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# Lipid-modifying therapy and low-density lipoprotein cholesterol goal attainment in patients with familial hypercholesterolemia in Germany: The CaReHigh Registry

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## HIGHLIGHTS

- LDL-C target values were only achieved by a minority of FH patients in the registry.
- Gap to target LDL-C was lowest if PCSK9 inhibitors were added to the treatment.
- More than 20% of patients with oral lipid lowering therapy would be eligible for additional PCSK9 inhibitor treatment.

## ARTICLE INFO

*Keywords:*
Familial hypercholesterolemia
LDL-C goal attainment
PCSK9 inhibitor
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## ABSTRACT

*Background and aims:* Familial hypercholesterolemia (FH) is amongst the most common genetic disorders encountered in primary care. Yet, only a minority of affected patients is diagnosed and treated. This interim analysis of the CaRe High Registry aims at examining the state of treatment and attainment of lipid goals in German FH patients.

*Methods:* The CaRe High registry includes FH patients from lipid clinics and private practices. Data have been collected using questionnaires filled in by the recruiting physicians and by interviewing the participating patients.

*Results:* We examined 512 FH patients diagnosed according to clinical criteria. Median age at the time of the first FH diagnosis was 39 (25th and 75th percentile: 27–50) years, median treatment naïve LDL cholesterol (LDL-C) was 239.4 mg/dl (6.19 mmol/l), 25th to 75th percentile 191.8–342.5 mg/dl (4.96–8.86 mmol/l). 27% of the participants did not receive lipid-lowering drugs. Among the patients treated with lipid-lowering drugs, 19% received a PCSK9 inhibitor (PCSK9i) in combination with a statin, 9% were treated with a PCSK9i alone and 3% were treated with a combination of PCSK9i and a non-statin drug. Patients with pre-existing CVD were more

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likely to be treated with lipid-lowering drugs and more likely to receive a PCSK9i, but LDL-C targets were only achieved by a minority of patients (< 20%). Gap to target LDL-C was lowest and the median achieved LDL-C reduction was 1.4 times higher with PCSK9i treatment than with (oral) lipid-lowering therapy without PCSK9i. *Conclusions:* The Care High registry has included patients with the typical clinical features of familial hypercholesterolemia. PCSK9i treatment in addition to standard therapy allows attainment of target values in many patients with initially very high LDL-C.

## 1. Introduction

Familial hypercholesterolemia (FH) is a monogenic disorder of lipoprotein metabolism, which results in increased LDL cholesterol (LDL-C) concentrations. It is associated with a several-fold increased risk of cardiovascular events. Most frequently, co-dominant FH is caused by mutations in the low-density lipoprotein (LDL) receptor-gene (approx. 90%) [1–3]. In addition, it may be attributable to mutations of the genes coding apolipoprotein (Apo) B100 [4,5], the primary ligand of the LDL receptor or proprotein convertase subtilisin/kexin type 9 (PCSK9) [6], one of the key regulators of the LDL receptor.

FH is mostly inherited in an autosomal dominant fashion; this implies that 50% of the first-degree relatives of an index patient are also affected. A distinction is made between the heterozygous and the more severe compound heterozygous and homozygous forms of FH. In homozygous patients, the atherosclerotic vascular disease progresses aggressively and at accelerated pace. Unfortunately, in many instances, FH is diagnosed and treated only after the occurrence of an initial cardiovascular event [7,8]. If FH patients remain untreated they have in general a shorter life expectancy than non-FH individuals.

With an estimated prevalence of 1:300 [9] in Germany, heterozygous FH is amongst the most common genetic diseases seen in general medical practice with about 270 000 patients affected. FH may account for up to 20% of myocardial infarctions before the age of 45 and for 5% of myocardial infarctions before the age of 60 [10,11]. Less than 2% of FH patients in Germany appear to be properly diagnosed and treated [8]. Registry data suggest that cardiovascular disease (CVD) in FH can be prevented by early treatment with lipid lowering medication [12].

Latest Guidelines for Management of Dyslipidemia classify FH patients as being at high risk for CVD. Given the clinical sequelae of FH, affected individuals should be identified as early as possible. Treatment goals are LDL-C lower than 100 mg/dl (2.6 mmol/l) for patients without pre-existing CVD and lower than 70 mg/dl (1.8 mmol/l) for patients with pre-existing CVD [13].

Treatment of FH patients is commonly initiated with statins, which can be combined with bile acid sequestrants or cholesterol absorption inhibitors if the treatment goal cannot be reached with a statin alone. If such combination therapy is not sufficient, PCSK9-Inhibitors (PCSK9i) should be used before lipoprotein apheresis is considered as a last option [13].

We have established a cascade screening and registry program for FH in Germany (CaRe High – Cascade Screening and Registry for High Cholesterol [14]). Effectively, in December 2017 more than 500 F H patients have been included. This interim analysis examines the state of treatment and the attainment of lipid goals in our study population.

## 2. Patients and methods

The design of the CaRe High registry has been described before [14]. Written informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study protocol has been approved by the ethics committee on research on humans at the Medical Association of the federal state of Baden-Württemberg and the ethics committees in charge of all participating centers. Inclusion criteria are LDL-C ≥190 mg/dl (4.9 mmol/l) without lipid lowering therapy (LDL-C concentrations under lipid lowering therapy are corrected for drug and dose [15]) or total cholesterol > 290 mg/dl (7.5 mmol/l) and one of the following: tendon xanthomas, family history of hypercholesterolemia, family history of myocardial infarction before the age of 50 in grandparents, uncles, aunts or before the age of 60 in parents, siblings or children. These inclusion criteria comply with the suggestions previously made by Klose et al. [16]. For descriptive purposes, we also calculated the Dutch Lipid Clinics Score (DLCN) score for FH as previously recommended [8]. Genetic testing for FH causing mutations has not been mandatory for participation in the registry. Rather, we left the indication for genetic testing to the decision of the treating physician. We did not exclude individuals with a known mutation, but low LDL-C levels. Upon joining the registry, participating physicians were instructed about the inclusion criteria, which placed emphasis on familial hypercholesterolemia. They were asked not to include patients with overt secondary hyperlipidemia and check for the

