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ORIGINAL RESEARCH ARTICLE

PCSK9 Inhibitors in a German Single-Center Clinical Practice: Real-World Treatment of Patients at High Cardiovascular Risk Over 68 Weeks

Tim Hollstein[1] · Ursula Kassner[1] · Thomas Grenkowitz[1] · Friederike Schumann[1] · Thomas Bobbert[1] · Elisabeth Steinhagen-Thiessen[1]

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Abstract

Aims Several lipid guidelines recommend the use of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) for patients at high/very high cardiovascular risk who are inadequately treated with maximally tolerated lipid-lowering therapies (LLTs).

Objectives We assessed the effectiveness and safety of the PCSK9i alirocumab and evolocumab in a single-center clinical practice for up to 68 weeks.

Methods In this prospective, open-label study conducted in Germany, 635 enrolled patients were treated with alirocumab [75 or 150 mg every 2 weeks (Q2W)] or evolocumab (140 mg Q2W) according to European Society of Cardiology/European Atherosclerosis Society guidelines (low-density lipoprotein cholesterol [LDL-C] > 1.81/2.59 mmol/L (70/100 mg/dL), depending on cardiovascular risk]. Investigators were able to adjust LLTs, including PCSK9i, according to their own clinical judgment. The primary effectiveness endpoint was LDL-C reduction from baseline to week 68.

Results At baseline, approximately 50% of patients were statin intolerant, and approximately 90% reported a history of cardiovascular disease. LDL-C reductions remained generally unchanged from weeks 4 to 68 in each treatment group. At week 68, LDL-C mean percentage changes from baseline were −41.7% (alirocumab 75 mg Q2W), −53.7% (alirocumab 150 mg Q2W), and −54.1% (evolocumab 140 mg Q2W). LDL-C reduction was 7.1% greater in patients receiving statins than in those not receiving statins because of statin intolerance ($P < 0.0001$). PCSK9i consistently improved levels of other lipoproteins throughout. Overall, 47.1% of patients reported adverse events at week 68.

Conclusions Consistent with clinical trial findings, alirocumab and evolocumab improved lipid levels in a real-world setting in patients with high baseline LDL-C levels despite receiving maximally tolerated LLTs. PCSK9i were generally well-tolerated.

1 Introduction

Reductions in low-density lipoprotein cholesterol (LDL-C) are associated with reduced cardiovascular risk [1]. Several lipid guidelines and consensus statements recommend that it may be reasonable to consider protein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) for patients at high/very high cardiovascular risk, including those with cardiovascular disease (CVD) or heterozygous familial hypercholesterolaemia (HeFH) who have persisting high LDL-C levels despite receiving maximally tolerated statin treatment with or without other non-PCSK9i lipid-lowering therapies (LLTs) [1, 2], also including patients who are statin intolerant [1]. In 2019, the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) LDL-C target recommendations for patients at very high and high cardiovascular risk were lowered from < 1.81 mmol/L (< 70 mg/dL, very high risk) or < 2.59 mmol/L (< 100 mg/dL, high risk) to < 1.42 mmol/L (< 55 mg/dL) or < 1.81 mmol/L (< 70 mg/dL), respectively [1–3].

In 2015, two PCSK9i—alirocumab and evolocumab—became available to treat therapy-refractory

Tim Hollstein and Ursula Kassner Shared first author.

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✉ Elisabeth Steinhagen-Thiessen
elisabeth.steinhagen-thiessen@charite.de

[1] Division of Lipid Disorders, Department of Endocrinology, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, Ostring 3, 13353 Berlin, Germany

Key points

In a clinical single-center practice, the PCSK9 inhibitors alirocumab and evolocumab demonstrated long-term reductions of low-density lipoprotein cholesterol (LDL-C) similar to previously reported clinical trial data.

In addition, a greater LDL-C reduction was observed in patients receiving both PCSK9 inhibitor and statin therapies compared with those who received PCSK9 inhibitor treatment but were intolerant to statins.

PCSK9 inhibitor therapy was generally well tolerated and 8.5% of study participants discontinued treatment due to adverse events.

hypercholesterolemia [4–7]. An ongoing patent infringement lawsuit means that alirocumab is not currently available in Germany [8], but it remains on the market and approved for use in other European countries. Treatment with alirocumab 75 mg every 2 weeks (Q2W; with possible dose adjustment to 150 mg Q2W), alirocumab 150 mg Q2W, or evolocumab 140 mg Q2W resulted in significant percentage reductions in LDL-C in clinical phase III trials including patients with or without prior cardiovascular events or HeFH [9–12]. Both PCSK9i therapies have been shown to improve cardiovascular outcomes [11, 12].

In contrast to clinical studies that enrolled patients using more tightly controlled inclusion criteria, PCSK9i are prescribed to patients with a variety of comorbidities in real-world routine care; however, limited real-world data are available [13–19].

The aim of this study was to assess the short-term (2–4 weeks) and long-term (68 weeks) effectiveness and safety of alirocumab 75 mg Q2W, alirocumab 150 mg Q2W, and evolocumab 140 mg Q2W in a large patient cohort ($n = 635$) in a real-world setting in a single-center practice in Germany.

