Metabolic Effects of PCSK9 Inhibitors in a Tertiary Care Center – Real World Data

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Abstract

Background

The lipid-lowering and positive cardiovascular effect of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors was shown in several studies, hence, they are more widely used in the lipid-lowering management of patients with high cardiovascular risk. As real-world data are still scarce, the aim of this retrospective analysis was to investigate the efficacy of PCSK9 inhibitors in lowering low-density lipoprotein cholesterol (LDL-C) in an outpatient clinic of a tertiary care center in routine care.

Methods

A retrospective analysis of data extracted from the electronic patient record was performed. Patients who were routinely prescribed with PCSK9 inhibitor therapy (Alirocumab or Evolocumab) during the years 2016 and 2019 were included in the analysis. Characteristics of the patient population, the effects on LDL-C and HbA1c levels were assessed over the course of treatment.

Results

We identified 237 patients treated with PCSK9 inhibitors between January 2016 and September 2019. Almost all patients (97.5%) received PCSK9 inhibitors for secondary prevention. Comorbidities at baseline included: arterial hypertension (68.8%), diabetes mellitus (25.3%), smoking (5.9%). Vascular disease at baseline was present as follows: coronary heart disease (74.7%), history of stroke or transient ischemic attack (13.5%), carotid artery disease (30.8%), peripheral artery disease (18.1%), chronic kidney disease (9.7%), history of percutaneous coronary intervention (46.4%), history of coronary artery bypass surgery (16.0%).

Intolerance to statins (83.1%), ezetimibe (44.7%), and both agents was reported frequently (42.6%).

Six to nine months after initiation of PCSK9 inhibitor therapy, 61.7% of the patients achieved LDL-C levels ≤70 mg/dl, and 44.3% achieved LDL-C levels ≤55 mg/dl. The median LDL-C was lowered from 141 (IQR 117 - 188) mg/dl at baseline, to 60 (43 - 91) mg/dl (6 to 9 months) and 67 (44 - 89) mg/dl (12 to 18 months) indicating a reduction of LDL-C as follows: -54.9% (interquartile range (IQR) 44.4 – 57.3) after 6 to 9 months, -53.2% (IQR 42.6 – 67.1) after 12 to 18 months from baseline.

Conclusions

Significant reductions in LDL-C and a high percentage of patients achieving recommended treatment targets were observed. Still some patients did not achieve LDL-C levels recommended in current guidelines. Special attention to the characteristics of these patients is required in the future to enable achievement of treatment goals and avoid adverse cardiovascular outcomes.

Background

Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor in the development of atherosclerotic cardiovascular disease (ASCVD). Several studies have shown unequivocal evidence that high levels of LDL-C have an unfavorable effect on ASCVD and contribute to cardiovascular death.(1-3) At present,

statins are the first-line therapy for LDL-lowering, in addition to lifestyle interventions, in most patients. Further pharmacological lipid-lowering options include combinations of ezetimibe, bile acid sequestrants, fibrates and proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors.(4)

Both, the FOURIER trial on Evolocumab and the ODYSSEY OUTCOMES trial on Alirocumab showed that PCSK9 inhibitors were not only capable to significantly lower LDL-C levels, but also result in a substantial reduction of the cardiovascular event rate without relevant risk of adverse events.(5, 6)

Pathophysiologically elevated concentrations of circulating PCSK9 are adversely associated with cardiovascular metabolic markers and inferior cardiovascular outcome(7). As recommended in the guidelines for the management of dyslipidemias by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) published in 2019, treatment with a PCSK9 inhibitor is indicated for secondary prevention to lower plasma LDL-C in very-high risk patients who do not achieve their target LDL-C or even for primary prevention in particular very-high risk patients as those with familial hypercholesterolemia (FH) who do not achieve their LDL-C goal despite maximal tolerated therapy with statins and ezetimibe.(4) In 2015, the PCSK9 inhibitors Alirocumab and Evolocumab were approved in the European Union by the European Medicines Agency.

Data on the beneficial effects such as cardiovascular event reduction and achievement of LDL-C goals of PCSK9 inhibitors was confirmed in several clinical trials. (5, 6) However, real-world data from routine clinical practice are still scarce. Since patients who participate in clinical trials are usually seen frequently throughout the course of the study, are provided free of charge with study medication and adherence to medication is closely monitored which can be subsumed as study effect, there might be differences in routine care that are worth investigating.

The aim of this retrospective analysis was to investigate the effect of PCSK9 inhibitor therapy on markers of lipid metabolism, to determine patient characteristics, to assess the indications for introduction and to evaluate the tolerability of PCSK9 inhibitor therapy in routine care in an outpatient setting at a tertiary care center. In addition, we intended to examine potential influence of PCSK9 inhibition on glycemic control assessed by HbA1c in patients with or without diabetes mellitus.

Methods

This study was a retrospective data analysis approved by the Medical University of Graz, Austria (EK number 32-018 ex 19/20). Data was extracted from the electronic patient records of the University hospital in the years January 2016 - September 2019. Electronic records of adult patients with current or past PCSK9 inhibitor treatment in routine care at the outpatient clinic of the Division of Endocrinology and Diabetology were searched and included in the analysis. Inclusion criteria: age >18 years, treatment with locally available PCSK9 inhibitors (Alirocumab 75 or 150 mg, or Evolocumab 140 mg), available data records of LDL-C levels at first application and LDL-C follow-up >3 months.

