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STATIN DRUGS (R. CESKA, SECTION EDITOR)

PCSK9 Inhibitors in Real-world Practice: Analysis of Data from 314 Patients and 2 Years of Experience in a Center of Preventive Cardiology

Tereza Altschmiedová[1] · Veronika Todorovová[1] · Michaela Šnejdrlová[1] · Martin Šatný[1] · Richard Češka[1]

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Abstract

Purpose of Review PCSK9 inhibitors have been shown to be the most effective class of drugs modifying the levels of LDL-cholesterol as the main risk factor for atherosclerotic cardiovascular disease. The aim of this paper is to assess the effect of monoclonal antibodies on lipid and lipoprotein metabolism in real-world practice.

Recent Findings The outcome trials showed effective reduction of LDL-C by 56–62%. Landmark studies enrolling over a total of 46,000 patients with CHD in their medical history demonstrated the beneficial effect of both agents on cardiovascular morbidity and mortality. The data from real everyday clinical practice are very limited or missing.

Summary Even in real-world practice, PCSK9 inhibitors have been shown to be an effective, safe, and well-tolerated class of drugs with effects comparable with those reported from large randomized controlled trials.

Keywords Atherosclerotic cardiovascular disease (ASCVD) · LDL cholesterol · PCSK9 inhibitors · Alirocumab · Evolocumab · Real-world data (RWD)

Introduction

Despite the incessant advances in diagnostic and therapeutic technology and strategies, atherosclerotic cardiovascular disease (ASCVD) remains — not only in the Czech Republic — the leading cause of death responsible for almost 50% of total mortality [1]. A large body of evidence has accumulated about the role of low-density lipoprotein cholesterol (LDL-C) as the main risk factor for atherosclerosis as a springboard for the development of cardiovascular disease. Hence, LDL-C is the ultimate target in the management of dyslipidemias, with the current first-line class of drugs of choice being statins. In line with the guidelines developed by the respective European professional societies [2], statins are administered at their maximum tolerated doses, and, in patients failing to achieve LDL-C targets, it is recommended to add ezetimibe. In recent years, the arsenal of lipid-lowering drugs has expanded with the advent of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

The pace of research in the field of PCSK9 inhibitors has been astonishingly fast. The proprotein convertase subtilisin kexin type 9 (PCSK9) protein was discovered in the early 2000s and was soon shown to bind to the LDL-C receptor. The discovery that individuals with hereditary loss-of-function mutations in the *PCSK9* gene have low LDL-C levels accelerated research with the first clinical trials launched in 2009 [3, 4]. Currently, 2 active substances — evolocumab and alirocumab — are available; both are administered subcutaneously every 2 weeks and were approved for the Czech market on June 1, 2018.

Aim of Study

Our study was designed to establish the extent to which the outcomes of therapy with PCSK9 inhibitors in real-world practice compare with those reported by large randomized

Between 1 October 2020 and 1 February 2021, the target LDL-levels for alirocumab and evolocumab, respectively, were further decreased, a fact not reflected in this manuscript given the time of patient enrolment.

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✉ Tereza Altschmiedová
Tereza.Altschmiedova@vfn.cz

[1] Center of Preventive Cardiology, 3rd Department of Internal Medicine, General University Hospital, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic

trials. The endpoints included a host of variables of lipid and lipoprotein metabolism as well as safety and tolerability of PCSK9 inhibitors.

We assessed the effect of PCSK9 inhibitor therapy on the entire study group and compared separately groups of patients with vs. without the diagnosis of familial hypercholesterolemia (FH), patients in primary and secondary ASCVD prevention and, also, those treated with a PCSK9 inhibitor in monotherapy vs. those receiving a PCSK9 inhibitor in combination with a statin.

Further, we were interested to know whether or not there is a correlation between baseline LDL-C levels and their decrease relative to therapy. Likewise, we focused on any potential differences in the effect and tolerability of both active substances — alirocumab and evolocumab. Given the size of our study group and study duration, the protocol did not include cardiovascular endpoints.