2 Methods

This noninterventional, prospective, observational, single-center study was performed at the lipid clinic of the Charité Universitätsmedizin Berlin in Germany (noninterventional study number 342) [20]. The decision to prescribe either alirocumab or evolocumab was independent from study participation, and all treatment decisions remained at the discretion of the treating physician. The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and all applicable amendments laid down by the World Medical Assemblies and the International Conference Harmonization guidelines for good clinical practice. The protocol was approved by the institute's ethics committee on human research (EA4/178/15). All patients provided written informed consent prior to documentation.

2.1 Study Design

Patients recruited from the outpatient lipid clinic of the Charité Universitätsmedizin Berlin (Berlin, Germany) between 2015 and 2018 were eligible for participation if their LDL-C levels were (1) ≥ 1.81 mmol/L (≥ 70 mg/dL) with established CVD or (2) ≥ 2.59 mmol/L (≥ 100 mg/dL) with HeFH and without CVD. Enrolled patients were treated with either alirocumab or evolocumab according to the summary of product characteristics [5, 6].

All patients had hypercholesterolemia, with either very high cardiovascular risk according to ESC/EAS guidelines [1], HeFH and family history of early CVD despite maximally tolerated LLT, or homozygous FH. Cardiovascular risk was defined according to ESC guidelines [1]. HeFH diagnosis was defined by clinical criteria (World Health Organization/Dutch Lipid Clinic Network score > 8 points).

PCSK9i were prescribed Q2W on top of statin therapy and other LLTs. Patients were allocated to receive either alirocumab 75 mg Q2W, alirocumab 150 mg Q2W, or evolocumab 140 mg Q2W according to investigator's judgement, with both study drugs being equally prescribed. Throughout the study, physicians were able to adjust the treatment dose (75 mg Q2W, 150 mg Q2W, or 140 mg Q2W) of the PCSK9i (alirocumab or evolocumab) and other non-PCSK9i LLTs according to their own clinical judgment and the summaries of product characteristics [5, 6].

Statin intolerance was defined as the inability to tolerate three or more statins according to patient's adverse events (AE) and/or objective parameters (i.e., increased levels of creatine kinase, aspartate aminotransferase, or alanine aminotransferase) [21, 22]. For statin-treated patients, the intensity of statin therapy was categorized as low intensity (simvastatin 10 mg, pravastatin 10–20 mg, or fluvastatin 20–40 mg), moderate intensity (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–80 mg, pravastatin 40 mg, or fluvastatin 80 mg), and high intensity (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) [23].

Prior to treatment start, patients completed a standard questionnaire regarding medical history and underwent a routine clinical examination. Diabetes mellitus, hypertension, and CVD (defined as coronary artery disease and/or cerebral artery disease and/or peripheral artery disease) were identified from medical records.

All patients received usage instructions from a physician. The study inclusion criteria were PCSK9i prescription, informed consent in the form of written authorization, and patient age ≥ 18 years.

2.2 Study Endpoints

The primary effectiveness endpoint of this study was percentage change in LDL-C from baseline to week 68.

Secondary effectiveness endpoints included (1) percentage change from baseline to week 4 in LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, triglycerides, apolipoprotein (Apo) B, lipoprotein (a) [Lp(a)], total cholesterol, and Apo A1 and (2) percentage change from baseline to week 68 in HDL-C, non-HDL-C, and triglycerides.

Patient blood samples were taken and lipid data were recorded before the start of PCSK9i therapy (baseline; week 0) and after 4 weeks and approximately 68 weeks of treatment. Laboratory tests using fasting blood samples were performed at a local laboratory (Labor Berlin, Berlin, Germany) before and after 1 month of treatment during routine visits to the outpatient clinic. At weeks 4 and 68, laboratory data were obtained from the most recent available blood sample. Apo A1, Apo B, and Lp(a) were only measured at baseline (week 0) and week 4.

LDL-C was measured via beta-quantification. Pre-LLT LDL-C levels (LDL-C value without any concomitant LLT) were calculated based on conversion factors as previously described [24].

Safety was assessed regardless of treatment allocation by monitoring AEs during an in-clinic interview after 2 weeks and during either a telephone interview or routine in-clinic visit after approximately 68 weeks. No severity of AEs was recorded.

2.3 Statistical Analysis

All quantitative data of continuous and categorical variables were summarized using means and standard deviations or medians and interquartile ranges (IQRs) (Q3: 75% percentile minus Q1: 25% percentile) where appropriate. Changes in lipid levels are shown as absolute changes (defined as arithmetic mean/median of week 4 or week 68 minus baseline) and percentage changes (defined as ratio of mean/median). The paired and unpaired sample *t*-test was used to compare normally distributed values; skewed data were log transformed before analyses. The Wilcoxon rank-sum test was used for skewed variables (triglycerides and Lp(a)) to compare absolute changes; the *t*-test was used to compare percent changes. The chi-quadrat test was used to compare categorical data. Pearson correlation coefficients were used to examine associations between variables. Comparisons among the groups were made with analysis of variance. To account for missing follow-up data, linear mixed-model analyses were performed as post hoc sensitivity analyses including all percentage LDL changes from baseline to weeks 4 and 68 (both calculated from baseline LDL) while accounting for missing follow-data and repeated measures using a first-order autoregressive covariance structure and adjusting for follow-up time and prescribed PCSK9i. All statistical analyses were carried out using SAS Enterprise Guide V7.15 (SAS Institute, Cary, NC, USA).