The following search terms were used to screen for eligible patients: *PCSK*, Repatha, Praluent, *cumab.* From eligible patients the following parameters were drawn from the electronic patient record: age, sex, lipid-lowering therapy at baseline (i.e. statins, ezetimibe, fibrates), cause for prescription of PCSK9 inhibitor (intolerance to

lipid-lowering medications at baseline, failure to achieve individual LDL-C levels; primary or secondary prevention as indication), type of PCSK9 inhibitor (i.e. Alirocumab or Evolocumab), PCSK9 inhibitor therapy adjustments (agent, discontinuation). Baseline macrovascular (coronary heart disease, stroke, transient ischemic attack, peripheral artery disease, carotid artery disease) and microvascular (retinopathy, nephropathy) comorbidities, previous cardiovascular interventions (i.e. percutaneous coronary revascularization or coronary artery bypass grafting) and further cardiovascular risk factors (i.e. smoker status, hypertension, diabetes mellitus) were assessed. The following laboratory parameters were extracted: LDL-C, high-density lipoprotein cholesterol [HDL-C], triglycerides, total cholesterol, lipoprotein (a), and HbA1c at baseline and during PCSK9 inhibitor therapy for up to 18 months whenever collected in routine care. Number of patients who were lost to follow-up (missing documentation regarding PCSK9 inhibitor therapy ≥1 year) or patients who discontinued therapy (i.e. adverse drug effects towards PCSK9; noncompliance) were also determined. Baseline was defined as the day of the first PCSK9 inhibitor application.

Results

Patient characteristics and laboratory parameters at baseline

We identified 237 eligible patients who received Alirocumab or Evolocumab (104 and 133 patients) between January 2016 and September 2019.

The median age of the population was 65.2 years (interquartile range [IQR] 57.8 – 71.5), 47.7% were female. Almost all patients (97.5%; n=231) received PCSK9 inhibitors for secondary prevention.

Medical history included 74.7% (n=177) coronary heart disease, 46.4% (n=110) at least one percutaneous coronary intervention, 16.0% (n=38) coronary artery bypass graft (CABG), 13.5% (n=32) stroke or transient ischemic attack, 30.8% (n=73) carotid artery stenosis, 18.1% (n=43) peripheral artery disease, and 9.7% (n=23) chronic kidney disease. Any type of familial hypercholesterolemia (mostly diagnosed using clinical criteria, no one identified with homozygous FH) was present in 21.5% (n=51) of the patients. The following relevant comorbidities were identified at baseline: arterial hypertension (68.8%; n=163), diabetes mellitus (25.3%; n=60) (10.0% [n=6] type 1, 86.6% [n=52] type 2, and 3.3% [n=2] other forms) and active smoker status (5.9%; n=14).

Out of the 237 included patients, 83.1% (n=197) reported intolerance to at least one statin, 44.7% (n=106) reported side-effects to ezetimibe. 42.6% (n=101) indicated statin and ezetimibe intolerance.

The full characteristics of the patient cohort including the distribution among PCSK9 treatment agent are listed in Table 1.

The majority of patients (n= 231; 97.5%) received PCSK9 inhibitor therapy for secondary prevention. Apart from hypercholesterolemia, more than half of the study population (53.6%) had two or more additional cardiovascular risk factors (arterial hypertension, chronic kidney disease, Age ≥ 65 years, diabetes mellitus, smoking). About one third (31.2%) had clinical manifest vascular disease affecting two or more sites (coronary heart disease, stroke or TIA, peripheral or carotid artery disease). Table 2 indicates further comorbidities present at baseline.

At baseline LDL-C levels were ≥100 mg/dl in 86.9% of the patients, ≥150 mg/dl in 46.4% and ≥200 mg/dl in 18.6% (Figure 1). Two patients were prescribed PCSK9 inhibitor therapy despite LDL-C ≤55 mg/dl because they were at high cardiovascular risk (secondary prevention), but required discontinuation of statin therapy due to side effects.

At the time of the first prescription of a PCSK9 inhibitor 29.5% of the patients were on statin therapy (mostly rosuvastatin or atorvastatin, Table 3), 39.7% on ezetimibe and 2.5% on fibrates. 48.9% did not receive lipid-lowering medication (i.e. no statins, ezetimibe or fibrates) at that time. Statin intolerance was reported in 83.1% of the patients.

Effect on LDL Cholesterol Levels

Due to the retrospective design of this study, we were not able to ascertain laboratory data at predefined time-points from all patients (i.e. every 3 months after therapy initiation) due to loss of follow-up, discontinuation of treatment or infrequent outpatient clinic visits. Ten patients (4.2%) discontinued PCSK9 inhibitor therapy (five after 3 months from baseline, one after 6 months, one after 9 months, three after 12 months) and were not further included in the analysis after discontinuation. 35 patients (14.8%) were lost to follow-up (missing documentation regarding PCSK9 inhibitor therapy ≥1 year).

Time-course changes of LDL-C are shown in Figure 2. During course of treatment, a substantial proportion of patients achieved LDL-C levels ≤70 mg/dl or ≤55 mg/dl. However, in some patients LDL-C remained above 100 mg/dl during the course of treatment (16.5% after 3 to 6 months, in 16.5% after 6 to 9 months, in 13.4% after 9 to 12 months, in 21.3% after 12 to 18 months).