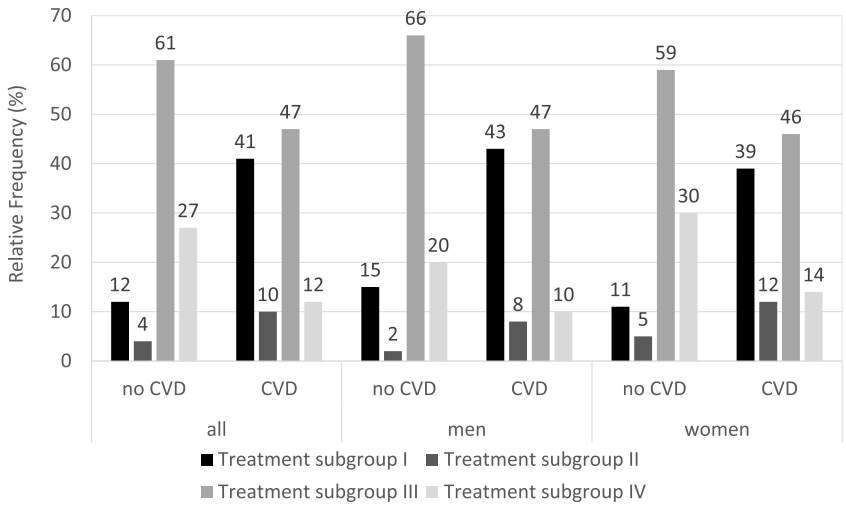



**Fig. 1.** Relative frequencies of lipid -lowering treatments according to the presence or absence of CVD in the entire cohort (left panel), in men (medium panel), and in women (right panel).
Black bars: Patients treated with PCSK9is alone or in combination with other lipid-lowering drugs (treatment subgroup I); dark grey bars: patients on PCSK9is only (treatment subgroup II); medium grey bars: patients treated orally with lipid-lowering drugs (statins, ezetimibe, fibrates, bile acid sequestrants or any combination thereof) without using a PSCK9-inhibitor (treatment subgroup III); light grey bars: patients not treated with any lipid lowering medication (treatment subgroup IV).

most common forms of secondary hyperlipidemia by laboratory examinations and clinical features. Consequently, patients suspicious of secondary hyperlipidemia were not considered for inclusion.

In patients referred to lipid clinics or lipid experts, we used the status of their initial presentation. Consequentially, this survey does not encompass recommendations issued, discharge medication nor the clinical course of the patients. The treatment status "no lipid lowering drug" reflects the treatment status at the point of registry entry and does not rule out that a patient had been treated earlier and discontinued therapy.

Coronary artery disease (CAD) was defined as a positive history of at least one myocardial infarction or coronary revascularisation. CVD was defined as a history of at least one CAD event, angina pectoris, peripheral artery disease (PAD) or cerebrovascular disease.

Therapy-naïve LDL-C values were obtained from the physicians. If no therapy-naïve LDL-C value was available, correction factors published by Walma and Wiersma were used [15]. In the case of additional PCSKi treatment, we assumed an LDL-C lowering by 50%.

For analyses presented in Figs. 1 and 3, we subdivided the cohort into four treatment groups: patients on PCSK9i plus oral drugs (treatment subgroup I), PCSK9i only (treatment subgroup II), oral lipid lowering only (treatment subgroup III), and no lipid-lowering drugs (treatment subgroup IV). Patients on PCSK9i treatment were only assigned to the PCSK9i treatment groups (subgroup I and II) if treatment had continued for more than 4 weeks before laboratory analysis. Otherwise, earlier LDL-C values and preceding treatment were considered. To analyze age- and gender-adjusted associations of binary outcome variables with other variables, we performed logistic regressions to estimate odds ratios (ORs) and (z-value-based) p values. The exact two-sided Fisher test was used to analyze the associations between categorical variables. Comparisons of metric data between two groups were performed with the aid of the Wilcoxon rank sum test. To compare metric data between more than two groups we performed the Kruskal-Wallis rank sum test, followed by pairwise comparisons with the Wilcoxon rank sum tests.

All statistical computations have been performed by R version 3.3.1. For the exact Fisher test, the Kruskal-Wallis test, the Wilcoxon test and the linear and logistic regression, the R functions *fisher. test*, *kruskal. test*, *wilcox. test* and *glm* from the R library *stats* have been used, respectively [17].

## 3. Results

At the time of this analysis, 29 centers (7 lipid clinics at university hospitals, 8 licensed lipid specialists, 3 rehabilitation clinics, 11 general/internal medicine specialists) were participating in the registry (cf. Acknowledgments). The median number of patients per centre was 6, with a range of 1–101; 46 (7–101) patients at lipid clinics at university hospitals, 9 (1–32) at licensed lipid specialists, 5 (3–15) at rehabilitation clinics, 4 (1–14) at general/internal medicine physicians.

### 3.1. Patient population

We considered 516 patients for the analysis. Four of them were excluded because of inconclusive information on their treatment status, so that we finally included 512 patients. Median age (25th and 75th percentiles in brackets) at the point of registry entry was 57.4 years (48.7–64.7 years), median age at the first diagnosis of FH was 39 years (27–50 years). Median untreated LDL-C concentration was 239.4 mg/dl (6.19 mmol/l) (191.8–342.5 mg/dl; 4.96–8.86 mmol/l), median treated LDL-C 151 mg/dl (3.9 mmol/l) (107–204 mg/dl; 2.77–5.27 mmol/l), median HDL-C 52 mg/dl (1.35 mmol/l) (44–65 mg/dl; 1.14–1.69 mmol/l), median triglycerides 132 mg/dl (1.51 mmol/l) (96–189 mg/dl; 1.10–2.16 mmol/l) and median Lp(a) was 41 nmol/l (17.1 mg/dl) (8–99 nmol/l; 3.3–41.3 mg/dl) (Table 1). Upon inclusion, we sought to rule out obvious secondary hypercholesterolemia by requesting TSH, HbA1c, fasting glucose, high-sensitivity CRP, ALAT, ASAT, bilirubin, alkaline phosphatase, uric acid, urea, and creatinine. These laboratory parameters were within the reference range indicating that we mainly included patients with primary hypercholesterolemia (see Table 1 for characteristics of our cohort). Genetic testing for FH had been conducted in 56 out of the 512 individuals. In 49 (87.5%) of the 56 tested individuals a FH causing mutation was found.

