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PCSK9 inhibitors in clinical practice: Delivering on the promise?

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ABSTRACT

Background and aims: In clinical trials, protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors robustly lowered LDL-cholesterol (LDL-c) and had a favorable tolerability and safety profile. Based on these findings, PCSK9 inhibitors are incorporated in updates of clinical treatment guidelines. However, trial results do not necessarily predict the effectiveness under real-world conditions. The aim of the current study is to determine the efficacy and tolerability of PCSK9 inhibitors in routine outpatient care.
Methods: The cohort comprised all patients who were prescribed evolocumab or alirocumab at the outpatient clinic of a large university hospital in the Netherlands. Eligible patients required additional lipid-lowering despite maximally tolerated statin therapy and ezetimibe, or were statin intolerant. Data were systematically collected during routine outpatient visits.
Results: The study included 238 patients of whom 67.2% had familial hypercholesterolemia (FH) and 42.9% were statin intolerant. The mean LDL-c reduction was 55.0% from a baseline of 4.4 mmol/L. LDL-c goals were attained by 62.3% of patients. Side effects were reported by 15.5% of patients and 2.5% discontinued treatment. No meaningful differences in efficacy or tolerability were observed between patients with FH or statin intolerance, or across treatment regimens.
Conclusions: The observed lipid reductions and side effects profile of PCSK9 inhibitors in a routine care setting were comparable to observations in clinical trials.

1. Introduction

It has been unequivocally shown that a log-linear relation exists between low-density lipoprotein cholesterol (LDL-c) and the risk of cardiovascular disease (CVD), without a lower threshold below which the strength of the relationship is attenuated [1]. The advent of statin therapy in the 1990s has enabled unparalleled cardiovascular risk reduction and these drugs should be regarded as one of the major advances in contemporary medicine. However, a considerable number of patients are unable to tolerate statins at sufficiently high doses to achieve acceptable lipid levels due to side-effects, whereas other patients are unable to reach lipid goals even despite highly dosed statin therapy [2,3]. The clinical consequences of the ensuing undertreatment are particularly detrimental for high-risk patients, such as those with familial hypercholesterolemia (FH). Protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have recently emerged as a valuable addition to the repertoire of lipid-lowering drugs [4]. Until the introduction of PCSK9 inhibitors, there was little that could be done to effectively treat high-risk patients who needed additional cholesterol reduction beyond addition of ezetimibe, which has only modest effects on LDL-c and clinical outcomes [5].

Large-scale clinical trials have consistently shown that PCSK9 inhibitors yield an incremental 50–60% reduction in LDL-c when added to statin therapy [6,7]. In the FOURIER clinical outcomes trial, it was recently confirmed that evolocumab reduces cardiovascular event rates in line with expectations based on the observed LDL-c reduction [8,9]. Importantly, no serious adverse effects of PCSK9 inhibition have been observed in clinical trials and discontinuation rates were generally similar between treatment and placebo groups (approximately 5% per year) [6,7].

Based on these clinical trial results, the PCSK9-inhibiting monoclonal antibodies evolocumab and alirocumab have been approved by regulators for use by patients with a high CVD risk who need additional lipid-lowering and by those who are unable to tolerate statin therapy. PCSK9 inhibitors are incorporated in updates of clinical guidelines of major professional societies [10–13].

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However, in contrast to the wealth of evidence from clinical trials, there is limited data regarding the efficacy and tolerability of PCSK9 inhibitors in routine patient care. Due to differences between clinical trials and the real world setting, extrapolation of trial results could possibly lead to inflated expectations regarding the efficacy of new therapies (e.g., due to better adherence in trials). Determining whether PCSK9 inhibitors are capable of 'delivering on their promise' is of crucial importance, particularly given their high costs. Hence, the objective of the current report is to describe the efficacy and tolerability in a cohort of patients prescribed PCSK9 inhibiting monoclonal antibodies in routine care.

2. Materials and methods

All patients who used alirocumab or evolocumab up to June 2017 were identified from the electronic hospital system of the Academic Medical Center (AMC) in Amsterdam, which is a secondary and tertiary referral center for the Amsterdam region of the Netherlands. The cohort comprised both patients who initially participated in a clinical trial and patients who started using alirocumab or evolocumab in routine care. The decision to start treatment with PCSK9 inhibitors was made by Vascular Medicine specialists. In the Netherlands, PCSK9 inhibitors are reimbursed by standard health insurance (without copayment) for all inhabitants since April 2016 (evolocumab) and June 2016 (alirocumab). The reimbursement criteria include all clinical indications for PCSK9 inhibitors as defined in the European Society of Cardiology (ESC) Guidance (i.e., patients who need additional lipid-lowering despite receiving maximally tolerated statin therapy, including patients with FH or statin intolerance) [13,14]. Prior to market approval, patients were able to receive either of the therapies by participating in clinical trials or through the open-label Compassionate Use Program.