3 Results

3.1 Baseline Characteristics

Of 704 eligible patients, 635 were included in this study at baseline and 69 were excluded because of incomplete clinical or laboratory data (electronic supplementary material [ESM] Fig. S1). Overall, 310 patients with complete follow-up data who received PCSK9i therapy for at least 1 year were included in the follow-up analysis. The remaining 325 patients were not included in the follow-up analysis because follow-up data were missing as these patients received PCSK9i therapy for less than 1 year.

At baseline (prior to study drug treatment), the study cohort consisted of 635 patients. Across all PCSK9i treatment groups, 19.4–26.4% of patients had diabetes mellitus, 56.9–66.7% reported hypertension, and 86.3–92.0% had a history of CVD, with coronary heart disease (CHD) being most common (49.5–57.9%; ESM Table S1). In total, 50.4–60.3% of patients were statin intolerant. The mean LDL-C levels prior to receiving any LLT (including statins) were 5.3–6.2 mmol/L (203.5–238.0 mg/dL). Before receiving PCSK9i treatment, patients enrolled in the alirocumab 75 mg group had lower mean LDL-C levels (3.5 mmol/L [135.6 mg/dL]) than those in the remaining groups (4.3–4.4 mmol/L [167.7–170.2 mg/dL]). The median follow-up period was 68 weeks (IQR 20) after enrolment, with data being available for 310 patients. In total, 2.4% (14/635) of patients discontinued the study after 4 weeks and an additional 6.8% (21/310) discontinued after 68 weeks (reasons: AEs, $n = 33$; pregnancy, $n = 1$; no improvement in LDL-C levels with both PCSK9i, $n = 1$; ESM Fig. S1).

3.2 Effectiveness Analysis—Overall Patient Population

The initial study drug dose was alirocumab 75 mg Q2W in 19.7% of patients ($n = 125$), alirocumab 150 mg Q2W in 30.7% ($n = 195$), and evolocumab 140 mg Q2W in 49.6% ($n = 315$). In total, 81.0% ($n = 51$) of patients in the alirocumab 75 mg Q2W, 75.0% ($n = 81$) in the alirocumab 150 mg Q2W, and 84.9% ($n = 118$) in the evolocumab

140 mg Q2W groups remained on their initially prescribed PCSK9i dose throughout the study (ESM Table S2). At week 68, in total, 15.9% and 3.2% of patients in the alirocumab 75 mg Q2W group were initially prescribed alirocumab 150 mg Q2W and evolocumab 140 mg Q2W, respectively.

In patients who remained on their initially prescribed PCSK9i dose, mean percentage change from baseline to week 68 in LDL-C was − 41.7% in the alirocumab 75 mg Q2W group, − 53.7% in the alirocumab 150 mg Q2W group ($P < 0.05$ vs. alirocumab 75 mg Q2W group), and − 54.1% in the evolocumab 140 mg Q2W group ($P < 0.05$ vs. alirocumab 75 mg Q2W group; ESM Table S3). Similar results were obtained with linear mixed-model analyses, which account for missing follow-up data. LDL-C reductions remained largely similar from weeks 4 to 68 in each treatment group (Fig. 1 and ESM Table S3). At week 4, alirocumab 150 mg Q2W and evolocumab 140 mg Q2W reduced LDL-C from baseline by 59.0% and 57.5%, respectively. In the alirocumab 75 mg group, the LDL-C reduction of 48.1% from baseline to week 4 was significantly lower than in the other treatment groups (all $P < 0.05$). Waterfall plots of individual patient data at weeks 4 and 68 showed a similar distribution of percentage LDL-C reduction in all PCSK9i groups (Fig. 2). No nonresponders with LDL-C reduction < 10% from baseline were observed.

Regardless of treatment allocation, 59.5% of patients at week 4 and 57.3% at week 68 achieved LDL-C < 1.81 mmol/L (70 mg/dL) or < 2.59 mmol/L (100 mg/dL), depending on cardiovascular risk. Overall, 57.5% and 54.8% of patients achieved LDL-C < 1.81 mmol/L (70 mg/dL) at weeks 4 and 68, respectively.

Regardless of PCSK9i treatment, improvements in lipid levels from baseline to weeks 4 and 68 were observed (Fig. 1 and ESM Table S3). At week 4, percentage reductions from baseline in non-HDL-C, total cholesterol, Lp(a), and Apo B were significantly lower in the alirocumab 75 mg Q2W versus alirocumab 150 mg Q2W and evolocumab 140 mg Q2W groups (all $P < 0.05$; ESM Table S3). Similar results were observed at week 68, except for nonsignificant differences in LDL-C percentage reduction between the alirocumab 75 mg Q2W and alirocumab 150 Q2W groups. No week 68 data were available for Lp(a), Apo B, and Apo A1.