Thirty-five percent of the patients presented with CAD, 46% presented with CVD and 6% with previous stroke and/or TIA. 60% of patients had a family history of elevated cholesterol, whereas 37% could not provide respective information. 64% of patients had a family history of early CVD, while 7% could not provide relevant data. 13% of patients had a family history of early TIA/stroke, 13% could not provide respective information. FH patients with pre-existing CVD (median 59 years, 25th and 75th percentiles 53–66 years) were older than patients without CVD (median 54 years, 25th and 75th percentile 41–62 years).

### 3.2. Treatment status

*Entire cohort.* Of all patients, 17% were treated with a PCSK9i in combination with other lipid-lowering drugs (treatment subgroup I); 32 patients (6%) were on PCSK9i only (treatment subgroup II), 50% had been treated orally with lipid-lowering drugs (statins, ezetimibe, fibrates, bile acid sequestrants or any combination of the above) without using a PSCK9-inhibitor (treatment subgroup III), and 27% of patients

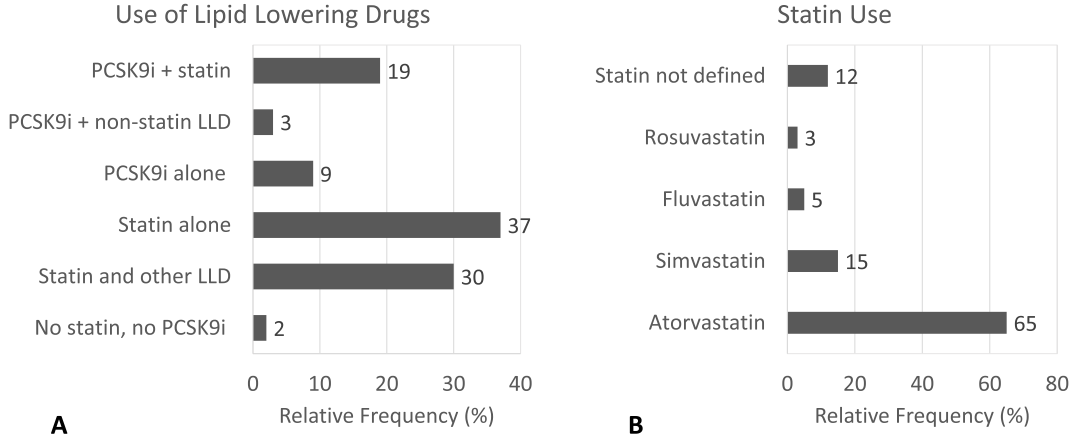
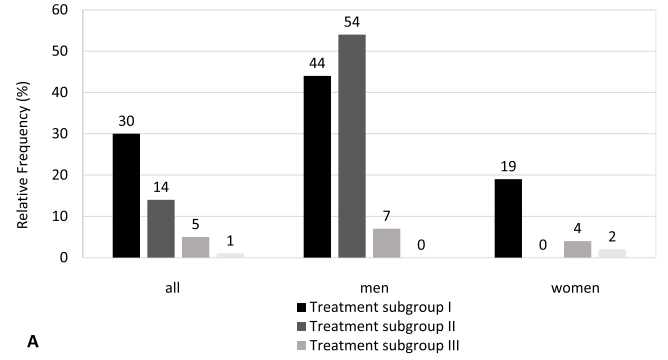
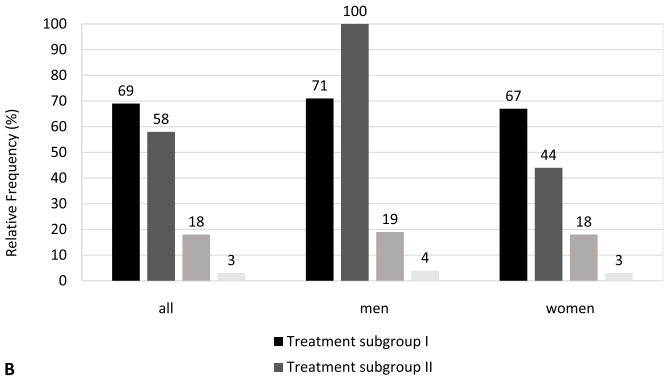



**Fig. 2.** Relative frequency of treatment strategies amongst patients receiving any lipid lowering drugs (alone or in combination).
A) Distribution of lipid lowering strategies. (B) Distribution of individual statins amongst statin users. LLD: lipid-lowering drugs.




A




B


| | Treatment subgroup I | Treatment subgroup II | Treatment subgroup III | Treatment subgroup IV |
|---|---|---|---|---|
| Difference to treatment-naive LDL-C (mg/dl)(A) | 184 | 142 | 113 | 0 |
| Difference to target LDL-C (mg/dl)(B) | -9.5 | 10 | 59 | 101 |

