrently (i.e., overlapping with or on the index date), to ensure that lipid levels best reflected the impact of the current treatment regimen.

2.5. Statistical analysis

All statistical analyses conducted for this study were descriptive in nature. Demographic, clinical, and medication characteristics, LLT utilization, and achieved lipid levels were summarized using proportions or mean ± standard deviation (SD) per the character of the variable (categorical or continuous). All analyses were conducted with SAS® software V.9.4.

3. Results

3.1. Patient demographics and clinical characteristics

From 600,813 patients living in Germany, who were represented in the database, 42,767 patients met the inclusion criteria and were included in the sample (Supplementary Fig. 2). The mean age was 69.3 years (SD 11.9), and 52.9% were male (Table 1). Sixty percent of patients had evidence of ASCVD, and per hierarchical disease categorization, 1% had recent ACS, 48% had other CHD, 3% had a history of ischemic stroke, and 8% had PAD. Forty percent of patients had DM without ASCVD. Baseline characteristics of the ASCVD and non-ASCVD groups by prevalent categorization are presented in Supplementary Table 2.

1 Withdrawn from German market in January 2013.
26.4%) (Fig. 4B).

Among patients not on LLT, when the disease states were defined hierarchically, the highest levels of achievement of both goals (<1.8 mmol/L [<70 mg/dL] and 1.8 to <2.6 mmol/L [70 to <100 mg/dL]) were observed in patients with recent ACS (2.7% and 23.1%), followed by ischemic stroke (2.5% and 16.2%), and PAD (3.3% and 14.4%), and were lowest among other CHD patients (3.3% and 13.8%) (Fig. 4C).

### 3.3. DM (non-ASCVD population)

Among non-ASCVD patients with DM, the mean (SD) LDL-C was 3.3 (1.0) mmol/L (127.4 mg/dL).

When defined hierarchically, the proportion of patients with DM achieving target LDL-C thresholds (<1.8 mmol/L [<70 mg/dL] and 1.8–2.6 mmol/L [70–100 mg/dL]) were 5.1% and 18.5%, respectively (Fig. 4A) (i.e. 23.6% < 2.6 mmol/L [<100 mg/dL]). When defined by prevalence, the proportion of patients with DM achieving the target LDL-C thresholds were 7.6% and 22.4% (Fig. 4B). The proportions of DM patients not on LLT achieving LDL-C thresholds were 15.0% and 3.3% (Fig. 4C).

### 4. Discussion

In this study, despite patients being at high or very-high risk of CV events, only 35% received statins, and most statin-treated patients (32.2%) were receiving low-to-moderate intensity statin. Additionally, LDL-C threshold attainment in the overall cohort of German patients with established ASCVD and/or DM was low, with only 7.2% reaching <1.8 mmol/L (70 mg/dL) and 22.8% reaching 1.8 to <2.6 mmol/L (70 to <100 mg/dL).
The use of statins is consistently recommended globally, including in Germany, for reducing LDL-C levels, as well as preventing CV events and ASCVD development. The 2011 EAS/ECS guidelines, which were effective at the time of the current investigation, recommended that patients at high CV risk should receive LLT to reach target LDL-C levels <2.6 mmol/L (<100 mg/dL), whereas patients at very-high CV risk should receive LLT to reach target LDL-C levels <1.8 mmol/L (<70 mg/dL) and/or ≥50% reduction from baseline LDL-C levels [15]. Contrary to the 2011 EAS/ESC guidelines recommendations, a high percentage of German
Fig. 4. Achievement of LDL-C thresholds in the overall cohort.
(A) By hierarchical CV risk group on the index date. * (B) By prevalent classification of CV risk categories* on index date. (C) Achievement of LDL-C goals among patients not on lipid-lowering therapy by hierarchical CV risk group on index date. *Regardless of therapy received. ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease.
patients in the overall cohort were not currently receiving any LLT (63.7%), despite being at high or very high CV risk. Among patients with ASCVD, 43.6% were currently prescribed statin treatment; 39.8% received low-to-moderate intensity statins, and 3.8% received high-intensity statins. Percentages were lower in the non-ASCVD group, with 21.9% prescribed statin treatment, of which 20.6% received low-to-moderate intensity statins, and 1.3% received high-intensity statins. The results of our study suggest that many German patients in need of LDL-C-lowering are not receiving statin LLT, and that there is considerable discordance between clinical practice in 2013 in Germany and the 2011 EAS/ESC guidelines that were in effect at the time of this study [15]. It is well established that a reduction in LDL-C levels among high and very-high risk patients can significantly reduce the risk of CV events [6]. Therefore, closely implementing the guidelines represents best practice, and would ultimately reduce the risk of CV events.