In exploratory analyses, we assessed the associations between changes in Lp(a) due to PCSK9i therapy and concomitant changes in LDL-C and baseline Lp(a) (Fig. 3). At week 4, increased percentage Lp(a) reduction was associated with a greater concomitant percentage LDL-C reduction ($r = 0.31$, $P < 0.0001$; Fig. 3a), and a higher Lp(a) concentration at baseline was associated with reduced percentage reduction in Lp(a) ($r = 0.21$, $P < 0.0001$; Fig. 3b). In patients with baseline Lp(a) levels < 72 mmol/L, a higher baseline Lp(a) was associated with a greater percentage reduction in Lp(a) with PCSK9i therapy ($r = –0.26$, $P = 0.0003$; Fig. 3c). In contrast, no association was observed in patients with baseline Lp(a) levels > 72 mmol/L ($P = 0.21$; Fig. 3d).

In total, 12.6% of patients reported cardiovascular events over the course of the study, with revascularization being the most common (8.1%; ESM Table S4).

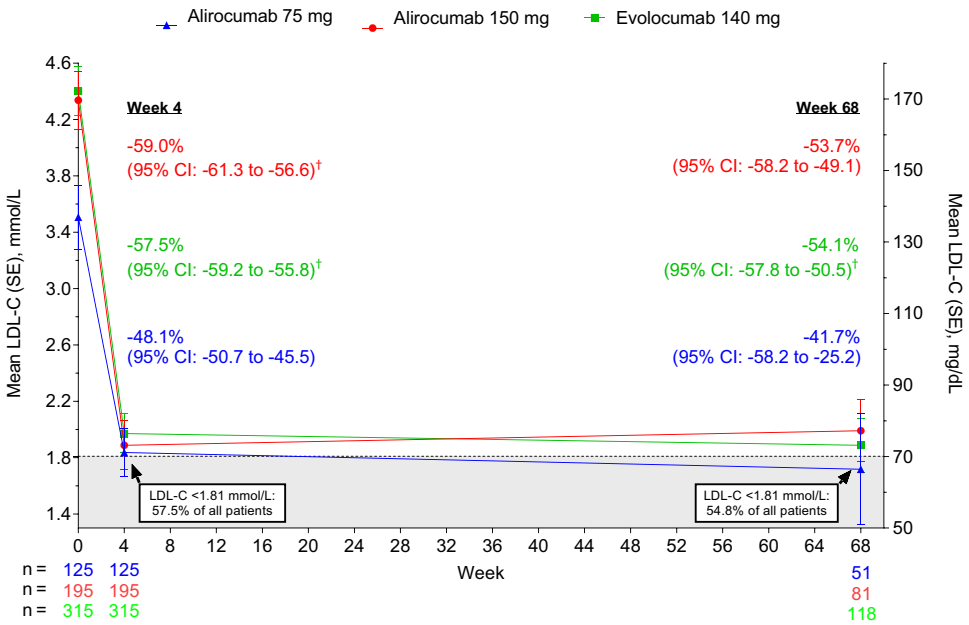

Fig. 1 LDL-C levels over time in patients continuously treated with alirocumab 75 mg Q2W, alirocumab 150 mg Q2W, or evolocumab 140 mg Q2W. The area highlighted in *grey* shows LDL-C ≤ 1.81 mmol/L (≤ 70 mg/dL). Data values show mean percentage LDL-C reduction from baseline at weeks 4 and 68 (95% CI). [a]$P < 0.05$ vs. alirocumab 75 mg. *CI* confidence interval, *LDL-C* low-density lipoprotein cholesterol, *Q2W* every 2 weeks, *SE* standard error