C

**Fig. 3.** Target value attainment, median of lipid lowering and median difference of current LDL cholesterol to individual target in the entire cohort (left), in men (centre), and in women (right).
(A) Percentage of patients with prevalent CVD reaching their individual LDL target (< 70 mg/dl, < 1.8 mmol/l) according to lipid-lowering regimens. (B) Percentage of patients without prevalent CVD reaching their individual LDL target (< 100 mg/dl, < 2.6 mmol/l) according to lipid-lowering regimens. (C) Absolute differences between the treatment-naïve LDL-C concentrations and current LDL-C (dark grey) and between current LDL-C and the individual LDL-C target (light grey) in four groups of patients. Overall, both the differences (A and B) were significantly different between the four patient groups ($p < 0.001$, Kruskal-Wallis rank sum test), and statistically different on all pairwise comparisons between the four patient groups ($p \leq 0.0002$). Black bars: Patients treated with PCSK9 inhibitors alone or in combination with other lipid-lowering drugs (treatment subgroup I); dark grey bars: patients on PCSK9 inhibitors only (treatment subgroup II); medium grey bars: patients treated orally with lipid-lowering drugs (statins, ezetimibe, fibrates, bile acid sequestrants or any combination of the above) without using a PSCK9-inhibitor (treatment subgroup III); light grey bars: not treated with any lipid lowering medication (treatment subgroup IV).

were not treated with any lipid lowering medication (treatment subgroup IV). The four subgroups are significantly different in weight, body mass index, and waist-to-hip-ratio, with lower values in the untreated group (subgroup IV, Supplementary material, Table 1). There were also significant differences in LDL-C on treatment, treatment naïve LDL-C, HDL-C, on treatment total cholesterol and apolipoprotein B. Treatment naïve LDL-C was lowest in subgroup IV and highest in subgroup I. LDL-C, total cholesterol, and apolipoprotein B at the time of recruitment in the registry were highest in subgroup IV and lowest in subgroup I. ALAT and ASAT values are also significantly different with highest values in subgroup III and I.

### 3.3. CVD versus no CVD

Patients with pre-existing CVD were more likely to be treated at all (88% *vs.* 73%, $p = 0.0002$, Fisher's exact test). Patients with pre-existing CVD were also more likely to receive PCSK9i treatment (41% *vs.* 12%, $p < 0.0001$, Fisher's exact test, Fig. 1). The age- and gender-adjusted odds ratio for the probability of PCSK9i treatment with pre-existing CVD compared to the group without CVD was 4.1 (95% confidence interval 2,51–6,71, $p \leq 0.0001$, logistic regression). Patients without pre-existing CVD were more likely to be treated with conventional lipid lowering medication alone (61% *vs.* 47%, respectively, $p = 0.0023$, Fisher's exact test, Fig. 1). After adjustment for age and gender, the odds ratio for receiving conventional lipid lowering medication in the absence of CVD was 1.73 (95% confidence interval for OR: 1.16–2.59, $p = 0.007$, logistic regression). Men were more likely to be treated than women (OR after adjustment for age and CVD yes/no: 1.7, 95% confidence interval for OR: 1–2.76, $p = 0.05$, logistic regression).

*Use of lipid lowering drugs* (Fig. 2). Nineteen percent of the patients using lipid-lowering medication were treated with a PCSK9i in combination with a statin, 3% of the patients using lipid-lowering medication were treated with a combination of a PCSK9i and a non-statin drug (together constituting treatment subgroup I). 9% of the treated patients received a PCSK9i alone (treatment subgroup II) (Fig. 2A). Altogether, 31% thus had a PCSK9i. 69% of the patients using lipid-lowering medication had been treated orally with lipid-lowering drugs only (treatment group III): 37% of the patients using lipid-lowering medication received statin monotherapy, 30% statins and other (non PCSK9i) drugs and 2% neither had a statin nor a PCSK9i (Fig. 2A). If a statin was used for lipid-lowering (alone or in combination with any other drug) atorvastatin was most commonly prescribed (65%), followed by simvastatin (15%), fluvastatin (4%) and rosuvastatin (3%). In 12% of the patients another statin was used, or the statin was not specified (Fig. 2B).

### 3.4. Attainment of target values

We examined whether patients with or without CVD attained their individual LDL-C target values of 70 mg/dl (1.8 mmol/l) or 100 mg/dl (2.6 mmol/l) according to the EAS/ESC guidelines, respectively. Despite lipid lowering therapy, only 18% of patients with CVD and 15% of patients without CVD were at or below their target values.

We further analyzed how the attainment of target values was related to the kind of lipid lowering therapy used. In the group with CVD, 30% of the patients in treatment subgroup I (PCSK9i plus oral drugs), 14% of patients from treatment subgroup II (PCSK9i only) and 5% of patients from treatment subgroup III (oral only) achieved the target value of 70 mg/dl (1.81 mmol/l) or less (Fig. 3A). In the group without CVD, 69% of patients from treatment subgroup I, 58% of patients from treatment subgroup II and 18% of patients from treatment subgroup III achieved the target value of 100 mg/dl (2.59 mmol/l) or less (Fig. 3B). Overall target value attainment was in tendency worse in women compared to men (Fig. 3A and B).

We also compared a) the difference between the treatment-naïve LDL-C concentrations and current LDL-C and b) the difference between the current LDL-C concentrations and the individual LDL-C target between the four treatment subgroups (Fig. 3C). The median achieved differences between the treatment-naïve LDL-C and current LDL-C (differences a) were 184 mg/dl (4.76 mmol/l), 142 mg/dl (3.67 mmol/l), 113 mg/dl (2.92 mmol/l) in treatment subgroups I through III,

