

Prevalence of high-risk cardiovascular patients with therapy-resistant hypercholesterolemia

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Introduction Hypercholesterolemia is a causal risk factor for cardiovascular diseases, which is recommended to be treated at least in high-risk patients. Yet, currently there is a lack of epidemiological data on the number of high-risk patients in Germany who do not respond adequately to high-dose statin monotherapy or statin therapy in combination with other lipid-lowering agents.

Methods Of a total of over 2.6 million patient records from general practitioners in the IMS Disease Analyzer database, all high-risk cardiovascular patients with hypercholesterolemia who did not reach target low-density lipoprotein-cholesterol (LDL-C) levels despite at least 12 months of maximum lipid-lowering therapy and optimal medication supply (medication possession rate $\geq 80\%$) were selected over a defined period.

Results On the basis of the practice data, a total of 602 133 patients with a high cardiovascular risk who were treated with statin monotherapy or statin combination therapy with optimal medication supply (medication possession rate $\geq 80\%$) for at least 12 months were identified. Of them, 49 406 patients received high-dose statin therapy, and 51 869 patients received statin therapy in any dose in

combination with another lipid-lowering agent. A total of 79 848 high-risk patients did not reach the target LDL-C level of 70 mg/dl or less despite consistent lipid-lowering therapy; of them, 12 808 had a documented LDL-C level of at least 130 mg/dl.

Conclusion The prevalence of high-risk cardiovascular patients with therapy-resistant hypercholesterolemia is substantial in Germany. *Cardiovasc Endocrinol* 6:81–85 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Hypercholesterolemia is a major risk factor for cardiovascular diseases. The 2009 German Federal Health Monitoring report shows a 12-month prevalence rate of 20.8% of people who were diagnosed with and treated for dyslipidemia among the overall German population [1]. According to the German Health Interview and Examination Survey for Adults (DEGS1) conducted by the Robert Koch Institute in 2013, 64.5% of men and 65.7% of women had a total cholesterol level of more than 190 mg/dl or had been diagnosed with dyslipidemia [2]. The large number of individuals affected by elevated cholesterol levels to greatly varying degrees includes a relatively small group with familial hypercholesterolemia [3].

The fundamental significance of all forms of hypercholesterolemia lies in the related high risk for cardiovascular complications. Depending on other risk factors,

guidelines recommend different target levels and therapeutic options. The ESC/EAS guideline recommends lipid-lowering drug therapy and a low-density lipoprotein-cholesterol (LDL-C) target level of below 100 mg/dl in high-risk patients. An LDL-C target level of below 70 mg/dl applies for very high-risk patients [4]. On the basis of NCEP ATP III guidelines, the goal for at-risk patients is an LDL-C level of below 100 mg/dl, with optionally lower levels in cases where the risk is particularly high [5,6]. An LDL-C level of below 100 mg/dl is recommended in patients with familial hypercholesterolemia; in the case of concomitant clinical manifestations of atherosclerosis, an LDL-C level of 70 mg/dl is advisable [7]. Information regarding the achievement of treatment goals varies considerably. It has been reported [5] that between 3 and 40% of patients achieved an LDL-C level of below 100 mg/dl. Register studies show that considerable therapeutic deficits exist – even in high-risk patients who are being treated with statins [8,9].

Although the prevalence of hypercholesterolemia has been widely studied, data on refractory patients are scarce. Therefore, the present analysis is designed to identify those from the large overall number of patients

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who already had a high cardiovascular risk and then responded insufficiently to an established pharmacotherapy with statins and other lipid-lowering agents (refractory patients).

Methods

Database

The present study was performed using the IMS Disease Analyzer database. This database records anonymized diagnoses, lab results, prescriptions, and other therapy-related data pertaining to statutory (SHI) and private (PHI) health insurance funds in Germany on a daily basis and differentiated by specialist groups. This allows tracing back individual courses of therapy over many years. The validity and representativeness of the database has been proven for various variables such as age and sex distribution, type of patients' health insurance, and prescribed medications and their pack sizes [10].