As illustrated in Figure 3 and Supplemental Table 1, a relevant LDL-C reduction from baseline level and a stable median percentage reduction in LDL-C (-58.3% [45.4 – 70.5] after 3 to 6 months; -54.9% [44.4 – 57.3] after 6 to 9 months; -58.1% [47.5 – 68.3] after 9 to 12 months; -53.2% [42.6 – 67.1] after 12 to 18 months was found over time.

As illustrated in Figure 2, a reduction of ≥50% from baseline LDL-C level was achieved in 66.9% of the patients after 3 to 6 months, 61.7% after 6 to 9 months, 70.1% after 9 to 12 months, and 56.2% after 12 to 18 months.

Triglyceride levels slightly decreased compared to median level of 138 (99 – 215) mg/dl at baseline, to 120 (80 – 193) mg/dl after 3 to 6 months; 104 (72 – 171) mg/dl after 6 to 9 months; 115 (89 – 169) mg/dl after 9 to 12 months; 111 (84 – 177) mg/dl after 12 to 18 months. Median percentage changes are shown in Supplemental Table 2.

Considering lipid-lowering medication at baseline (i.e. patients taking neither statins nor ezetimibe at baseline; patients taking statins at baseline; patients taking ezetimibe at baseline; patients taking statins and ezetimibe at baseline), the median level of LDL-C differed significantly between these groups at baseline ($p<0.001$), after 3 to 6 months from baseline ($p = 0.001$), after 6 to 9 months from baseline ($p=0.018$), after 9 to 12 months ($p=0.001$). No statistical significance ($p=0.079$) was found after 12 to 18 months (Supplemental Table 3). The median LDL-C levels of the groups are illustrated in Figure 3. After initiation of PSCK9-inhibitor therapy, there was no difference in the percentage reduction of LDL-C between these groups (Supplemental Table 4).

Concurrent lipid-lowering medication was only assessed at baseline; dose adjustments or discontinuations of additional lipid-lowering treatment over time were not considered in the analysis.

In a separate analysis there was no significant difference in LDL reduction when people with diabetes were compared to those without diabetes at baseline (Supplemental Table 5).

Effect on HbA1c Levels

The baseline HbA1c of the overall cohort was 41 mmol/mol (37-49). HbA1c level did not significantly change over time: 1 to 3 months (42 mmol/mol [38-50; p=0.268]), 3 to 6 months (40 mmol/mol [37-52; p=0.666]), 6 to 9 months (43 mmol/mol [37-52; p=0.349]), 9 to 12 months (41 mmol/mol [37-48; p=0.397]), and 12-18 months (40 mmol/mol [37-48; p=0.195]).

The baseline HbA1c level of patients diagnosed with any type of diabetes mellitus was 52 mmol/mol (48-60). Also in these patients no significant changes were observed over time: 1-3 months (51 mmol/mol [45–59; p=0.696]), 3-6 months (54 mmol/mol [45–65; p=0.726]), 6-9 months (53 mmol/mol [47–57; p=0.812]), 9-12 months (52 mmol/mol [46– 56; p=0.812]), and 12-18 months (49 mmol/mol, [44–56; p=0.325]). Detailed data on HbA1c can be found in the Supplementary Appendix (Supplemental Table 6 and Supplemental Table 7).

Therapy Adjustments, Discontinuation, Adverse Effects

In eight patients, adjustments of the PCSK9 inhibitor agent (i.e. change from Alirocumab to Evolocumab and vice versa) occurred. Eight patients discontinued PCSK9 inhibitor treatment due to side-effects (mostly because of joint or muscle pain, skin lesions or pruritus, or gastrointestinal symptoms), one discontinued PCSK9 inhibitor treatment because of insufficient response the therapy and one did not fulfill the criteria for health insurance coverage of PCSK9 inhibitor treatment (ongoing smoking). Adverse effects to PCSK9 inhibitor therapy were documented in 27 patients; all of the reported effects were of mild quality. Side effects associated with the PCSK9 inhibitor therapy are shown in Table 4. The most frequent side effects were joint or muscle pain (ten patients), rhinitis (five patients), flu-like symptoms (five patients), fatigue (four patients), skin lesions or pruritus (four patients). Side effects were reported by the patients, documented in patient letters and were not systematically inquired.

Discussion

This real-world data analysis evaluated data from patients in a tertiary center who received PCSK9 inhibitors for the treatment of hypercholesterolemia. Within this setting PCSK9 inhibitors are mainly prescribed for secondary prevention for patients with established cardiovascular disease and multiple cardiovascular risk factors. Statin intolerance and side-effects of ezetimibe was reported in the majority of cases (83.1% and 44.7% of the patients) and appears to be a main driver for prescription of PCSK9 inhibitor therapy. This frequent intolerance to these first-line agents explains why about half of the patients had no lipid-lowering medication on board at the time of the first prescription of a PCSK9 inhibitor.

21.5% of the patients were diagnosed with familial hypercholesterolemia, none of them was identified with homozygous familial hypercholesterolemia. The diagnosis was usually based on the clinical criteria derived

from the Dutch Lipid Clinic Network as genetic analysis is not reimbursed by the Austrian health insurance. Therefore, the actual prevalence may differ from the ascertained data.