Patients and Methods

As the use of PCSK9 inhibitors in the Czech Republic is currently limited by the local healthcare reimbursement policies, study participants were enrolled based on the applicable criteria allowing to reimburse treatment in 2 indications.

The first major subgroup included FH patients (in primary or secondary ASCVD prevention) with LDL-C levels ≥ 4 mmol/l despite maximum tolerated statin doses. For therapy to be reimbursable, ezetimibe has also to be administered as add-on therapy except for cases where LDL-C levels are $> 50\%$ than the target for the respective the cardiovascular risk category (in statin-naïve patients) or $> 20\%$ (in patients already receiving a statin at a maximum tolerated dose). If the patient does not take a statin because of intolerance, this fact must be noted in their medical records. In our study participants, the diagnosis of FH was established using the Dutch Lipid Clinic Network Criteria (DLCNC) [5].

The second major subgroup included patients in secondary ASCVD prevention defined by the Czech healthcare reimbursement policies as the presence of coronary heart disease (CHD), peripheral arterial disease (PAD), or post-stroke status including transient ischemic attack (TIA) as well as status post-revascularization. These patients were indicated for therapy on condition that, despite maximum tolerated lipid-lowering therapy, their LDL-C levels were ≥ 3 mmol/l [5].

Patients not meeting the reimbursement criteria and self-payers were not eligible for inclusion.

Overall, the study group included 314 patients (138 men and 176 women) with a mean age of 63 years (range, 24–89 years), enrolled in a Prague-based hospital between 31 July 2018 and 30 September 2020. Data were collected until 31 December 2020. Study participants had laboratory tests before therapy initiation and, subsequently, at 12 and 24 weeks, and at 1 and 2 years to assess the trajectories of 6 pre-defined endpoints over time: LDL-cholesterol (LDL-C), total cholesterol (TC), lipoprotein (a) Lp(a), apolipoprotein B (apoB), high-density lipoprotein cholesterol (HDL-C), and triglycerides (Tg). Further, the study investigated the impact of therapy on variables of glucose metabolism (glycemia, glycated hemoglobin). The safety of therapy was evaluated using both physical examination and laboratory tests.

Complete lipid profile is available for all 314 patients at the beginning of the observation and in week 12. As the study progressed, depending on the time when the patient was included, the number of patients for whom we have complete data decreased gradually from 271 patients in week 24, 201 patients after 1 year to 73 patients after 2 years of treatment.

The subgroup of FH patients included 207 (65% of total) individuals, of which number 142 (69%) were in primary prevention and 65 (31%) in secondary prevention of ASCVD. On therapy initiation, secondary ASCVD prevention had been underway in 172 patients (55%) with FH diagnosed in 65 (38%); hence, secondary prevention (without FH) was indicated in 107 participants. The mean baseline LDL-C levels in FH and non-FH patients were 5.03 ± 1.43 (2.21–14.30) mmol/l and 3.75 ± 0.80 (2.02–6.28) mmol/l, respectively. Regarding cardiovascular prevention, baseline LDL-C levels in patients not diagnosed with ASCVD were 5.40 ± 1.40 (3.56–14.30) mmol/l whereas the values of patients in secondary ASCVD prevention were 3.93 ± 0.96 (2.02–9.30) mmol/l.

Patients were treated with evolocumab 140 mg or alirocumab 75 mg (150 mg if necessary).

They were not randomized to the treatment; therapy was selected according to the decision of indicating physicians in an effort to maintain an approximately equal representation of both of them, alirocumab as well as evolocumab. There were 156 patients receiving only evolocumab and 113 patients treated exclusively with alirocumab. The remaining 45 participants used both active substances (but separately) during the study, with therapy switched because of side effects or inadequate effect of therapy with one of the study drugs. To avoid any bias, data of the latter subgroup were put aside and will not be further discussed.

A total of 166 (53%) study participants were statin-intolerant patients thus taking a PCSK9 inhibitor either in monotherapy or in combination with ezetimibe. Conversely, 148 of those enrolled (47%) had a history of statin use, of whom 82 (26% of the entire group) were using statin even at a maximum dose. The mean baseline LDL-C levels in patients receiving a statin at a maximum dose were 4.18 mmol/l $\pm$ 1.62 mmol/l; in completely statin-intolerant patients, the levels were 4.95 ± 1.26 mmol/l.