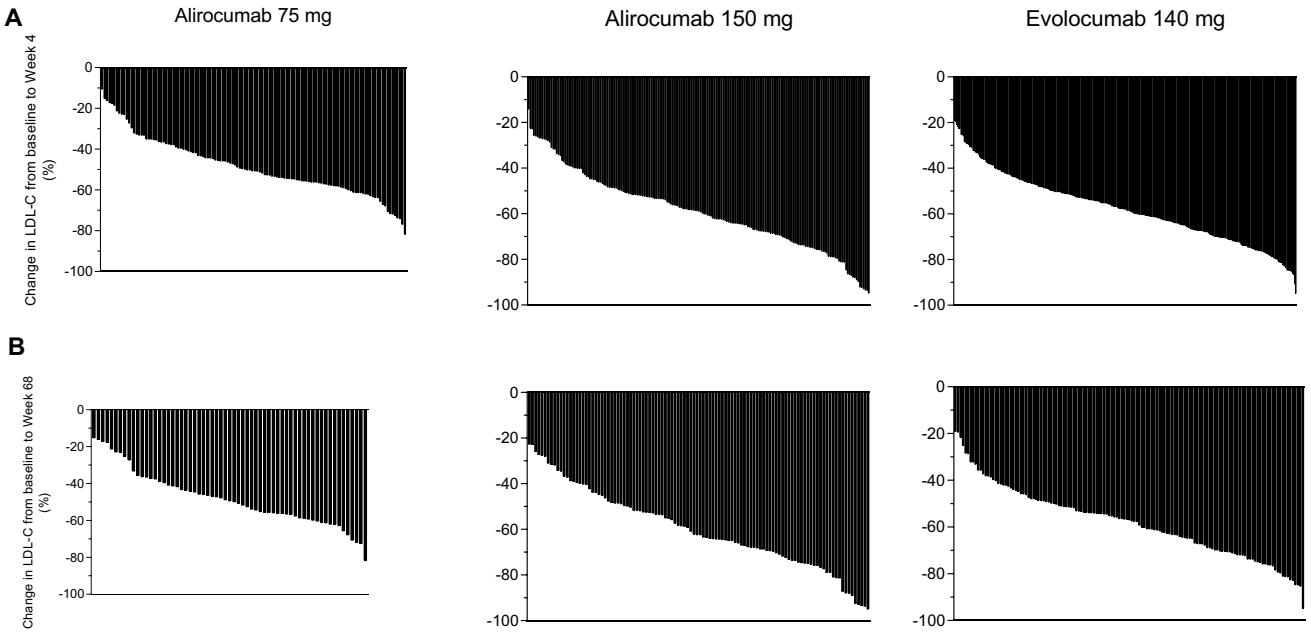

Fig. 2 Waterfall plots of percentage low-density lipoprotein cholesterol (LDL-C) reduction from baseline to (**a**) week 4 and (**b**) week 68 according to treatment received at week 68

3.3 Effectiveness Analysis According to Statin Therapy Status

Greater percentage reductions from baseline to week 4 in LDL-C, total cholesterol, and triglycerides were observed in patients receiving statin therapy than in those with statin intolerance ($P < 0.05$; Fig. 4a). In patients with statin intolerance, a higher baseline Dutch Lipid Clinic Network Score was associated with a reduced percentage LDL-C reduction from baseline at week 4 ($r = 0.22$, $P < 0.0001$; Fig. 4b). In contrast, no association was observed in patients receiving statins (Fig. 4c).

3.4 Safety Analysis

Overall, a total of 47.7% of patients had reported AEs by week 2 (after the first treatment dose), with rhinitis (17.4%), fatigue (15.7%), and myalgia (9.1%) being among the most common (ESM Table S5). In total, 47.1% of patients reported AEs throughout the study, with myalgia (12.6%), rhinitis (11.6%), and fatigue (10.3%) being the most common. A total of 2.4% of patients discontinued the study due to AEs at week 2 and a further 6.1% discontinued by week 68. By week 68, a total of 8.7% of patients had changed PCSK9i treatment because of AEs.

In a safety analysis by sex, 41.1% of male patients and 57.1% of female patients had reported AEs by week 2 (ESM Table S6). Significant differences were observed between both groups for fatigue, joint pain, back pain, headache, sore throat, nausea, vertigo, and pruritus (all $P \leq 0.05$). These sex-specific differences were not observed at week 68 (ESM Table S6).

4 Discussion

In this study presenting real-world data from patients receiving maximally tolerated statin and other non-PCSK9i LLTs, LDL-C levels were reduced from baseline to week 68 by 43.2% in the alirocumab 75 mg Q2W group, 53.8% in the alirocumab 150 mg Q2W group, and 53.3% in the evolocumab 140 mg Q2W group.

The observed alirocumab effectiveness data were consistent with results from a pooled analysis from eight ODYSSEY phase III studies ($n = 4629$), in particular the study pool with the dosing regimen 75 mg Q2W (with possible dose adjustment to 150 mg Q2W) showing 48.6–48.9% reduction in LDL-C levels from baseline to week 24 in alirocumab-treated patients (placebo, 4.2% increase; ezetimibe, 19.3% reduction) [9]. Clinical study results for evolocumab 140 mg Q2W were generally similar to effectiveness results from this study, showing reductions in LDL-C levels from baseline to week 12 of an average of 57.0% in 614 patients with LDL-C ≥ 2.59 mmol/L (100 mg/dL) and < 4.91 mmol/L (190 mg/dL; placebo, 0.1% reduction) [25]. These data are