The significant reduction of LDL-C levels after only a few weeks shows the effective potential of PCSK9 inhibitor drugs as lipid-lowering therapy. Nevertheless, in some patients the LDL-C levels remained at an inadequate level. Even though studies on PCSK9 inhibitors in routine practice are still scarce, real-world studies showed comparable efficacy and safety to randomized clinical trials (RCTs).(8, 9) RCTs like the FOURIER and ODYSSEY OUTCOMES trials showed impressive results in lowering LDL-C. As compared to our study, in the FOURIER trial more patients achieved LDL-C levels ≤70 mg/dl and ≤40 mg/dl (87% and 67% of the patients after 48 weeks vs. 61.1% and 20.9% after 9 to 12 months in our study). In these RCTs it was possible to reduce LDL-C to lower levels (median LDL-C of 30 mg/dl after 48 weeks in the FOURIER trial; mean LDL-C of 48 mg/dl after 12 months in the ODYSSEY OUTCOMES trial vs. median LDL-C of 64 mg/dl after 9 to 12 months in our study). However, it should be considered that the baseline LDL-C was considerably lower in these RCTs (median LDL-C of 92 mg/dl in the FOURIER trial; mean LDL-C of 92 mg/dl in the ODYSSEY OUTCOMES trial vs. median LDL-C of 141 mg/dl in our study), and that the patients were taking statins as add-on therapy (at baseline 69.3% in the FOURIER trial and 88.8% in the ODYSSEY OUTCOMES trial received high-intensity statin therapy) with or without ezetimibe (5.2% in the FOURIER trial; 2.9% in the ODYSSEY OUTCOMES trial), which may explains the differences to our findings in our real-world study.(5, 6) Besides, the trial population differed from ours, as in the ODYSSEY OUTCOMES study only those with cardiovascular event during the last 12 months were included. (6) Although a history of cardiovascular diseases was frequent our patients, a recent cardiovascular event was no criteria for inclusion in our study.

In reference to percentage LDL-C reduction, our study showed concordant results with findings of a systematic review investigating the effects of PCSK9 inhibitors (mean LDL-C reduction of 53.86% after 6 months, compared with placebo). (10)

Real-world studies also observed inter-individual response in LDL-C lowering and postulated that LDL-C goals could not be reached in all patients.(8, 9, 11) This should be considered in the PCSK9 inhibitor treatment in clinical practice and routine control examinations should strive for optimal therapy adherence.

Clinical trials and genetic studies on the effect of statin therapy on the glucose homeostasis showed a slightly increased risk for new-onset diabetes in statin users (approximately 1:1.000 per year of exposure). Patients with additional risk factors of development of diabetes mellitus (e.g. age, prediabetes, metabolic syndrome) are more likely to be affected by this adverse effect. [12]

Schmidt et al. investigated the relation of PCSK9 gene variants and glycemic parameters in a mendelian randomization study, suggesting a potential risk for new-onset diabetes in PCSK9 inhibitor treatment. Mimicking the pharmacological effects of PCSK9 inhibition, this study found increased glucose concentrations and an increased risk of type 2 diabetes in carriers of PCSK9 variants associated with low LDL-C levels. However, these findings represent the life-long effect of these gene variants and may not reflect the pharmacological PCSK9-targeted intervention later in life. (13)

No significant changes on patients' Hb1Ac levels were found in our study, in both people with and without preexisting diabetes, but long-term data was only available for a part of the investigated population.

Nevertheless, it is consistent with findings of past studies, which showed no relevant change on glycemic variables during PCSK9 inhibitor therapy. [14-18]

Adjustments of diabetes therapy were not assessed in the analysis. Of note, due to refund claims by the Austrian health insurance only patients with well controlled diabetes (HbA1c <7.0% or 53 mmol/mol) are eligible for PCSK9 inhibitor therapy (certain exceptions allowed). Thus baseline HbA1c in our patient population was close to recommended targets (52 mmol/mol (48-60)).

Adverse effects of Alirocumab or Evolocumab were rare. Since the documented symptoms stated by the patients were mainly unspecific (e.g. joint or muscle pain, rhinitis), they may or may not be associated with PCSK9 inhibitor therapy. The adverse effects described in our study are similar to those found in other studies. (5, 6, 19, 20) Overall, PCSK9 inhibitors appear to be well tolerated, although long-term data on adverse health effects are not available yet.

As a result of the retrospective setting the study has several limitations. The major limitation is the varying availability of data, especially laboratory data, as routine outpatient clinic visits do not follow such a stringent protocol like a clinical trial. The high number of patients lost to follow-up (14.8%; N=35) also has a certain impact on results as there can be a selection bias, by including more motivated patients and potentially by losing patients who do not observe a beneficial effect of PCSK9 inhibitor therapy.

Also, concurrent lipid-lowering medication was ascertained only at baseline and potential adjustments were not considered in the analysis. In addition, besides other lipid-lowering therapeutic measures, adherence to lifestyle recommendations were not analyzed either.

The efficacy of PCSK9 inhibitors to prevent cardiovascular events was not investigated in our analysis which is owed to the short period of observation. The population will be followed for up to 10 years to also determine the real-world benefit of PCSK9 inhibitors with regard to cardiovascular outcomes.

Conclusions

In conclusion, significant reductions in LDL-C and a high percentage of patients achieving the recommended treatment targets were observed in a real-world population over the course of 18 months. Still some patients did not achieve LDL-C levels as recommended in current guidelines. Special attention to these patients is required in the future to enable more sufficient achievement of treatment goals and avoid adverse cardiovascular outcomes.