Regarding smoking status, a greater proportion of the participants was made up of smokers and ex-smokers (157) vs. non-smokers (138). No information about smoking status was available in 19 patients.

Statistical Analysis

Statistical analysis was performed using STATISTICA 13 software (TIBCO Software Inc., Palo Alto, CA, USA). To assess the development of individual variables over time, their mean values at pre-defined time points were calculated and compared with baseline using the two sample *t*-test.

Results

The primary endpoint was change in LDL-C levels declining from a mean baseline of 4.59 ± 1.39 mmol/l to 1.87 ± 1.24 mmol/l at 12 weeks (–59.4%). The effect was persistent to become even stronger with LDL-C levels reaching a mean value of 1.72 ± 0.98 mmol/l at 2 years (–62.6%), statistically significant values.

The levels of TC decreased from a mean baseline of 6.88 mmol/l to 3.86 mmol/l at the end of the study showing a mean decrease of 41.7% at 12 weeks and 43.9% at 2 years, again a significant outcome.

Lipoprotein Lp(a) levels declined from a mean baseline of 0.79 to 0.59 g/l (–25.4%) at 12 weeks and further down to 0.51 g/l (–35.5%) at 24 weeks into the study. Results at 1 and 2 years were available in only a small number of patients and were statistically non-significant.

The changes in apolipoprotein B levels followed the pattern seen in LDL-C levels. While mean apoB levels fell by 54.2% at 12 weeks, the decrease vs. baseline was 58.1% at 2 years, again statistically significant improvement.

No major changes were noted in HDL-C levels, which rose slightly (by 4%) at 12 weeks and by 5.6% at 2 years; however, the differences were non-significant.

The decrease in Tg levels from 2.13 mmol/l at baseline to 1.62 mmol/l at 12 weeks and further down to 1.49 mmol/l at 2 years was statistically significant (–30.3% vs. baseline), with the levels reaching targets set by the 2019 ESC/EAS Guidelines for the management of dyslipidemias [2]; this variable, however, was not the primary focus of treatment with PCSK9 inhibitors.

Glucose metabolism was not affected by the therapy.

An overview of the development of all variables overtime is available in Table 1 and Fig. 1.

Apart from the courses of the above variables across the whole group, our study sought to identify any differences in the effect of therapy between individual patient subgroups. On entering the study, LDL-C levels of FH patients were higher (5.03 mmol/l) than those of non-FH patients (3.75 mmol/l).

However, the dynamics of decrease after therapy initiation were similar, with LDL-C dropping by 56.7% and 61.8% at 12 and 24 weeks in FH patients as against 67.4% and 68.8% in non-FH patients, respectively. In addition, while, in the FH group, LDL-C levels continued to decline steadily from 1 year onward, an opposite trend (a slight increase) was observed in non-FH patients. The LDL-C levels in FH patients (at 2 years) at the end of the study were 1.83 mmol/l (a drop by 3.19 mmol/l, i.e., –63.5% vs. baseline); the respective figures in non-FH patients were 1.42 mmol/l (a drop by 2.34 mmol/l, i.e., –62.3% vs. baseline). The differences were significant.

Patients in primary ASCVD prevention enrolled in the project with higher LDL-C levels (5.40 mmol/l) than those in secondary prevention (3.93 mmol/l). However, the dynamics of decrease after therapy initiation showed an almost similar pattern, with LDL-C levels falling by 55.7% and 61.5% at 12 and 24 weeks in patients in primary prevention and by 63.9% and 66.3% in those in secondary ASCVD prevention. In addition, while, in the primary prevention group, LDL-C levels continued to decline steadily from 1 year onward, an opposite trend (a slight increase) was observed in the secondary prevention group. At 2 years into the study, LDL-C levels in primary prevention participants reached 2.07 mmol/l (a decrease of 3.33 mmol/l, i.e., –61.7% vs. baseline), with the respective figures for the secondary prevention subgroup being 1.41 mmol/l (a decrease of 2.52 mmol/l, i.e., –64.2% vs. baseline).