The study was reviewed and approved by the Institutional Review Board of the IMS Health, Frankfurt am Main, Germany.

Written patient consent was not required as no ethics votum is needed for studies based on anonym epidemiological data.

Inclusion and exclusion criteria

A total of 2 602 031 patients treated in 1262 practices by 1562 general practitioners in the period from 1 September 2014 to 30 August 2015 (selection period) were considered for the longitudinal analysis. From this sample, adults with SHI coverage who also met the following inclusion criteria were selected:

- (1) Hypercholesterolemia diagnosis according to the International Classification of Diseases 10 (ICD-10) codes E78.0, E78.2, E78.4, E78.5, E78.8, or E78.9.
- (2) Coronary heart disease diagnosis including myocardial infarction (ICD-10: I20–25) or ischemic stroke (I63, I64, G45).
- (3) At least one documented LDL-C value within the selection period.
- (4) One statin prescription within 6 months before LDL-C determination ('last observed' prescription).
- (5) At least one other statin prescription issued at least 12 months before the 'last observed' prescription ('first observed' prescription; the most recent prescription issued at least 12 months before the 'last observed' prescription was used here).
- (6) Medication possession rate (MPR) of at least 80% in the period between the 'first observed' and 'last observed' prescriptions.

The prescriptions were further divided into 'high-dose statin prescriptions' (rosuvastatin 20 or 40 mg, atorvastatin 40 or 80 mg, or simvastatin 80 mg daily), with or

without additional lipid-lowering agents, and prescriptions for any statin in any dose, broken down into prescriptions without additional lipid-lowering agents, prescriptions in combination with ezetimibe, and prescriptions combined with another lipid-lowering agent (other than ezetimibe).

To calculate the MPR, the 'observation period' between the 'first observed' and the 'last observed' prescriptions (actual duration of therapy) was compared with the maximum possible duration of treatment based on the packages prescribed (expected duration of therapy). The 'expected duration of therapy' is the number of daily doses prescribed during the observation period excluding the 'last observed' prescription. The MPR, which indicates the availability of the medication to the patient, is the quotient of the 'expected' and 'actual' duration of therapy.

Extrapolation

The calculated patient numbers were extrapolated to Germany's SHI population using the following method: in the first step, a quotient of the number of physicians (53 703) in the specialist group in Germany and the number of physicians (1562) on the panel were calculated (34.4). To avoid double counts, 'doctor hopping' had to be taken into account. For this purpose, IMS has determined a physician group-specific hopping factor on the basis of external longitudinal prescription data. On the basis of this factor, 18.6% of patients recorded as having visited one physician also visited another from the same specialist group within 1 year and were therefore counted multiple times. Reduced by 18.6% to eliminate these double counts, the provisional extrapolation factor is 28.0. However, as an LDL-C level was documented for only 56.8% of patients during the observation period, a final extrapolation factor of 49.3 (29.0/0.568) was applied to patients in this situation.

Results

The average observation period for calculating the MPR is 415 days (SD for high-dose statin therapy is 40 days; SD for any statin therapy is 38 days). Table 1 shows the patient distribution based on adult SHI patients with hypercholesterolemia according to the focused diagnostic criteria (see the Methods section) for whom a documented LDL-C level was recorded during the selection period.

High-risk patients are defined as patients with hypercholesterolemia and a history of either coronary artery disease or ischemic stroke not adequately controlled with maximal-tolerated lipid-lowering therapy. The extrapolation resulted in 602 133 high-risk adult SHI patients who were treated with statins for at least 1 year. Of them, 49 406 (8.2%) patients received the maximum dose (high-dose therapy). Of the remaining patients with any kind of statin therapy, the ones who received at least one