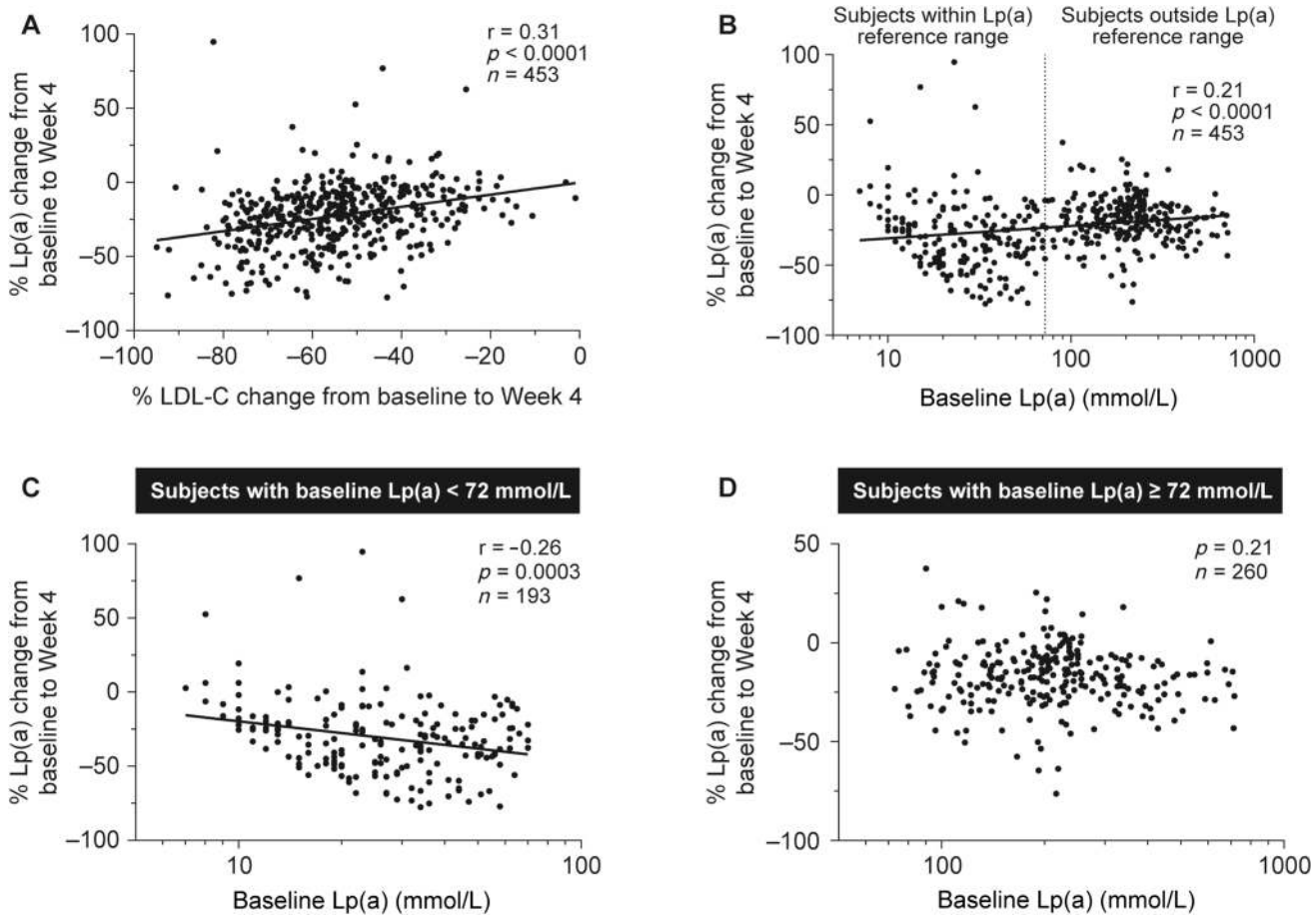

Fig. 3 Association between percentage Lp(a) reduction and (**a**) percentage LDL-C reduction from baseline to week 4, baseline Lp(a) (**b**) for the overall population and according to (**c**) Lp(a) < 72 mmol/L and (**d**) Lp(a) > 72 mmol/L. *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein (a)

also consistent with an audit study in the UK showing a reduction in LDL-C levels of 49% in patients ($n = 105$) on maximally tolerated statin who received PCSK9i therapy [18] and an alirocumab expanded use program demonstrating that alirocumab 150 mg Q2W reduced LDL-C levels by 55.1% at week 24 in patients with HeFH and/or CHD in the USA [26]. In an outpatient clinic in the Netherlands, approximately 17 months of treatment with either alirocumab or evolocumab resulted in a mean LDL-C reduction of 55% from baseline (4.4 mmol/L [170.1 mg/dL]) in a cohort of 238 patients, with similar reductions being observed across alirocumab (75 mg Q2W or 150 mg Q2W) and evolocumab dose regimens (140 mg Q2W or 420 mg monthly) [13]. In a retrospective study ($n = 122$) in Italy, a mean LDL-C reduction of 52% from baseline (4.5 mmol/L [174 mg/dL]) was observed after approximately 13 months of treatment with either alirocumab or evolocumab, with no difference between drug regimens [27].

In comparison, this present study enrolled more patients ($n = 635$) and assessed the effectiveness according to evolocumab and alirocumab dose regimens at weeks 4 and 68, demonstrating significantly ($P < 0.05$) lower LDL-C reductions in the alirocumab 75 mg Q2W group than in either the alirocumab 150 mg Q2W group or the evolocumab 140 mg Q2W group. In contrast to a previously published systematic review and network meta-analysis of LLTs (69 trials) demonstrating approximately 10% greater reduction with evolocumab than with alirocumab 150 mg Q2W, the reductions in LDL-C with alirocumab 150 mg Q2W and evolocumab 140 mg Q2W were similar in this study [28].