List Of Abbreviations

ASCVD	atherosclerotic cardiovascular disease
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
FH	familial hypercholesterolemia
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
PCSK9	proprotein convertase subtilisin/kexin type 9
RCTs	randomized controlled trials
TIA	transient ischemic attack

Declarations

Ethics approval and consent to participate

This study was a retrospective data analysis approved by the Medical University of Graz, Austria (EK number 32-018 ex 19/20). By the nature of the study, it was not necessary to obtain an individual patient consent an individual basis per Austria regulations.

Consent for publication

This study was a retrospective data analysis approved by the Medical University of Graz, Austria (EK number 32-018 ex 19/20). By the nature of the study, it was not necessary to obtain an individual patient consent an individual basis per Austria regulations. Consent for publication is covered within application and approval to ethics committee of Medical University of Graz.

Availability of data and materials

Data was extracted from medical records and saved on a separate password-protected file with anonymized data.

Competing interest

FA received speaker honoraria from Eli Lilly, Merck Sharp & Dome, Boehringer Ingelheim, Astra Zeneca. JKM is a member in the advisory board of Becton-Dickinson, Boehringer Ingelheim, Eli Lilly, Medtronic, Prediktor SA and Sanofi, and received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Eli Lilly, Dexcom, Medtronic, Novo Nordisk, Roche Diabetes Care, Sanofi, Servier, and Takeda.

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Author contributions

All of the authors have sufficiently contributed to this work. FA, JKM and LTF drafted the manuscript, TP and LTF performed the data collection. DAH, LK and TP approved the latest version to be published.

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Author´s information

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Tables

Table 1. Patient characteristics at baseline			
Characteristics	**Alirocumab (n=104)**	**Evolocumab (n=133)**	**Total (n=237)**
Age (years)	65.0 (57.8 – 71.5)	65.4 (57.9 – 71.6)	65.2 (57.8 – 71.5)
Female sex n (%)	53 (51.0)	60 (45.1)	113 (47.7)
Indication for PCSK9 inhibitor treatment n (%)			
Primary prevention	4 (3.8)	2 (1.5)	6 (2.5)
Secondary prevention	100 (96.2)	131 (98.5)	231 (97.5)
Medical history n (%)			
Coronary heart disease	80 (76.9)	97 (72.9)	177 (74.7)
Percutaneous coronary intervention	49 (47.1)	61 (45.9)	110 (46.4)
Coronary artery bypass graft	16 (15.4)	22 (16.5)	38 (16.0)
Stroke or transient ischemic attack	12 (11.5)	20 (15.0)	32 (13.5)
Carotid artery disease	37 (35.6)	36 (27.1)	73 (30.8)
Peripheral artery disease	15 (14.4)	28 (21.1)	43 (18.1)
Arterial hypertension	74 (71.2)	89 (66.9)	163 (68.8)
Familial hypercholesterolemia (heterozygous)	19 (18.3)	32 (24.1)	51 (21.5)
Retinopathy	5 (4.8)	5 (3.8)	10 (4.2)
Chronic kidney disease	6 (5.8)	17 (12.8)	23 (9.7)
Current tobacco smoker	9 (8.7)	5 (3.8)	14 (5.9)
Diabetes mellitus any type	25 (24.0)	35 (26.3)	60 (25.3)
Diabetes mellitus type 1	2 (1.9)	4 (3.0)	6 (2.5)
Diabetes mellitus type 2	22 (21.2)	30 (22.6)	52 (21.9)
Other types of diabetes	1 (1.0)	1 (0.8)	2 (0.8)
Intolerances/side effects to lipid-lowering medication n (%)			
Statin	83 (79.8)	114 (85.7)	197 (83.1)
Ezetimibe	36 (34.6)	70 (52.6)	106 (44.7)
Statin and Ezetimibe	34 (32.7)	67 (50.4)	101 (42.6)
Data are median (interquartile range) or number (%).			

Table 2. Cardiovascular disease at baseline (by medical condition)

Coronary heart disease (n=177)	-	17 9.6%	40 22.6%	21 11.9%	8 4.5%	132 74.6%	18 10.2%	95 53.7%	43 24.3%	7 4.0%
Stroke or TIA (n=32)	17 53.1%	-	14 43.8%	6 18.8%	0 0%	23 71.9%	5 15.6%	19 59.4%	8 25.0%	0 0%
Carotid artery disease (n=73)	40 54.8%	14 19.2%	-	19 26.0%	2 2.7%	51 69.9%	6 8.2%	49 67.1%	20 27.4%	4 5.5%
Peripheral artery disease (n=43)	21 48.8%	6 14.0%	19 44.2%	-	3 7.0%	33 76.7%	7 16.3%	23 53.5%	16 37.2%	7 16.3%
Retinopathy (n=10)	8 80.0%	0 0%	2 20.0%	3 30.0%	-	7 70.0%	3 30.0%	5 50.0%	6 60.0%	1 10.0%
Arterial hypertension (n=163)	132 81.0%	23 14.1%	51 31.3%	33 20.2%	7 4.3%	-	19 11.7%	94 57.7%	50 30.7%	8 4.9%
Chronic kidney disease (n=23)	18 78.3%	5 21.7%	6 26.1%	7 30.4%	3 13.0%	19 82.6%	-	18 78.3%	13 56.5%	0 0%
Age ≥65 years (n=123)	95 77.2%	19 15.4%	49 39.8%	23 18.7%	5 4.1%	94 76.4%	18 14.6%	-	35 28.5%	3 2.4%
Diabetes mellitus (n=60)	43 71.7%	8 13.3%	20 33.3%	16 26.7%	6 10.0%	50 83.3%	13 21.7%	35 58.3%	-	2 3.3%
Current smoker (n=14)	7 50.0%	0 0%	4 28.6%	7 50.0%	1 7.1%	8 57.1%	0 0%	3 21.4%	2 14.3%	-

Data are number of patients (% from subgroup).