**Table 1**
Characteristics of patients in the CaRe High registry.

| Parameter | Subpopulation | | | $p^c$ |
|---|---|---|---|---|
| | All | Men | Women | |
| | N[a] stab.[b] mean ± SD | N[a] stab.[b] mean ± SD | N[a] stab.[b] mean ± SD | |
| | Median (25th-75th percentile) | Median (25th-75th percentile) | Median (25th-75th percentile) | |
| Age, years | 512 | 221 | 291 | 0.0155 |
| | 56 ± 14 | 54 ± 13 | 57 ± 14 | |
| | 57 (49–65) | 56 (47–62) | 58 (51–66) | |
| Age of first diagnosis, years | 315 | 133 | 182 | 0.4016 |
| | 39 ± 15 | 38 ± 14 | 40 ± 16 | |
| | 39 (27–50) | 38 (29–47) | 40 (27–52) | |
| Height, cm | 435 | 185 | 250 | < 0.0001 |
| | 169 ± 10 | 177 ± 8 | 164 ± 8 | |
| | 170 (162–177) | 178 (172–182) | 163 (159–169) | |
| Weight, kg | 433 | 186 | 247 | < 0.0001 |
| | 79 ± 17 | 86 ± 15 | 73 ± 17 | |
| | 78 (66–89) | 85 (78–96) | 70 (62–82) | |
| Waist-to-hip ratio | 302 | 124 | 178 | < 0.0001 |
| | 0.91 ± 0.09 | 0.96 ± 0.07 | 0.88 ± 0.09 | |
| | 0.92 (0.85–0.97) | 0.96 (0.93–1) | 0.88 (0.83–0.93) | |
| BMI, kg/m$^2$ | 435 | 185 | 250 | 0.0873 |
| | 26.7 ± 5.2 | 27 ± 4 | 26.4 ± 5.9 | |
| | 26 (23–30) | 26 (24–29) | 26 (22–30) | |
| LDL-C (on treatment), mg/dl | 414 | 174 | 240 | 0.0791 |
| | 160 ± 71 | 154 ± 71 | 164 ± 71 | |
| | 151 (107–204) | 144 (101–202) | 160 (112–205) | |
| LDL-C (on treatment), mmol/l | 414 | 174 | 240 | 0.0791 |
| | 4.14 ± 1.84 | 3.99 ± 1.83 | 4.25 ± 1.84 | |
| | 3.9 (2.77–5.27) | 3.74 (2.6–5.22) | 4.12 (2.89–5.3) | |
| LDL-C (treatment-naïve), mg/dl | 365 | 152 | 213 | 0.6795 |
| | 271 ± 121 | 278 ± 127 | 266 ± 116 | |
| | 239 (192–342) | 245 (192–353) | 237 (192–334) | |
| LDL-C (treatment-naïve), mmol/l | 365 | 152 | 213 | 0.6795 |
| | 7.02 ± 3.13 | 7.2 ± 3.29 | 6.89 ± 3.01 | |
| | 6.2 (4.96–8.86) | 6.34 (4.98–9.13) | 6.12 (4.97–8.65) | |
| HDL-C (on treatment), mg/dl | 392 | 170 | 222 | < 0.0001 |
| | 55 ± 16 | 49 ± 14 | 60 ± 16 | |
| | 52 (44–65) | 48 (40–56) | 58 (48–69) | |
| HDL-C (on treatment), mmol/l | 392 | 170 | 222 | < 0.0001 |
| | 1.42 ± 0.42 | 1.26 ± 0.36 | 1.55 ± 0.42 | |
| | 1.34 (1.14–1.69) | 1.24 (1.03–1.44) | 1.5 (1.25–1.78) | |
| Total cholesterol (on treatment), mg/dl | 412 | 172 | 240 | 0.0082 |
| | 238 ± 81 | 225 ± 78 | 247 ± 81 | |
| | 230 (183–282) | 216 (167–281) | 236 (192–288) | |
| Total cholesterol (on treatment), mmol/l | 412 | 172 | 240 | 0.0082 |
| | 6.15 ± 2.09 | 5.81 ± 2.02 | 6.39 ± 2.1 | |
| | 5.93 (4.73–7.3) | 5.6 (4.32–7.27) | 6.1 (4.96–7.45) | |
| Triglycerides, mg/dl | 389 | 170 | 219 | 0.0411 |
| | 152 ± 80 | 163 ± 90 | 143 ± 69 | |
| | 132 (96–190) | 143 (99–223) | 126 (96–178) | |
| Triglycerides, mmol/l | 389 | 170 | 219 | 0.0411 |
| | 1.73 ± 0.91 | 1.86 ± 1.03 | 1.63 ± 0.79 | |
| | 1.51 (1.1–2.17) | 1.63 (1.13–2.55) | 1.44 (1.1–2.03) | |
| Lp (a), nmol/l | 247 | 108 | 139 | 0.957 |
| | 68 ± 45 | 71 ± 44 | 65.8 ± 46.8 | |
| | 40 (8–99) | 48 (8–100) | 36.2 (8.2–96.4) | |
| DLCN unlikely FH | 40 | 18 | 22 | 0.447[d] |
| | 8.8% | 9.3% | 8.3% | |
| DLCN possible FH | 173 | 65 | 108 | |
| | 37.9% | 33.7% | 40.9% | |
| DLCN probable FH | 119 | 52 | 67 | |
| | 26.0% | 26.9% | 25.4% | |
| DLCN definite FH | 125 | 58 | 67 | |
| | 27.4% | 30.1% | 25.4% | |
| TSH, μU/ml | 138 | 47 | 91 | 0.991 |
| | 1.92 ± 1.14 | 1.85 ± 0.77 | 1.96 ± 1.29 | |
| | 1.52 (1.1–2.4) | 1.59 (1.21–2.36) | 1.52 (1.07–2.46) | |
| HbA1c, % | 209 | 97 | 112 | 0.5289 |
| | 5.76 ± 0.76 | 5.75 ± 0.77 | 5.77 ± 0.75 | |
| | 5.6 (5.3–6) | 5.6 (5.3–6) | 5.68 (5.4–5.93) | |
| Fasting glucose, mg/dl | 214 | 87 | 127 | 0.1266 |
| | 98 ± 19 | 99 ± 18 | 97 ± 19 | |
| | 94 (86–104) | 97 (88–107) | 93 (86–102) | |

(*continued on next page*)