On therapy initiation, completely statin-intolerant participants had higher LDL-C than those already being treated with a statin at a maximum (or lower-than-maximum) dose. However, the dynamics in response to therapy was already similar in all 3 main subgroups. While, by week 12, LDL-C levels in patients not on statin therapy decreased by 55% to further decline after week 24 onward, in patients receiving maximum (or lower-than-maximum) statin dose, the levels fell by 65.2% (or 65%, respectively) to start rising steadily from week 24 onward. The values at the end of the study differed significantly at 2 years being 59.3% in completely statin-intolerant patients, and 64% and 63% in patients receiving statins at maximum and lower-than-maximum doses, respectively.

Statistically, significant differences were also found between the groups based on the agents received. Here, our entire study population was divided into another 3 subgroups. The first two subgroups comprised patients treated throughout the study with either evolocumab or alirocumab. The third subgroup was made up of patients switched over from evolocumab to alirocumab or vice versa; data of this subgroup were not analyzed.

Table 1 An overview of the development of all variables over time

	Baseline	Week 12	Week 12 vs. baseline			Week 24	Week 24 vs. baseline			Year 1	Year 1 vs. baseline			Year 2	Year 2 vs. baseline		
	Mean	Mean	Difference	%	*p*	Mean	Difference	%	*p*	Mean	Difference	%	*p*	Mean	Difference	%	*p*
LDL-C (mmol/l)	4.59	1.87	−2.73	−59.35%	$p < 0.001$	1.67	−2.92	−63.54%	$p < 0.001$	1.73	−2.87	−62.42%	$p < 0.001$	1.72	−2.87	−62.46%	$p < 0.001$
TC (mmol/l)	6.88	4.01	−2.87	−41.68%	$p < 0.001$	3.83	−3.05	−44.34%	$p < 0.001$	3.88	−3.00	−43.66%	$p < 0.001$	3.86	−3.02	−43.91%	$p < 0.001$
Lp(a) (g/l)	0.79	0.59	−0.20	−25.38%	$p = 0.023$	0.51	−0.28	−35.49%	$p = 0.002$	0.62	−0.17	−21.81%	$p = 0.221$	0.56	−0.24	−29.85%	$p = 0.167$
ApoB (g/l)	1.59	0.73	−0.86	−54.15%	$p < 0.001$	0.69	−0.90	−56.57%	$p < 0.001$	0.72	−0.87	−54.57%	$p < 0.001$	0.67	−0.93	−58.09%	$p < 0.001$
HDL-C (mmol/l)	1.42	1.48	0.06	3.99%	$p = 0.127$	1.47	0.05	3.33%	$p = 0.207$	1.47	0.05	3.52%	$p = 0.231$	1.50	0.08	5.58%	$p = 0.155$
TG (mmol/l)	2.13	1.62	−0.52	−24.21%	$p < 0.001$	1.58	−0.55	−25.88%	$p < 0.001$	1.58	−0.55	−25.85%	$p < 0.001$	1.49	−0.64	−30.25%	$p < 0.001$
Glc (mmol/l)	5.65	5.72	0.06	1.10%	$p = 0.546$	5.72	0.07	1.16%	$p = 0.584$	5.72	0.07	1.22%	$p = 0.553$	5.52	−0.14	−2.42%	$p = 0.241$
HbA1c (mmol/mol)	42.93	41.55	−1.38	−3.21%	$p = 0.294$	42.64	−0.30	−0.69%	$p = 0.831$	42.78	−0.15	−0.35%	$p = 0.911$	40.36	−2.57	−5.99%	$p = 0.071$