Table 3. Laboratory parameters and lipid-lowering therapy* at baseline

	Alirocumab (n=104)	Evolocumab (n=133)	Total (n=237)
LDL cholesterol (mg/dl)	135 (114 – 181) n=104	149 (118 – 191) n=133	141 (117 – 188) n=237
Total cholesterol (mg/dl)	210 (190 – 259) n=94	240 (202 – 272) n=122	229 (198 – 268) n=216
HDL cholesterol (mg/dl)	52 (44 – 63) n=100	55 (46 – 67) n=126	54 (45 – 65) n=226
Triglycerides (mg/dl)	138 (102 – 255) n=102	138 (97 – 197) n=138	138 (99 – 215) n=227
Lipoprotein (a) (mg/dl)	89 (34 – 140) n=16	54 (26 – 79) n=30	65 (27 – 97) n=46
HbA1c (mmol/mol)	40 (37 – 49) n=61	43 (37 – 50) n=78	41 (37 – 49) n=139
HbA1c of patients with diabetes mellitus (mmol/mol)	52 (45 – 63) n=23	52 (48 – 60) n=33	52 (48 – 60) n=56
Statins (n; %)	38 (36.5)	32 (24.1)	70 (29.5)
Fluvastatin	2 (1.9)	1 (0.8)	3 (1.3)
Pravastatin	0 (0)	0 (0)	0 (0)
Simvastatin	1 (1.0)	4 (3.0)	5 (2.1)
Rosuvastatin	15 (14.4)	14 (10.5)	29 (12.2)
Atorvastatin	21 (20.2)	14 (10.5)	35 (14.8)
Ezetimibe	46 (44.2)	48 (36.1)	94 (39.7)
Fibrates	2 (1.9)	4 (3.0)	6 (2.5)
No lipid-lowering medication	44 (42.3)	72 (54.1)	116 (48.9)

Data are median (interquartile range) and number of patients for laboratory parameters and number of patients (%) for lipid lowering therapy at baseline. *Patients could be treated with a combination of more than one lipid-lowering agent (i.e. statin plus ezetimibe).

Table 4. Documented side effects of PCSK9 inhibitor therapy reported by patients	
Adverse effect	Number of patients*
Joint or muscle pain	10
Rhinitis	5
Flu-like symptoms	5
Fatigue	4
Skin lesions or pruritus	4
Gastrointestinal symptoms	2
Insomnia	1
*Patients could have more than one symptom.	