Table 1 Identification of high-risk patients with therapy-refractory course

Patient population	Patients in the panel [n (%)]	Extrapolation (SHI population)
Adult SHI patients with HC according to the focused criteria and LDL-C value during the selection period	88 863 (100)	4 377 234
'Last' prescription of high-dose statin therapy within 6 months before LDL-C measurement	4669 (5.3)	229 987
'First observed' prescription of high-dose statin therapy at least 12 months before the 'last prescription'	2927 (63.7)	144 179
With prescription rate of at least 80% during the observation period	1717 (36.8)	84 576
With confirmed CHD diagnosis within 5 years before the 'first observed' prescription	1003 (21.5)	49 406
'Last' prescription of any statin therapy within 6 months before LDL-C measurement	50 358 (56.7)	2 480 546
'First observed' prescription of any statin therapy at least 12 months before the 'last' prescription	41 724 (82.9)	2 055 250
With prescription rate of at least 80% during the observation period	25 596 (50.8)	1 260 814
With confirmed CHD diagnosis within 5 years before the 'first observed' prescription	12 224 (24.3)	602 133
With at least one other lipid-lowering agent as part of the 'last observed' prescription	1053 (2.1)	51 869

CHD, coronary heart disease; HC, hypercholesterolemia; LDL-C, low-density lipoprotein-cholesterol; SHI, statutory health insurance.

additional lipid-lowering agent were considered in more detail. It is assumed that through the combination of both treatments they received their respective maximum-tolerated lipid-lowering therapy. According to the extrapolation, 51 869 (8.6%) patients received a combination of a statin and another lipid-lowering agent. The small percentage of patients with statin therapy or maximum-tolerated lipid-lowering therapy reflects the strict selection of cardiovascular risk patients by their treating physician.

The distribution of LDL-C values for these two patient groups is shown in Table 2. When combining the two groups, only patients without additional lipid-lowering agents should be considered in the high-dose statin therapy group, as the patients with combination therapy are already included in the group with maximum-tolerated lipid-lowering therapy. Overall, there are 79 848 high-risk patients (95% confidence interval: 79 313–80 385) who did not achieve the strict LDL-C target value of below 70 mg/dl despite consistent therapy. These patients are considered to be refractory to the established treatments. A total of 12 808 (95% confidence interval: 12 589–13 030) of these patients had an LDL-C value above 130 mg/dl.

Discussion

A total of 602 133 patients with a high cardiovascular risk who were being treated with a statin monotherapy or statin combination therapy with optimal drug supply (MPR \geq 80%) for at least 12 months were identified in the present study. Of them, however, only 49 406 (8.2%) patients received high-dose statin therapy and only 51 869 (8.6%) patients received statin therapy in any dose in combination with another lipid-lowering agent. A total of 79 848 (83.2%) of those patients identified as being at high risk (96 004) did not achieve the LDL-C target value of 70 mg/dl or less despite consistent lipid-lowering therapy; 12 808 even had a documented LDL-C level of over 130 mg/dl.

The 2014 German Heart Report [11] identified 665 654 inpatient cases with ischemic heart disease for 2012. This

corresponds approximately to the 602 133 high-risk patients in secondary prevention identified in the present study. High-risk patients with hypercholesterolemia whose LDL-C value is more than twice as high as their LDL-C target value are obligate candidates for LDL-apheresis according to the unanimous recommendation of experts from various medical societies [9]. However, only 1472 people with SHI coverage received LDL-C apheresis in 2015 [12]. As many potential apheresis patients presumably live far away from apheresis centers or decline such an invasive therapy, the actual target group is likely to be significantly larger. The present analysis indicates that the number is ~10–30 times higher, depending on the LDL-C target value – a patient population that still can be defined clearly.

The number of high-risk cardiovascular patients who do not achieve LDL-C target values corresponding to their level of risk when using established therapy options is particularly relevant with regard to future therapeutic strategies. Consequently, those patients who were treated as comprehensively and individually as possible using the standard therapies were identified. This is important because the patient can only be considered as refractory to treatment when he or she does not achieve the target value with the maximum-tolerated treatment applied. Therefore, the first part of the analysis included only patients who received high-dose statin therapy. However, the maximum dose of statins cannot be prescribed in all cases because of interactions with other drugs, contraindications, or other undesirable effects (e.g. myopathies) [5,13]. The FDA, for example, recommends avoiding simvastatin 80 mg in previously untreated patients [14]. In addition, the expected reduction in the LDL-C value when doubling the simvastatin dose is just 6% [15], whereas the treatment goals can be achieved much more easily with combination therapies [5,16]. Accordingly, the maximum-tolerated statin dose for the individual may be reached when administering a dose that is lower than the highest permitted dose, and the maximum-tolerated lipid-lowering therapy may, nonetheless, be achieved in combination with another lipid-lowering agent [17].