**Table 1** (*continued*)

| Parameter | Subpopulation | | | $p^c$ |
|---|---|---|---|---|
| | All | Men | Women | |
| | N[a] stab.[b] mean ± SD | N[a] stab.[b] mean ± SD | N[a] stab.[b] mean ± SD | |
| | Median (25th-75th percentile) | Median (25th-75th percentile) | Median (25th-75th percentile) | |
| HsCRP, mg/l | 58<br>1.79 ± 1.47<br>1.35 (0.62–3.49) | 27<br>1.68 ± 1.42<br>1.7 (0.57–2.91) | 31<br>1.87 ± 1.54<br>1.1 (0.68–3.65) | 0.7141 |
| ALAT, U/l | 258<br>32 ± 16.1<br>25.6 (17–37.8) | 114<br>36.9 ± 18.1<br>32 (21.2–43.3) | 144<br>27.7 ± 12.8<br>21 (15–30) | < 0.0001 |
| ASAT, U/l | 203<br>29.2 ± 11.5<br>25 (19.2–33) | 91<br>31.9 ± 13<br>27 (22–34.6) | 112<br>26.9 ± 9.5<br>23 (18–28) | 0.0011 |
| ApoA1, mg/dl | 65<br>164 ± 41<br>160 (139–184) | 33<br>148 ± 32<br>144 (132–160) | 32<br>181 ± 44<br>179 (162–201) | 0.0002 |
| ApoB, mg/dl | 115<br>128 ± 52<br>124 (93–162) | 54<br>125 ± 51<br>123 (95–158) | 61<br>131 ± 53<br>126 (92–164) | 0.6886 |
| Bilirubin, mg/dl | 73<br>0.51 ± 0.31<br>0.45 (0.31–0.6) | 32<br>0.56 ± 0.25<br>0.48 (0.39–0.7) | 41<br>0.48 ± 0.35<br>0.45 (0.27–0.6) | 0.0696 |
| Alkaline phospatase, U/l | 127<br>79 ± 27<br>72 (58–87) | 56<br>80 ± 30<br>74 (60–87) | 71<br>79 ± 24<br>69 (54–86) | 0.264 |
| Uric acid, mg/dl | 195<br>5.73 ± 1.71<br>5.7 (4.6–6.8) | 80<br>6.59 ± 1.21<br>6.6 (5.86–7.32) | 115<br>5.13 ± 1.76<br>4.87 (4–5.88) | < 0.0001 |
| Urea, mg/dl | 126<br>33 ± 15.4<br>30.2 (25–35) | 58<br>32.2 ± 8.1<br>31.6 (25.3–34.3) | 68<br>33.7 ± 19.7<br>28.9 (24–36.3) | 0.515 |
| Creatinine, mg/dl | 244<br>0.9 ± 0.23<br>0.86 (0.74–1) | 100<br>1 ± 0.18<br>0.98 (0.88–1.09) | 144<br>0.83 ± 0.24<br>0.77 (0.7–0.9) | < 0.0001 |
| Creatine kinase, U/l | 221<br>139 ± 87<br>115 (79–170) | 104<br>174 ± 101<br>148 (102–230) | 117<br>109 ± 57<br>95 (67–132) | < 0.0001 |

[a] Number of available values; all values were obtained from the records if the treating physicians.
[b] Only metric values above 0.2* median and below 5* median value (related to the totality of 512 persons) are taken into account.
[c] Wilcoxon test for gender difference.
[d] Chi$^2$ test.

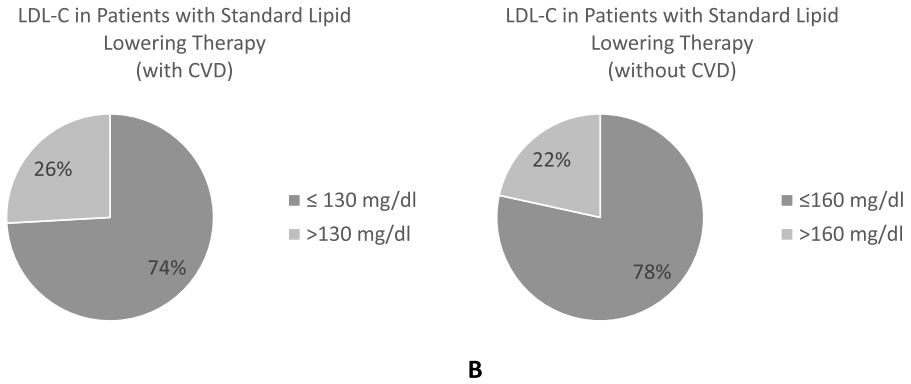



**Fig. 4.** Proportion of patients with standard lipid-lowering therapy exceeding the individual treatment target of 70 mg/dl (1.8 mmol/l) or 100 mg/dl (2.6 mmol/l) in the presence (A) or absence (B) of CVD by 60 mg/dl (1.5 mmol/l) [18].
Standard lipid lowering therapy includes treatment with statins, ezetimibe, fibrates and/or bile acid sequestrants.

respectively. As a matter of definition, there was no difference in treatment subgroup IV (no drugs).

The median gaps to treatment target (differences b) were −9.5 mg/dl (−0.25 mmol/l), 9.6 mg/dl (0.25 mmol/l), 59 mg/dl (1.53 mmol/l), and 101 mg/dl (2.61 mmol/l) in treatment subgroups I through IV (Fig. 3C).

Overall, both the differences between treatment-naïve LDL-C and current LDL-C, and between current LDL-C and target concentrations were different between the four patient groups ($p < 0.001$, Kruskal-Wallis rank sum test). In addition, differences were statistically different on all pairwise comparisons between the four patient groups (throughout, Fig. 3C).

### 3.5. Potential indication for PCSK9 inhibitor treatment

We further examined whether all FH patients were treated according to indication. For this purpose, we provisionally assumed that a distance of 60 mg/dl (1.5 mmol/l) to the individual LDL-C target

establishes a clear indication for PCSK9i prescription [18]. Thus, every FH patient without CVD and LDL-C above 160 mg/dl (4.1 mmol/l) or every FH patient with CVD and LDL-C above 130 mg/dl (3.4 mmol/l) and with conventional lipid-lowering (statins, ezetimibe, fibrates and/or resins) was considered a candidate for PCSK9i in addition. 26% of FH patients with CVD showed LDL-C levels above 130 mg/dl (3.36 mmol/l) and 22% of FH patients without CVD showed LDL-C level above 160 mg/dl (4.14 mmol/l) under conventional treatment (Fig. 4).