Figures

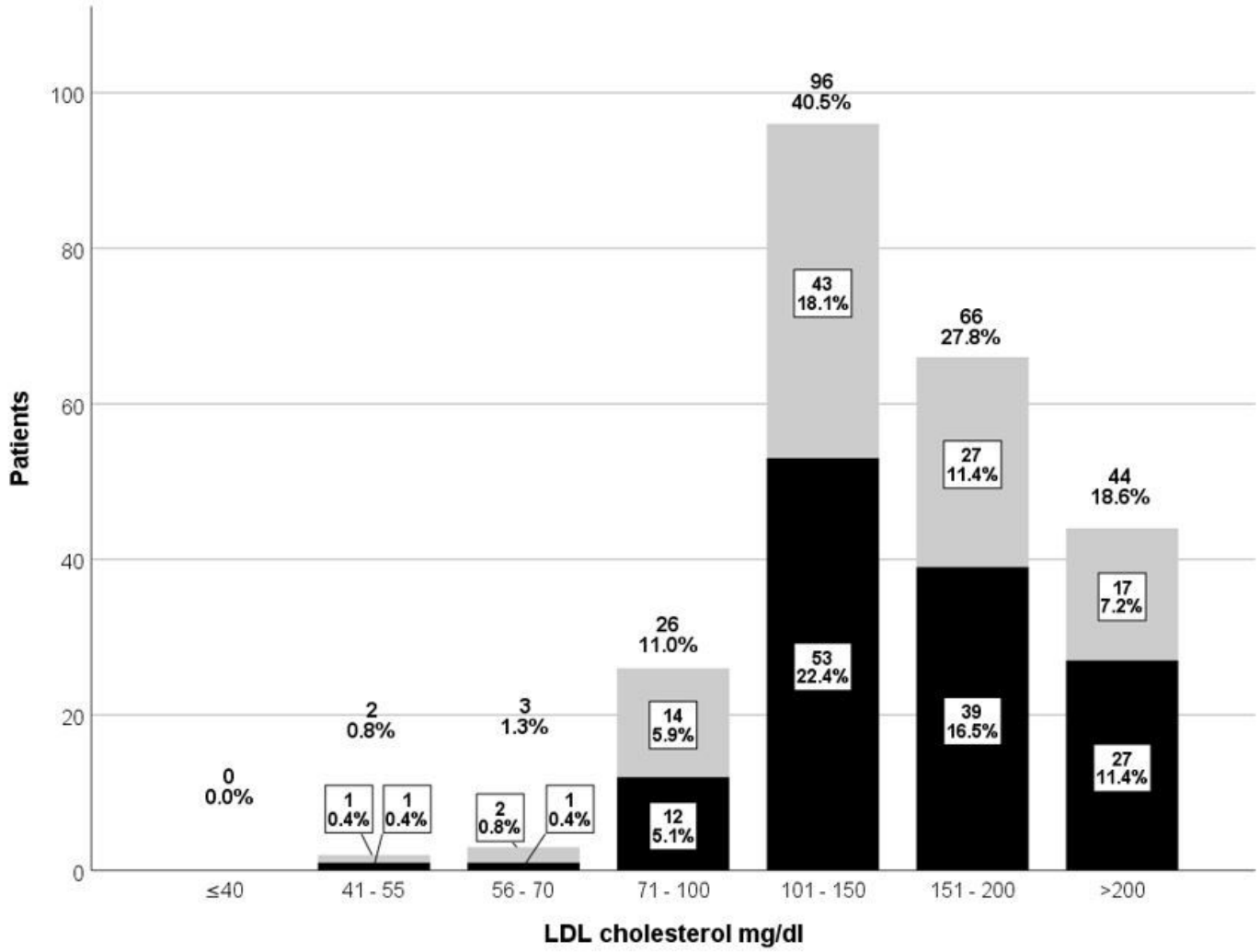


Figure 1

LDL cholesterol levels at baseline (n=237); gray bar = Alirocumab, black bar = Evolocumab; LDL = low-density lipoprotein; data are number of patients and percentage (%)

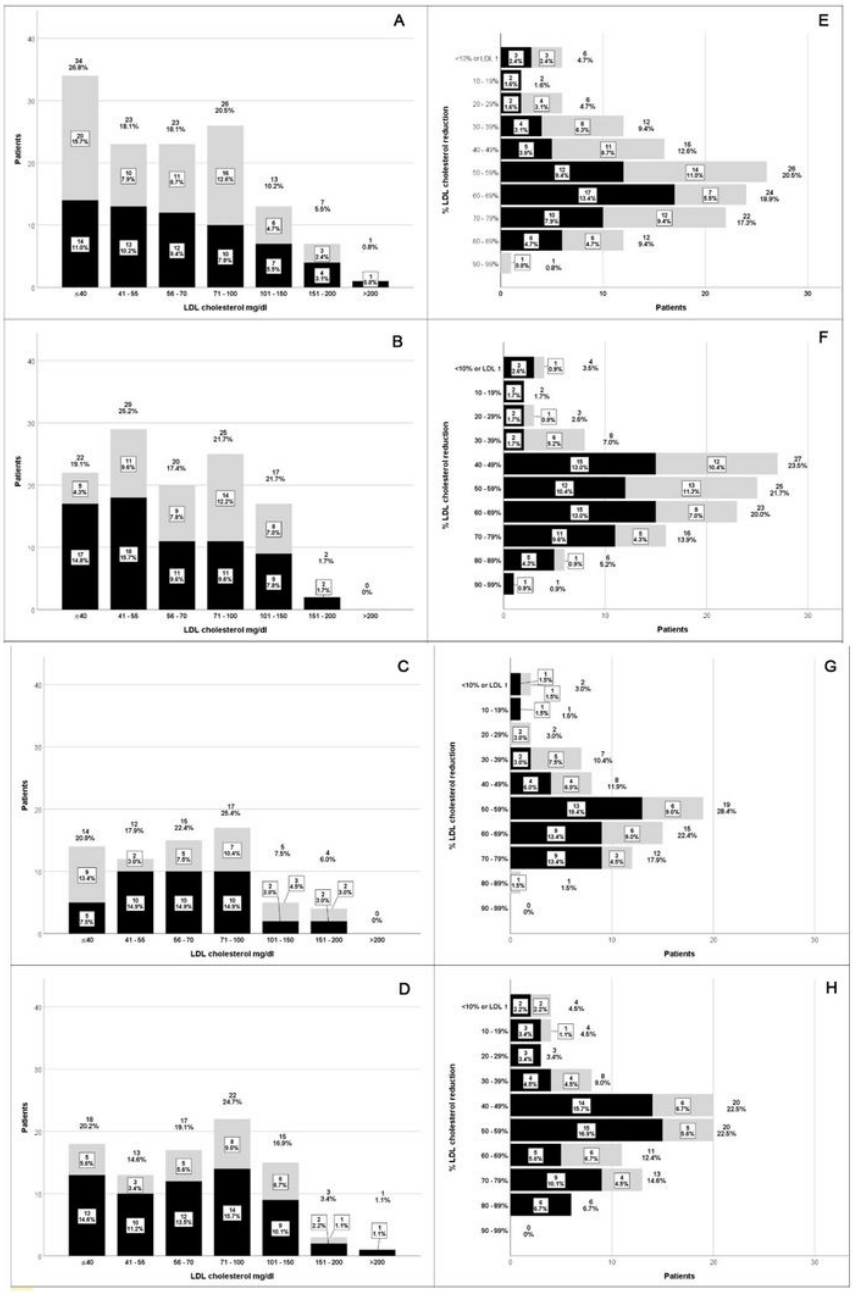
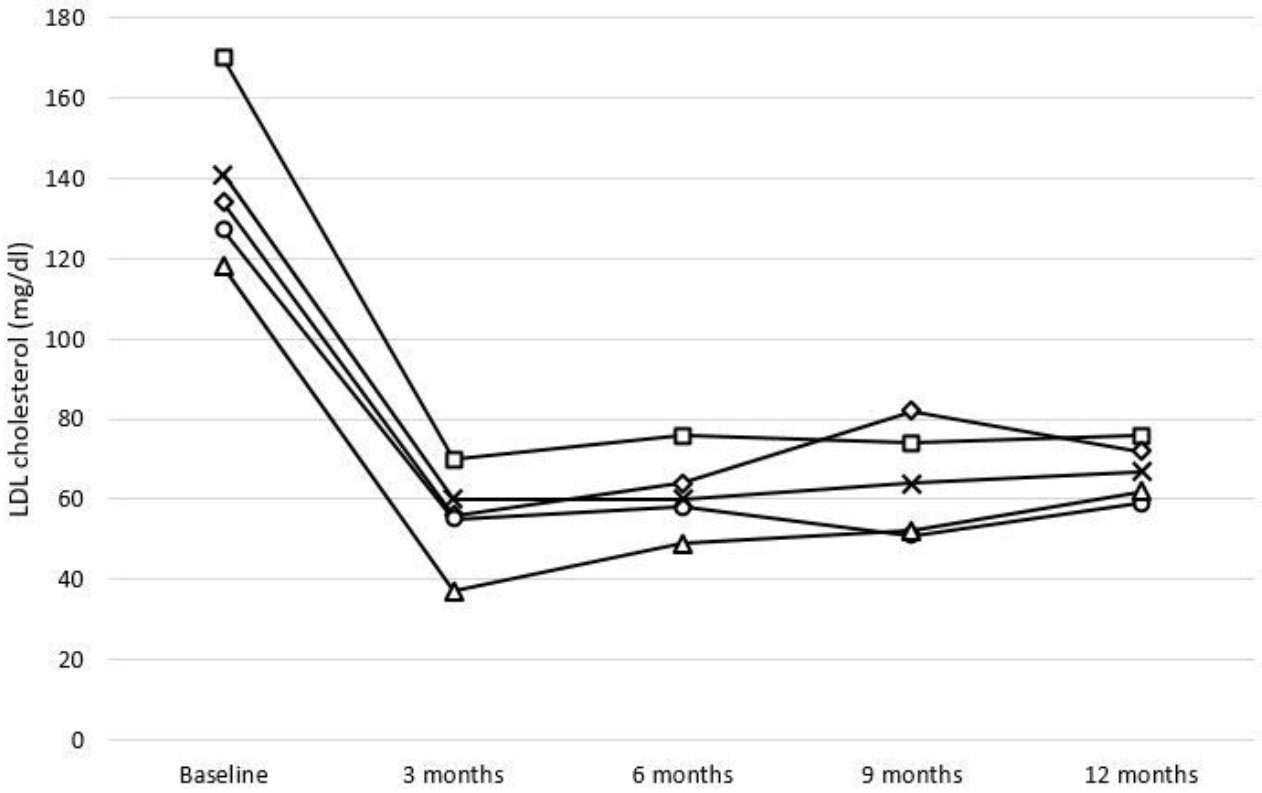