Despite the discordance with the 2011 EAS/ESC guidelines, our results are similar to those observed in other studies [10,11,20]. An analysis from the DYYSIS study comparing LDL-C goal achievement in patients enrolled in Germany versus patients in the UK found that patients in Germany received high-intensity statins less often than UK patients. Additionally, the daily dosages of statins used in Germany were significantly lower than in the UK, resulting in significantly fewer patients in Germany attaining the recommended treatment goal of LDL-C <1.8 mmol/L (<70 mg/dL) or LDL-C <2.6 mmol/L (<100 mg/dL) [21].

We have not investigated the reasons of the participating doctors for their therapeutic decisions, but they are probably complex. A recent paper provided possible explanations for the low use of high dose atorvastatin and achievement of LDL-C targets in only a minority of patients, including the physicians’ desire to avoid potential side effects which may be associated with higher doses (although this does not seem to be as much a concern for UK clinicians), and a lack of awareness of the applicable guidelines (EAS/ESC) [22].

Another reason for the relatively low goal attainment among the German population studied could be due to differences in the healthcare system compared with other countries. For example, in the UK, the Quality and Outcomes Framework is a system for the performance management and payment of GPs, which was in place at the time of this study. For CVD in particular, GPs were incentivized with additional remuneration to ensure patients who have a recorded QRISK2 (UK population derived CVD risk score like Framingham) score of ≥20% in the preceding 12 months are prescribed statins [23,24]. In Germany, in contrast to the UK, physicians have a restricted drug budget per patient, and are threatened penalty payments if they exceed this budget. This may explain why statin prescribing is lower than the UK, and fewer patients achieve LDL-C target levels in Germany [21]. Given that more high CV risk patients achieve target LDL-C levels in the UK through employing an alternative positive reimbursement, we suggest that German health politicians investigate alternative or additional reimbursement strategies rewarding preventive measures.

As mentioned previously, the EAS/ESC targets are defined per the total CV risk level of each patient. For patients at very-high CV risk, the goal is an LDL-C <1.8 mmol/L (70 mg/dL), whereas for patients at high CV risk, the goal is LDL-C <2.6 mmol/L (<100 mg/dL). All ASCVD patients are classified as very-high risk. Among the ASCVD population, when defined hierarchically, the proportion who achieved LDL-C <1.8 mmol/L (70 mg/dL) ranged from 6.0% to 11.5%. The highest levels of achievement of LDL-C thresholds were observed among patients with recent ACS, whereas the lowest levels of achievement were observed among patients with PAD. Findings were similar when patients were defined by prevalence.

Classification of DM patients without ASCVD as high or very-high risk was not feasible in this study for several reasons. Firstly, as DM patients with moderate or severe CKD are considered very-high risk, it would be necessary to determine CKD severity; however, CKD has been shown to be poorly documented within the German LPD. Although moderate and severe CKD is one of the EAS/ESC very-high CV risk categories, it was not possible to obtain estimated glomerular filtration rate (eGFR) results in a manner permitting rigorous CKD identification. Within this study, CKD stages 3–4–5 were captured from ICD codes as a comorbidity, and 3.7% of patients were observed to have CKD stage 3–4–5; however, in a recent study among a similar population of patients, the prevalence of CKD was estimated at almost 30% [25]. The lower number of patients observed to have CKD stage 3–4–5 within this study is likely to be underestimated due to missing coding of CKD by GPs. Secondly, SCORE risk was not calculated for these patients. Finally, it would be necessary to identify patients with severe hypertension (another additional risk factor that leads to classification as very-high risk), but there is no agreed definition for severe hypertension in DM patients. Therefore, our cohort of DM patients without ASCVD likely included patients at both high and very-high risk. The proportion of these who achieved target LDL-C thresholds were even lower than for the ASCVD cohort, at 5.1% and 7.6% for LDL-C <1.8 mmol/L (70 mg/dL), and 18.5% and 22.4% for LDL-C 1.8 to <2.6 mmol/L (70 to <100 mg/dL), when defined hierarchically and by prevalence, respectively. Increasing statin intensity may help greater numbers of patients reach the goal. However, even so, it is unlikely that an average LDL-C target of <1.8 mmol/L (<70 mg/dL), or 1.8 to <2.6 mmol/L (70 to <100 mg/dL), as recommended by the EAS/ESC guidelines, would be reached within this population with statin therapy alone. This highlights that there may be a role for alternative evidence-based therapies for further LDL-C lowering.