## 4. Discussion

This article provides the first comprehensive results of the CaRe High (Cascade Screening and Registry for High Cholesterol) which was initiated in Germany in January 2015. Our patients have the typical features of FH, including a personal and family history of CAD or CVD.

While amongst our index cases awareness of CVD in relatives was very common, their knowledge about cholesterol concentrations in relatives was limited. This may lead to under-diagnosis when one uses diagnostic algorithms such as the DLCN (Dutch Lipid Clinics Network) FH score [19].

FH patients are in general classified as patients at high or very high risk for CVD and intensive lipid lowering therapy is almost always warranted [13,19]. Yet, 27% of our FH patients received no lipid-lowering treatment whatsoever. While we did not specifically interrogate the reasons for not providing such treatment, this may be related to an underestimation of the patients' vascular risk by treating physicians or to fear of potential side effects (such as statin-associated muscle symptoms) of the medication. Misperception of the vascular risk may also explain that men were almost 2-fold more likely to receive lipid-lowering medicines than women. In discussions with patients, we also learned that they sometimes were themselves reluctant to get treated for high cholesterol at all.

Amongst the statins available in Germany, atorvastatin was mostly used in our registry. This stands in contrast to the German guidelines for pharmaceuticals [20] which demand that simvastatin and pravastatin be prescribed as the “lead compound” in 55%–76.5% of all patients needing lipid lowering. The obvious cause for this is that many patients have been recruited at specialized lipid outpatient centers at which atorvastatin is preferred due to its stronger effect on LDL-C. For the same reason, a substantial proportion of patients undergoing treatment was treated with combination therapy of statins and ezetimibe, colesevalam or fibrates (34%) or a combination therapy including PCSK9is (22% of all patients treated). Rosuvastatin, however, was used at a very low rate. The reason for this is that German Federal Joint Committee has included rosuvastatin into a group of drugs with fixed prices together with all other statins. The fixed prices are the maximum reimbursement rates granted by the statutory health insurance for a medicinal product of that group. As a result, patients must pay for the difference to the fixed amount from their own pocket, if the pharmaceutical manufacturer does not adjust his price to the fixed price, which has been the case until 2018.

Remarkably, 14 percent of patients undergoing treatment either received a PCSK9i alone or in combination with a non-statin oral lipid-lowering agent (treatment subgroup II). Although we did not examine reasons for treatment preferences in detail, this might indicate that statins were considered not tolerable in these patients in the past so that the treating physicians had chosen PCSK9is as an alternative. In general practice, the incidence rate of statin-associated muscle complaints has been estimated at 10 to 30 percent [21]. Hence the proportion of 14 percent of patients with PCSK9i alone, but without statins and with or without other oral agents lies within the range of the suspected prevalence of “statin intolerance. In particular, if one assumes that a certain enrichment of patients who are otherwise difficult to manage may have occurred in our registry. At least, we consider it unlikely that extremely high treatment naïve LDL-C made physicians to go for PCSK9i monotherapy, because treatment naïve LDL-C was 265 mg/dl (6.86 mmol/l) in treatment subgroup II compared to 300 mg/dl (7.76 mmol/l), 282 mg/dl (7.29 mmol/l), and 208 (5.37 mmol/l) in treatment subgroups I, III, and IV.

The differences in weight, body mass index and waist-to-hip ratio with lowest values in subgroup IV may show that overweight is considered as an additional risk factor and consequently lipid lowering therapy is initiated. In addition, treatment naïve LDL-C were lowest in subgroup IV, indicating an underestimation of cardio vascular risk in FH patients when assessing initiation of lipid lowering therapy.

Only 18% of FH-patients with CVD and 16% of patients without CVD attained the respective target values for LDL-C, despite lipid lowering therapy. However, the proportion of patients at goal increased, once a PCSK9is were used. In the absence of CVD, 69% of patients from treatment subgroup I (PCSK9i plus oral drugs) and 58% of patients from treatment subgroup II (PCSK9i only) reached the LDL-C of 100 mg/dl (2.59 mmol/l) or less. In the presence of CVD, 30% of the patients in treatment subgroup I and 17% of patients in treatment subgroup II reached 70 mg/dl (1.81 mmol/l) or less of LDL-C. In tendency, target value achievement was less in women than in men (Fig. 3A and B). This difference should be interpreted as descriptive and with caution, because splitting the population in treatment groups and in addition into men and women leads to very small subgroups.

It is also likely that many patients on PCSK9i may be very close to their individual target LDL-C. This is illustrated by the numbers in Fig. 4: Despite a substantial median absolute reduction in LDL-C of 113 mg/dl (2.92 mmol/l), the median gap-to-target without PCSK9i is still large (59 mg/dl (1.53 mmol/l)) in treatment group III. With PCSK9i there is no median gap-to-target (0 mg/dl, 0-mmol/l, in treatment subgroups I and II combined) with a median reduction of 161.5 mg/dl (4.18 mmol/l). We thereof conclude that PCSK9i treatment in addition to standard therapy allows attainment of target values in many patients with initially very high LDL-C concentrations. Nevertheless, all options of statin therapy including use of rosuvastatin and combination therapy with ezetimibe should be exploited before prescribing PCSK9 inhibitors.

Yet, the full potential of PCSK9 inhibition was apparently not fully exploited in our cohort. Assuming that every FH patient without CVD and LDL-C above 160 mg/dl (4.14 mmol/l) or every FH patient with CVD and LDL-C above 130 mg/dl (3.36 mmol/l) on conventional treatment would have an urgent indication for additional PCSK9i prescription [18] we found that 26% of patients with CVD and 22% of patients without would be eligible for these medicines, indicating under-treatment.

It should, however, be noted that many patients were included into the CaRe High registry on the occasion of their first presentation to lipid specialists, so that our data would not reflect their recommendation or the discharge medication. This information will be collected during a two years follow-up of our cohort and will hopefully demonstrate enhanced target value achievement.