Patients received either alirocumab (75 mg or 150 mg every two weeks [75Q2W or 150Q2W]) or evolocumab (140 mg every two weeks [140Q2W], or 420 mg every four weeks [420QM]). The choice of the particular PCSK9 inhibitor and dosing regimen was at the discretion of the medical specialist. Alirocumab treatment is typically started at a dose of 75 mg once per two weeks (75Q2W), or 150 mg (150Q2W) if the desired LDL-c reduction is >60% [15]. For other patients, the dose can be increased from 75Q2W to 150Q2W in case of insufficient response after 4 weeks of therapy. The treatment regimen for evolocumab is typically 140 mg per 2 weeks (140Q2W).

All patients received usage instructions by a nurse practitioner. Follow-up after initiation of the PCSK9 inhibitor typically consisted of bi-annual visits to the outpatient clinic (or more frequently depending on patient preferences, treatment results, tolerability, etc.). Laboratory assessments were performed prior to each outpatient clinic visit. Any changes in treatment, including concomitant (lipid-lowering) therapy, as well as tolerability and therapy adherence, were systematically discussed during each visit and documented.

Data were collected during routine visits to the outpatient clinic or during study visits for patients who initiated PCSK9 inhibitor therapy in clinical studies. Information about demographics, clinical characteristics, relevant medication and outcomes were collected from the hospital electronic health system. For the purpose of this study, CVD was defined as (history of) angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, cerebrovascular accidents or peripheral vascular disease. Patients were considered to have FH if they had a documented pathogenic mutation in the genes encoding the LDL receptor, APOB, or PCSK9, or if they had a Dutch Lipid Clinic Network (DLCN) score of $\geq$6. Statin intolerance was defined as inability to tolerate at least 3 statins due to muscle symptoms, in accordance with the European Atherosclerosis Society (EAS) Consensus Panel Statement and Dutch reimbursement criteria for PCSK9 inhibitors [2].

The primary outcome measures were 1) the %-reduction in LDL-c at the last available measurement from baseline (defined as the lipid measurement prior to starting the PCSK9 inhibitor), and 2) patient-reported side-effects. Secondary outcome measures were the effects on total cholesterol, high-density lipoprotein cholesterol (HDL-c), non-HDL-c, and triglycerides, as well as specification of side-effects, discontinuation rates and the proportion of patients who attained guideline-recommended treatment goals. The analyses were separately performed for patients with FH or statin intolerance (which are the primary indications for which PCSK9 inhibitors are used) and for the different dosing regimens.

Concomitant use of ezetimibe is a prerequisite for reimbursement of PCSK9 inhibitors in the Netherlands. For patients without available lipid measurements between initiation of ezetimibe and initiation of treatment with PCSK9 inhibitors, the effect of ezetimibe was accounted for by calculating new baseline values using previously reported mean treatment effects of ezetimibe [16].

All data are reported descriptively and summarized using means and standard deviations (SD) or medians and interquartile ranges (IQR) were appropriate. Categorical data are reported as numbers and percentages.

3. Results

The cohort consisted of 238 patients; 121 (53.3%) were initially prescribed evolocumab (118 [52.0%] 140Q2W and 3 [1.3%] 420Q4W) and 106 (47.7%) were prescribed alirocumab (42 [18.5%] 75Q2W and 64 [28.2%] 150Q2W). For 11 patients (4.6%) who initiated PCSK9 inhibitor therapy in a blinded clinical study, treatment allocation was not yet available. Patient characteristics are depicted in Table 1. The mean age of patients was 58 years, and 62.6% had a history of CVD. Mean body mass index (BMI) was 27.6 kg/m^2, 40.8% had hypertension and 16.5% were current smokers. In total, 99 patients (41.6%) started using PCSK9 inhibitors in a clinical study. (see Table 2).

Statin intolerance was the primary indication for initiation of

Table 1
Baseline characteristics.

	N = 238
Age, years (SD)	58 (11)
Male, n (%)	139 (58.4)
White, n (%)	232 (97.5)
Previous CVD, n (%)	149 (62.6)
FH, n (%)	160 (67.2)
Statin intolerance[a], n (%)	102 (42.9)
Smoking	
Current, n (%)	31 (16.5)
Former, n (%)	66 (35.1)
Never, n (%)	91 (48.4)
Unknown, n (%)	50
BMI, kg/m^2 (SD)	27.6 (4.6)
Hypertension, n (%)	97 (40.8)
Type 2 diabetes, n (%)	40 (16.8)
Concomitant lipid-lowering therapy	
Statins, n (%)	133 (55.9)
Ezetimibe, n (%)	217 (91.2)
Fibrates, n (%)	8 (3.4)
Bile acid sequestrants, n (%)	8 (3.4)

SD, standard deviation; n, number; BMI, body mass index; CVD, cardiovascular disease.
[a] Unable to tolerate at least three different statins due to muscle symptoms.

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