Although previous studies have looked at LLT utilization and goal attainment in European patients, the present study aimed to provide critical updates to extend the literature by providing recent estimates of LLT use and lipid goal attainment in Germany. The findings from this study are consistent with earlier studies on LLT utilization and poor goal attainment in patients considered at high risk of CV events [10,11,20]. A recent analysis of the international DYYSIS study showed that only 26.8% of patients attained their risk-based target LDL-C level, and of the 76% of patients classified as being at very-high risk, only 21.7% attained their LDL-C goal [26]. Furthermore, in the German DYYSIS cohort (approximately 4000 patients), only 10.7% attained the high or very-high risk-based LDL-C targets [12]. Similarly, a cross-sectional cohort study of Belgian DYSIS patients receiving statins showed that, overall, 56.2% of patients did not achieve the LDL-C target, and among patients at very-high risk almost three-quarters did not achieve LDL-C target [27].

The results of the present study are concerning, as it has been demonstrated that the greater the LDL-C reduction, the greater the CV risk reduction [6]; therefore, poor attainment of the LDL-C target is likely to be associated with poor CVD outcomes. Data on target attainment by CV risk group in European patients are limited, but in a Japanese study, attainment was lowest for CHD (55%) and highest for ischemic stroke, PAD and DM patients (80%). This contrasts with our findings, where DM had the lowest percentage achieving LDL-C treatment thresholds, which may reflect differences in clinical practice in Germany versus Japan [28], and the higher rates of DM in Germany.

4.1. Limitations

Some study limitations must be noted. As the analyses were conducted retrospectively, it was not possible to identify the causes of low LLT utilization and poor achievement of LDL-C targets in Germany. However, the data do allow us to expand our knowledge
on how LLTs are currently being utilized within a German population.

The cohort represents a German population within a general practice setting, which may limit the generalizability of results, as high or very-high CV risk patients being treated exclusively by a specialist (e.g., cardiologist, endocrinologist) would not be captured. Additionally, LDL-C measurements were not prospectively specified, which may introduce biases as the population with LDL-C measurement may differ compared with the overall population. The characterization of medical conditions was limited to EMRs. No information on additional risk factors such as smoking, diet and exercise habits were available. It cannot be guaranteed that the medication prescriptions given to patients were dispensed by pharmacists, or that the medicines dispensed were taken as prescribed. Results were reported as unadjusted descriptive summaries and cannot account for the influences of baseline characteristics on statin utilization or lipid levels. For example, importantly, adherence and its effects on LDL-C goal attainment for patients with LLT were not assessed. Insights into the underlying reasons for low or sub-optimal statin treatment are limited. Finally, the study did not include an evaluation of statin monotherapy versus statin plus other LLT (e.g., ezetimibe).

4.2. Conclusions

Safe and effective LLTs with proven CV protective effects are available in Germany. However, this study suggests that LLTs are not being utilized in the manner advised by ESC and EAS guidelines. This could be due to several factors, including patient preference, statin intolerance and prescribing patterns. In a large proportion of patients, this may contribute to suboptimal goal attainment and avoidable morbidity and mortality; however, it is important to note that other factors (e.g., treatment adherence), may also have a significant impact. These results highlight the need to ensure compliance with guidelines, so that patients receive adequate available LLT. Furthermore, for those patients who do not reach LDL-C goal despite statin therapy, it may be necessary to consider alternative therapeutic options to lower their CVD risk.

Conflict of interest

FW.D. and K.H.T. are employees of and stockholders in Sanofi Germany. At the time of this study, K.G. was an employee at SanoGenzyme, Inc., Germany. M.F.P. was a consultant for Roche, AstraZeneca, Pfizer, and BASF, and has received speaker honoraria from Aegerion Pharmaceuticals, Amgen, AstraZeneca, Danone Research, Sanofi-Genzyme, Pfizer, and BASF, and has received speaker honoraria from Aegerion Pharmaceuticals, Amgen, AstraZeneca, Danone Research, Sanofi/Genzyme, Pfizer, BASF, Hoffmann LaRoche, MSD, and Sanofi. D.A. is an employee of IMS Health.

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Author contributions

W.M. conceived and reviewed the manuscript. FW.D., K.G., K.T., D.A. and S.R.I. contributed to the study protocol development and were involved in the evaluation and interpretation of the results and the reviewing of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2017.11.020.

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disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), Atherosclerosis 252 (2016) 207–274.