### 4.1. Limitations

It is a limitation of the current study that we deliberately have chosen to leave it at the discretion of the treating physician to request genetic testing for the definite diagnosis of FH. At present, genetic information is available in 56 patients of whom 49 had a FH causing mutation. This corresponds to a proportion of 87.5 percent of genetically positive patients amongst those with clinical FH and matches well the typical diagnostic yield reported in the literature [22,23]. The low overall availability of genetic information in our cohort may also be indicative of a reluctance of German physicians to order genetic tests to establish the diagnosis of FH. We are currently seeking to increase the proportion of patients with genetic diagnosis during the follow-up period of our study and have, therefore, issued a call for action letter to the participating doctors and patients in describing the indications for genetic testing in detail.

Further, the CaRe High registry may not be representative of all FH

patients because the majority of the participating centers are specialized lipid clinics. This may lead to a selection bias regarding the treatment situation of FH patients because of the better expertise of the lipid clinic physicians. Yet, the degree of bias may be smaller than anticipated, because the current evaluation is a snapshot of the first presentation of patients to lipid clinics rather than a reflection of the patients' subsequent clinical course.

Although our study team interviewed each of the patients included personally, the current data rely on information and statements given by the patients and their physicians. Not all inquired information and laboratory values were available in every case. Thus, the total number of datasets varies for each analysis. LDL-C values before treatment were not known throughout so that we had to use correction factors depending on medication to calculate treatment-naïve LDL-C values (15).

Since we compared pre-treatment and on-treatment LDL-C in the same patients with comparatively high pre-treatment values, the "regression to the mean" phenomenon might have led to an over-estimation of the therapeutic differences postulated in the current study. However, we consider a major influence of the regression to the mean unlikely. First, in 217 out of 366 treated patients, we calculated the pre-treated LDL-C using factors derived from randomized clinical trials [15,24], which are not susceptible to regression to the mean. Second, comparison of calculated and actually measured pre-treatment LDL-C in patients in whom both were available did not reveal any substantial difference (supplementary material, Fig. 1). However, this of course does not rule out, that a slight regression to the mean may have occurred.

### 4.2. Conclusions

The CaRe High registry studies a population with many clinical features of FH and a high prevalence of CVD. A substantial proportion of our patients received PCSK9i either alone or combined with a non-statin lipid lowering agent. We speculate that statin associated side effects, at least their perception of treating physicians and/or patients, may limit the use of statins in clinical practice. Finally, the high proportion of LDL-C target achievement seen in patients on PCSK9i suggests that this class of drugs facilitates bringing patients with extremely high concentrations of LDL-C to their individual goals.

## Conflict of interest

NS is project lead of the CaRe High registry, which is financed in cooperation with Amgen GmbH and Sanofi-Aventis GmbH. AD is employed by the CaRe High registry. TBG, WR, CK, GK, US have nothing to disclose. UK reports personal fees from Sanofi, personal fees from Amgen, personal fees from Synlab academy, personal fees from Berlin Chemie, personal fees from Alexion, personal fees from Fresenius medical care, outside the submitted work. UJ reports personal fees from Amgen, personal fees from Sanofi, outside the submitted work. WK reports personal fees from AstraZeneca, personal fees from Novartis, personal fees from Pfizer, personal fees from The Medicines Company, personal fees from GSK, personal fees from DalCor, personal fees from Sanofi, personal fees from Berlin-Chemie, personal fees from Kowa, personal fees from Amgen, grants and non-financial support from Roche Diagnostics, grants and non-financial support from Beckmann, grants and non-financial support from Singulex, grants and non-financial support from Abbott, outside the submitted work. IGB reports personal fees and non-financial support from Amgen, personal fees and non-financial support from Sanofi, personal fees from Eli-Lilly, personal fees from Regeneron, personal fees from Aegereon, personal fees and non-financial support from Akcea, outside the submitted work. BO reports grants from Medizinische Klinik D, UKM, Lipidambulanz, Albert-Schweitzer-Campus 1 A, 48149 Muenster, Germany, during the conduct of the study; grants from • REVEAL-Trial "Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification" MSD (MERCK), grants from • NEFIGAN-Trial " Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind,Đrandomised, placebo-controlled phase 2b trial" Pharmalink, personal fees from Amgen, personal fees from Sanofi, personal fees from MSD, personal fees from Berlin Chemie, outside the submitted work. UL reports personal fees and other from Amgen, BerlinChemie, MSD, Sanofi outside the submitted work. EST received speakers' honoraria for presentations, advisory board activities and funding of research projects by Fresenius Medical Care Germany, Amgen, Sanofi and Berlin Chemie. HS reports personal fees from AMGEN, personal fees from Sanofi Aventis, personal fees from MSD SHARP&DOHME outside the submitted work. KP reports personal fees and non-financial support from Amgen, personal fees from Berlin-Chemie, personal fees from Boehringer-Ingelheim, personal fees from Merck Sharp & Dohme, grants, personal fees and non-financial support from Sanofi outside the submitted work. AV reports personal fees from Aegerion, personal fees from Amgen, personal fees from Fresenius, personal fees from Kaneka, personal fees from Regeneron/Sanofi, personal fees from Berlin Chemie outside the submitted work. WM reports grants and personal fees from grants and personal fees from AMGEN, grants and personal fees from Sanofi, during the conduct of the study; grants and personal fees from Siemens Diagnostics, grants and personal fees from Aegerion Pharmaceuticals, grants and personal fees from Astrazeneca, grants and personal fees from Danone Research, personal fees from Hoffmann LaRoche, personal fees from MSD, personal fees from Synageva, grants and personal fees from BASF, grants from Abbott Diagnostics, grants and personal fees from Numares AG, grants and personal fees from Berlin-Chemie, employment from Synlab Holding Deutschland GmbH, outside the submitted work.

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## Author contributions

NS drafted the manuscript and revised the statistical analysis. AD did the statistical analysis. TBG designed the study and wrote the study protocol. NS, WM and UL predefined the research questions. UL, IGB, UJ, UK, EST and KGP provided patient data and revised the manuscript. WR, GK, CK, BO, US, HS and AV provided patient data. WM and TBG revised the manuscript.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://

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