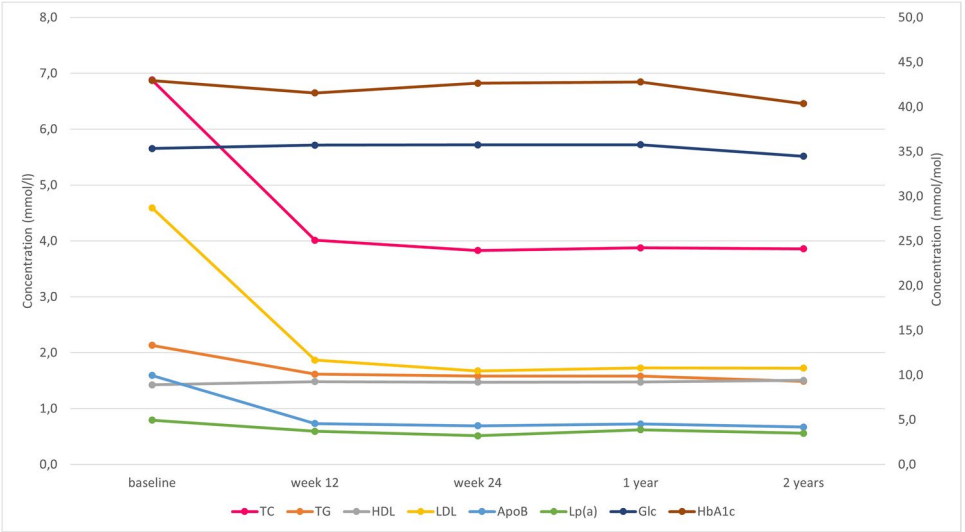

Fig. 1 An overview of the development of all variables over time

Patients in the two first subgroups had similar baseline LDL-C levels. By 12 weeks, the LDL-C levels of the alirocumab-only subgroup fell by 55.5% to continue decreasing steadily from week 24 onward while, in the evolocumab-only subgroup, the decrease at 12 weeks was 66.1% with the levels continuing to rise steadily from week 24 onward. At 2 years into the study, the decrease in the alirocumab-only and evolocumab-only subgroups was 64.7% and 61.0%, respectively, a statistically significant difference.

We also sought to determine whether or not there is a relationship between the absolute changes in LDL-C vs. baseline. Using Pearson's correlation coefficient (Pearson's *r*), the test showed a value of –0.7147, hence, a moderately strong inverse correlation, that is, the higher the baseline LDL-C levels, the less was the decrease in absolute numbers—again, a statistically significant difference.

To assess the rates of achieving LDL-C targets, we used participants' data available at 1 year of the study. Among 108 patients in primary ASCVD prevention, 71 (65.7%) were in the range of LDL-C ≤ 1.4 mmol/l thus achieving target LDL-C levels as defined by the guidelines of the 2019 ESC/EAS Guidelines for the management of dyslipidemias [2]. Among 92 FH patients in primary prevention, target LDL-C values (≤ 1.8 mmol/l) were found in 33 (35.9%).

Side effects were reported by a total of 28 study participants (9%), of which number 16 and 14 adverse reactions were considered evolocumab- and alirocumab-related, respectively. The most frequent side effect was flu-like syndrome (fatigue, malaise, and upper airways inflammation) reported by 13 patients whereas 5 study participants complained of pain at injection site and 5 of myalgia (a reason for their previous statin intolerance). Three patients experienced gastrointestinal intolerance of therapy and 2 reported various problems. Overall, 15 patients withdrew from the study for side effects.

During the 2 years of our study, PCSK9 inhibitor therapy was discontinued in a total of 36 study participants. Except for the 15 patients experiencing the above side effects, therapy was stopped in 8 for unsatisfactory effect of therapy defined as failure to reach LDL-C targets for the respective cardiovascular risk category and/or LDL-C reduction by a minimum of 40% vs. baseline; 6 patients were removed from the study for non-compliance, and 7 patients discontinued therapy for other reasons such as a condition not related to therapy or epidemiological situation related to COVID-19.

Discussion

Both molecules, evolocumab and alirocumab, have been evaluated in a number of clinical trials within the PROFICIO (evolocumab) and ODYSSEY projects (alirocumab). Early studies focused on the effect of the two agents on the levels of plasma lipids such as — most importantly — LDL-C followed by apoB or Lp(a). The outcomes were impressive with PCSK9 inhibitors effectively reducing LDL-C by 56–62% [6]. Landmark studies enrolling over a total of 46,000 patients with CHD in their medical history demonstrated the beneficial effect of both agents on cardiovascular morbidity and mortality. With both agents, cardiovascular death rates declined by 15–20% relative to placebo [7••, 8••].