ESC/EAS lipid guidelines recommend treatment goals of < 1.42 mmol/L (< 55 mg/dL) or < 1.81 mmol/L (70 mg/dL) in patients at very high and high cardiovascular risk, respectively [3]. In this study, LDL-C target levels were < 1.81 mmol/L (< 70 mg/dL) or < 2.59 mmol/L (< 100 mg/dL), depending on cardiovascular risk and based on 2016 ESC/EAS guidelines, which were relevant during patient enrolment in this study [1]. LDL-C target levels were achieved by 59.5% of patients at week 4 and

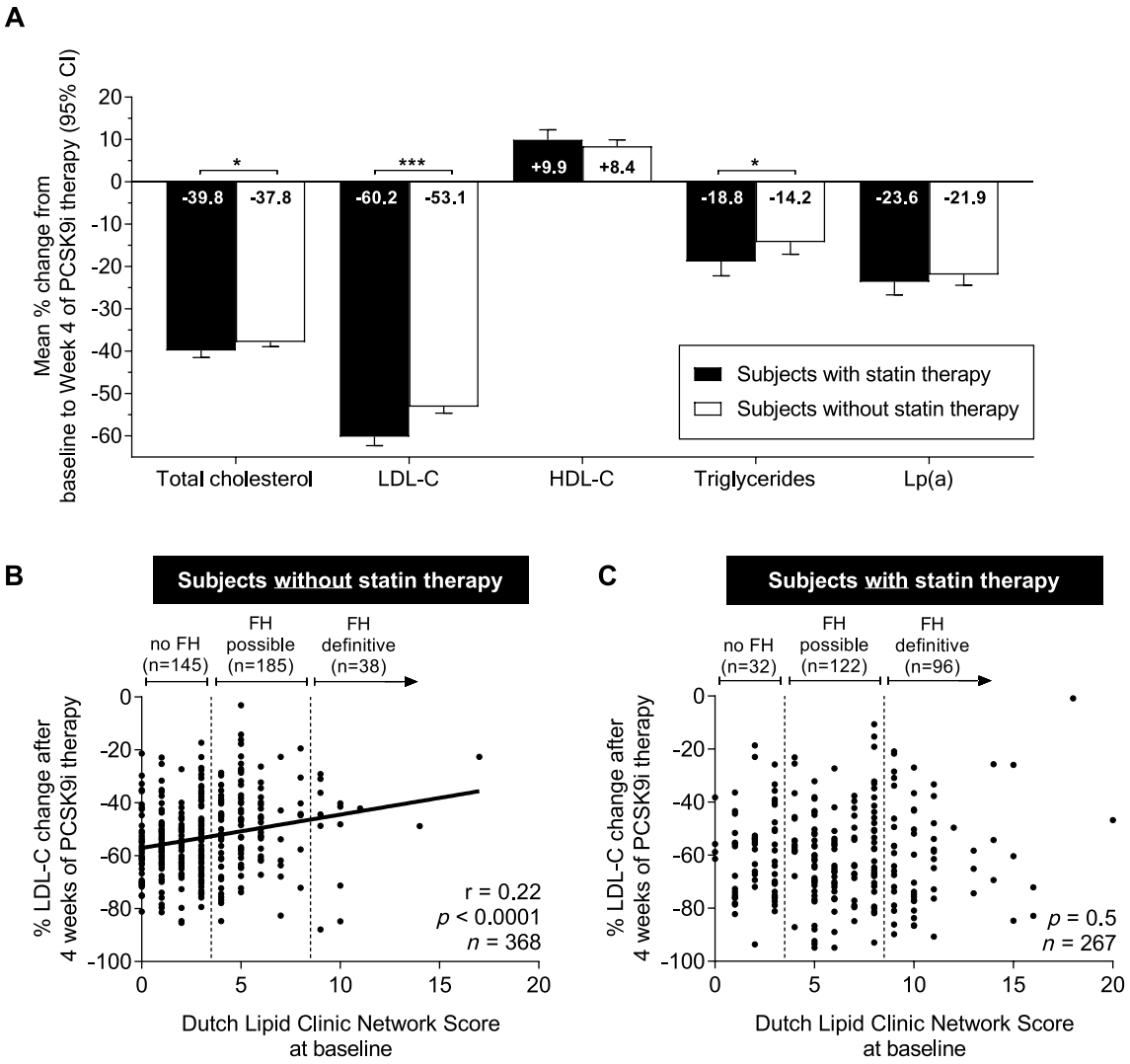

Fig. 4 Influence of statin therapy on PCSK9i effectiveness regardless of treatment allocation: (**a**) mean percentage change from baseline to week 4 for lipids, and correlation of percentage change of LDL-C from baseline to week 4 according to Dutch Lipid Clinic Network Score in (**b**) patients not receiving statins and (**c**) those receiving statins. $^{*}P < 0.05$ and $^{***}P < 0.0001$ (both assessed by unpaired *t*-test). *FH* familial hypercholesterolaemia, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein (a), *PCSK9i* protein convertase subtilisin/kexin type 9 inhibitor

by 57.3% at week 68 regardless of PCSK9i treatment. Similar results were observed at week 24 in the ODYSSEY ALTERNATIVE study (41.9%) and at week 96 in the ODYSSEY OLE study (55.3%) [29, 30].