Table 2 Low-density lipoprotein-cholesterol values for patients with high-dose statin therapy or maximum-tolerated therapy throughout the observation period

Patient population	Patients in panel	Extrapolation to SHI population	LDL-C				
			≥ 70 mg/dl	≥ 100 mg/dl	≥ 130 mg/dl	≥ 160 mg/dl	
Patients fulfilling all inclusion criteria and high-dose statin therapy	1003	49 406	41 968	22 511	7438	2315	
Without other lipid-lowering agents (2)	896	44 135	37 587	1995	6207	1675	
With other lipid-lowering agents (3)	107	5271	4384	2561	1231	640	
Patients with all inclusion criteria and any statin therapy and at least one other lipid-lowering agent (4)	1053	51 869	42 264	21 132	6601	2414	
With ezetimibe	132	6502	5271	3251	1478	591	
With ezetimibe	921	45 367	36 993	17 881	5123	1823	
Sum of rows (2) and (4)	-	96 004 (95 399–96 613)	79 848 (79 313–80 385)	41 082 (40 693–41 474)	12 808 (12 589–13 030)	4089	

LDL-C, low-density lipoprotein-cholesterol; SHI, statutory health insurance.

These patients are examined in the second part of the study, which presupposed the use of any kind of statin therapy and subsequently identified those patients who also received ezetimibe or another lipid-lowering agent. The fact that the maximum-tolerated lipid-lowering therapy is considered in addition to high-dose statin therapy approximately doubles the number of patients identified. The comparison of rows (1) and (4) in Table 2 shows that the patients in both groups are distributed similarly between the LDL-C categories and that both groups thus contain a similar number of refractory patients. An additional filter was included to ensure consistent implementation of the therapy, requiring an MPR of at least 80% throughout the observation period.

The present study is fundamentally different from other epidemiological analyses previously conducted in Germany because it is the first not only to include information on the prevalence of hypercholesterolemia as a collective term for patients affected to very different degrees and with various underlying diseases, comorbidities, and risks but also to identify high-risk cardiovascular patients in secondary prevention who received intensive medical lipid-lowering therapy.

The analysis has several limitations. First, uncertainties arise from the lack of information on compliance and from the extrapolation for patients without known LDL-C levels. For example, the database only allows checking the availability of medications to patients (prescribed daily dose). The actual amount of medications used (consumed daily dose) can therefore only be deduced indirectly. Second, patients who did not receive statins – that is, in particular patients with complete intolerance to statins – were not considered. Third, validation of diagnosis and assessment of comorbidities relied only on ICD-10 by primary care physicians. Furthermore, no valid information on detailed patient characteristics (e.g. BMI, smoking habits) and additional risk factors such as diabetes, hypertension, or renal impairment were available.

Nevertheless, the analysis allowed for a good estimate of the number of patients with a high cardiovascular risk who are eligible for invasive or innovative lipid-lowering therapies such as LDL-apheresis or PCSK9 inhibitors. Given the high cost of apheresis therapy, additional drug therapy options are also desirable from an economic perspective.

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Professor Dr K.G. Parhofer contributed to the evaluation and interpretation of the results as a consultant free of charge. Dr rer. med. F.-W. Dippel drafted the study protocol and was involved in the evaluation and interpretation of the results as well as the preparation of the

manuscript for publication. Professor Dr K. Kostev performed the database analysis.

Conflicts of interest

Professor Dr K.G. Parhofer is a senior physician at Medizinische Klinik II-Großhadern at the Klinikum Großhadern of the Ludwig Maximilians University of Munich. Dr rer. med. F.-W. Dippel is a project manager in the field of evidence-based medicine at Sanofi Germany GmbH. Professor Dr K. Kostev is an employee of IMS Health, Frankfurt.

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