Given the size of our study group and study duration, the aim of the present project was not to assess cardiovascular endpoints. Still, we were interested to know whether or not the new class of drugs has, in the real-world setting, an effect comparable to that reported by clinical trials since, in the above clinical trials, the percentage LDL-C reduction was

compelling, uniform across the individual subgroups and consistent over time.

Our study demonstrated that PCSK9 inhibitors offer an effective therapeutic option in statin-intolerant patients. While more encouraging outcomes were obtained in the statin-treated group (consistent with the finding that PCSK9 inhibition may enhance the LDL-C-lowering effect of statins [9]), the 55% LDL-C reduction seen in completely statin-intolerant patients as early as 12 weeks after initiation of therapy with a PCKS9 inhibition provides a long-awaited new hope to this patient population.

Furthermore, we sought to determine the proportion of patients achieving target values — also not optimal in the Czech Republic in the long run — an issue addressed also by major international studies. In the EUROASPIRE survey (enrolling 6648 patients with CHD in 24 European countries), LDL-C targets were achieved in only 19.3% of patients [10]. The results of the Czech participants ($n = 493$) were similar, with target LDL-C levels attained in 23.5% of CHD patients [11]. More optimistic data about dyslipidemia control were offered by a Czech observational study of Zlatohlávek et al. assessing, between June and December 2016, a total of 201 patients at high- and very-high cardiovascular risk in 11 centers across the country. In the high-risk and very-high risk subgroups, LDL-C targets were achieved in 46.4% and 56.1% of patients, respectively [12•]. This situation changed dramatically with the advent of PCSK9 inhibitors, with most encouraging outcomes reported in a study by Raal et al., where 80% of FH patients receiving standard therapy reached LDL-C targets when using a PCSK9 inhibitor as add-on therapy [13].

In the present study, target LDL-C levels were attained by 35.9% of patients in primary prevention (33 out of the 92 patients whose data were available at 1 year into the study). Among the 108 very high-risk patients in secondary ASCVD prevention, whose data were available at 1 year into the study, target LDL-C levels were reached by 71 (65.7%). The reason of this apparently less optimistic outcome should be first sought in the differently defined target LDL-C levels. While all the above studies [10–13] used the 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias [14] defining target LDL-C values for high-risk and very high-risk patients as < 2.5 mmol/l and < 1.8 mmol/l, respectively, the present study had stricter limits of < 1.8 mmol/l and < 1.4 mmol/l, respectively [2]. If including patients with LDL-C levels of > 1.8 and > 2.6 mmol/l, the target values would have been achieved by 68.48% of FH patients, and by 79.6% of those in secondary prevention and at very high risk.

Nonetheless, we are in the year 2021 with more ambitious goals, so the fact that a "mere" 20.4% of patients in secondary ASCVD prevention have LDL-C levels ≥ 1.8 mmol/l is simply unsatisfactory and further causes must be identified. One of these — in relation to the present study — may be that our patients are being followed up and treated in 1 national center. There are only 2 national centers for the management of dyslipidemias with the implication being their patients are mostly those with generally more severe forms of dyslipidemia or those failing to respond to any therapeutic option currently available. The same may apply to the higher proportion of statin-intolerant patients. The pool of patients with failed therapeutic options was built long before PCSK9 inhibitors had been approved for use in the Czech Republic, and therapy was instituted soon after the respective healthcare reimbursement policy had been defined. By contrast, a definite plus in enrolling patients from only a single center is that we were able to eliminate potentially different approaches by various centers to the creation of and keeping patient medical records and data entry and, hence, to minimize the potential for data misinterpretation.

The effect of monoclonal antibodies on Lp(a) levels seems to be most encouraging. It is well known that this variable is yet another (and independent of other variables) risk factor of atherosclerosis, and, until the advent of PCSK9 inhibitors, no drugs were available to modify its levels. The reduction in Lp(a) levels by 24% vs. baseline seen in our study is consistent with data reported from large randomized studies [15].