Figure 2

LDL cholesterol levels and percentage of LDL-C reduction over time; LDL = low-density lipoprotein; data are number of patients (n) and percentage (%); gray bar = Alirocumab, black bar = Evolocumab. A: LDL-C levels after 3 to 6 months (n=127), B: LDL-C levels after 6 to 9 months (n=115); C: LDL-C levels after 9 to 12 months (n=67); D: LDL-C levels after 12 to 18 months (n=89) E: % LDL-C reduction from baseline level after 3 to 6 months (n=127); F: % LDL-C reduction from baseline level after 6 to 9 months (n=115); G: % LDL-C reduction from baseline level after 9 to 12 months (n=67); H: % LDL-C reduction from baseline level after 12 to 18 months (n=89)



	Baseline	3-6 months	6-9 months	9-12 months	12-18 months
No Statin/no Ezetimibe	170 (130 – 203) (n=117)	70 (50 – 100) (n=64)	76 (44 – 106) (n=59)	74 (59 – 96) (n=33)	76 (52 – 110) (n=48)
Statin	134 (115 – 171) (n=26))	56 (36 – 85) (n=17)	64 (50 – 88) (n=14)	82 (39 – 110) (n=7)	72 (48 – 89) (n=8)
Ezetimibe	127 (117 – 158) (n=50)	55 (34 – 75) (n=24)	58 (35 – 74) (n=21)	51 (42 – 65) (n=12)	59 (42 – 70) (n=22)
Statin + Ezetimibe	118 (93 – 140) (n=44)	37 (30 – 63) (n=22)	49 (44 – 59) (n=21)	52 (33 – 64) (n=15)	62 (35 – 94) (n=11)
Total	141 (117 – 188) (n=237)	60 (38 – 82) (n=127)	60 (43 – 91) (n=115)	64 (47 – 86) (n=67)	67 (45 – 89) (n=89)

Figure 3

LDL cholesterol levels of patients with additional Lipid-lowering medication at baseline. Data are median (interquartile range). Square indicates patients with no statin and no ezetimibe therapy; rhombus statin therapy; circle ezetimibe therapy; triangle statin and ezetimibe combination therapy; cross total study population.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalAppendix.docx