In many countries, such as the USA, PCSK9i accessibility is limited because they are more expensive than other LLTs [31, 32]. However, in Germany, there is no possible barrier to access PCSK9i as they can be prescribed according to directives from the Federal Joint Committee ("Gemeinsamer Bundesausschuss"), which are based on ESC guidelines [33, 34]. Compulsory health insurance accepts full responsibility for these costs.

For this study, the dose interval remained at Q2W throughout the study period and was not adjusted to every 4 weeks; however, possible benefits from extending the dosing interval to every 3 weeks to further individualize treatment were shown [35].

It has been shown that statin treatment increases PCSK9 expression in hepatocytes [36], which might reduce the effectiveness of statins by increasing LDL-receptor degradation [37]. In this study, at least 50% of patients had statin intolerance (50.4–60.3%, depending on treatment allocation). This relatively high number of statin-intolerant patients is due to enrolled patients were being treated at

a lipid clinic that specializes in the treatment of statin-intolerant patients. A similar ratio of statin-intolerant patients was observed in the German PEARL real-world study [38]. Patients without statin therapy demonstrated significantly lower reductions in LDL-C from baseline to week 4 than did patients on background statins (53.1% and 60.2%, respectively; $P < 0.0001$). These data concur with clinical study data that might indicate greater efficacy of PCSK9i in patients receiving background statins [9, 10] versus those with statin intolerance [39, 40].

Alirocumab and evolocumab were generally well-tolerated, with 47.7% and 47.1% of patients reporting AEs at weeks 2 and 68, respectively, and with 2.4% and 6.1% of enrolled patients discontinuing the study due to AEs after week 2 and after week 68, respectively (most common were myalgias and gastrointestinal side effects). In a pooled analysis of 14 clinical studies with alirocumab (8–104 weeks study duration), 76.0–78.4% of alirocumab-treated patients ($n = 3340$) reported treatment-emergent AEs (placebo, 78.7% [$n = 1276$]; ezetimibe, 73.9% [$n = 618$]) [41]. In a pooled analysis of four evolocumab studies (12-week study), 56.1% of patients treated with evolocumab 140 mg Q2W ($n = 123$) reported treatment-emergent AEs [10].

In this study, more women than men reported fatigue, joint pain, back pain, headache, sore throat, nausea, vertigo, and pruritus at week 2. Sex differences in AEs were previously reported [42]; however, to our knowledge, no data have been previously published for PCSK9i therapy.

Cardiovascular events were reported for 12.6% of patients, which is a higher frequency than in ODYSSEY OUTCOMES (9.5% of patients in the alirocumab group) and FOURIER (9.8% in the evolocumab group) [11, 12]. However, this study was neither designed nor powered for analysis of the effects of alirocumab or evolocumab on cardiovascular events; this was assessed in the ODYSSEY OUTCOMES [11] and FOURIER [12] studies. Furthermore, the patient population included in this real-world study was more heterogenous because patients with severe CVD, renal impairment, and other comorbidities would be excluded from participating in clinical trials.

Limitations of this study include the restriction of assessments to routine clinical visits and lack of comparison to a control group not receiving PCSK9i therapy. Patients knew they were receiving PCSK9i treatment, which may have influenced their adherence to background LLTs and diet, thereby creating a bias. Furthermore, in patients who remained on stable PCSK9i therapy throughout the study, adjustment in concomitant LLTs might have altered the effectiveness results at week 68. This study also enrolled patients at only one study center, which further limits the generalizability of the study results. In addition, alirocumab is currently withdrawn from the market in Germany.

To our knowledge, this is the largest real-world study in Germany observing the effectiveness and safety of alirocumab 75 mg Q2W, alirocumab 150 mg Q2W, and evolocumab 140 mg Q2W, analyzing data from 635 patients with a diverse range of comorbidities treated for up to 68 weeks with PCSK9i therapy.

5 Conclusions

The results of this single-center real-world study in Germany demonstrate that individualized therapy with alirocumab 75 mg Q2W, alirocumab 150 mg Q2W, or evolocumab 140 mg Q2W improved LDL-C levels and other lipoproteins and was generally well-tolerated; the overall discontinuation rate due to AEs was 8.5%.

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Compliance with Ethical Standards

Conflicts of Interest Tim Hollstein received non-financial support from Sanofi during the conduct of the study and has received non-financial support from Sanofi and Amgen unrelated to the submitted work. Ursula Kassner has received speaker honoraria from Amgen, Sanofi, Alexion, Amrhyt, Berlin Chemie, Fresenius Medical Care, and Synlab Academy. Thomas Grenkowitz has received personal fees from Sanofi and Fresenius Medical Care unrelated to the submitted work. Friederike Schumann has received grants from Amgen unrelated to the submitted work. Thomas Bobbert has no potential conflicts of interest that might be relevant to this work. Elisabeth Steinhagen-Thiessen has received speakers' honoraria from Sanofi, Amgen, Pfizer, Berlin Chemie, and Akcea.

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