Conclusion

Data from the first 314 patients treated with PCSK9 inhibitors in a Prague-based center of preventive cardiology confirm that PCSK9 inhibitors are a most effective, safe, and well-tolerated class of lipid-lowering agents. Their effect was uniform, sustained, clear-cut, and comparable with that reported by large randomized trials. Low-density lipoprotein cholesterol is generally recognized as a major risk factor for atherosclerosis and its complications. To succeed in our efforts to substantially reduce the incidence of atherosclerosis and its complications, LDL-C targets must be achieved in a greater proportion of patients. While LDL-C control across the subpopulations of our patients has not been satisfactory to date, the approval of PCSK9 inhibitors for the Czech market gives our healthcare providers a promising chance for reversing this unfavorable situation in the near future.

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Declarations

Conflict of Interest Tereza Altschmiedová, Michaela Šnejdrlová, Martin Šatný, and Richard Češka report grants and personal fees from Amgen and Sanofi, outside the submitted work.
Veronika Todorovová has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Townsend N, Wilson L, Bhatnagar P, et al. Cardiovascular disease in Europe: Epidemiological update 2016. Eur Heart J. 2016;37(42):3232–45. https://doi.org/10.1093/eurheartj/ehw334 Erratum in: Eur Heart J. 2019 Jan 7;40(2):189.
2. Mach F, Baigent C, Catapano AL, et al. [ESC Scientific Document Group]. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88. https://doi.org/10.1093/eurheartj/ehz455 Erratum in: Eur Heart J. 2020;41(44):4255.
3. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006;354(12):1264–72. https://doi.org/10.1056/NEJMoa054013.
4. Cohen J, Pertsemlidis A, Kotowski IK, et al. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet. 2005;37(2):161–5. https://doi.org/10.1038/ng1509 Erratum in: Nat Genet. 2005;37(3):328.
5. Češka R, Táborský M, Vrablík M. Společné stanovisko odborných společností k předepisování PCSK9-inhibitorů. AtheroRev. 2018;3(3):201–7.
6. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: A systematic review and meta-analysis. Ann Intern Med. 2015;163(1):40–51. https://doi.org/10.7326/M14-2957.
7.•• Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713–22. https://doi.org/10.1056/NEJMoa1615664. **Key clinical trials confirming the effect on cardiovascular risk reduction during PCSK9 inhibitors treatment.**
8.•• Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379(22):2097–107. https://doi.org/10.1056/NEJMoa1801174. **Key clinical trials confirming the effect on cardiovascular risk reduction during PCSK9 inhibitors treatment.**
9. Poirier S, Mayer G, Poupon V, et al. Dissection of the endogenous cellular pathways of PCSK9-induced low density lipoprotein receptor degradation: Evidence for an intracellular route. J Biol Chem. 2009;284(42):28856–64. https://doi.org/10.1074/jbc.M109.037085.
10. Reiner Z, De Backer G, Fras Z, et al. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries--Findings from the EUROASPIRE IV survey. Atherosclerosis. 2016;246:243–50. https://doi.org/10.1016/j.atherosclerosis.2016.01.018.
11. Bruthans J, Mayer O, Galovcova M, et al. State of secondary prevention in Czech coronary patients in the EUROASPIRE IV study. Cor Vasa. 2014;56(2):e105–12. https://doi.org/10.1016/j.crvasa.2014.02.012.
12.• Zlatohlavek L, Snejdrlova M, Bridges I, et al. Observational study of dyslipidemia management in the Czech Republic. Athero Rev. 2019;4(3):162–9. **This article provides detailed information about lipid-lowering treatment in the Czech Republic.**
13. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: The reduction of LDL-C with PCSK9 inhibition in heterozygous familial hypercholesterolemia disorder (RUTHERFORD) randomized trial. Circulation. 2012;126(20):2408–17.
14. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2016;37(39):2999–3058. https://doi.org/10.1093/eurheartj/ehw272.
15. Lipinski MJ, Benedetto U, Escarcega RO, et al. The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. Eur Heart J. 2016;37(6):536–45. https://doi.org/10.1093/eurheartj/ehv563.