second, and subsequent doses, as well as for sampling before further approvals. The prepared application was then sent by mail or electronically, and the response was mostly recorded within a week. After approval of therapy for 2 doses and scheduling the patient for the administration date, the current dose of inclisiran was ordered based on the approval code from any pharmacy directly by our office, as it is a category A drug. The invoice due date for the pharmacy is usually 60–75 days, so the office incurs no costs before the payment of health therapy by the insurance company, which is guaranteed by the issued approval. During the administration of inclisiran, we encountered no problems. While submitting the application for therapy approval, 5 requests were rejected, due to the non-utilization of prescribed statin therapy by the pharmacy (for 2 patients), due to concurrent titration of the maximum tolerated dose of statin by the general practitioner (1 patient), and due to a one-week pause in the prescription of the maximum tolerated dose of statin (2 patients).

In terms of therapy efficacy, we observed similar results in our cohort of patients indicated for the therapy with inclisiran as in large clinical studies (10–13). We recorded a similar therapeutic effect on LDL-C levels, overall efficacy, and safety of therapy. However, we observed interindividual differences in the reduction of LDL-C, as well as in other monitored parameters. In this study, we found a median LDL-C reduction of 57.5 ± 7.5 %, which is higher than the reduction reported in other studies, where it ranged from 41 % to 46 % (or 49 % to 52 % when adjusted to placebo). Overall, the reduction of LDL-C in our study ranged from 41.88 % to 86.25 %.

Recently, several observational studies have been published with real clinical data regarding the efficacy and safety of inclisiran administration. Some of them pointed to similar LDL-C reductions as in the ORION-9–10–11 studies, while others indicated a lower decrease (14, 15). The authors reported a lower reduction in LDL-C levels than in clinical studies, with a median of 38 % in patients without statin co-medication and 45 % in patients with statin co-medication. Another study from the UK described an average decrease of 49 %, with the group receiving statin co-medication achieving up to 56% decrease, which represents similar results as in our cohort and in clinical studies (16). A lower efficacy was also demonstrated in a German cohort of 153 patients, which showed a reduction of 32 % in non-statin users and 42 % in patients with statin co-medication after a 3-month follow-up. After 9-month follow-up, reduction in LDL-C levels was observed compared to the 3-month follow-up (17). Since we did not have data from patients without statin medication after 2 doses of statins, we compared LDL-C reduction based on titrated statin therapy. We found that patients who had a maximum statin dose experienced a higher reduction in LDL-C (61.5 ± 12.3 %) compared to patients with a reduced statin dose (53.2 ± 5.9 %).

Differential efficacy in clinical studies and real-world data can be explained by several factors. First, some studies had follow-ups lasting 2 months instead of 3, while in our study, we compared LDL-C values one month after the third dose, which represents the standard procedure for approving the continuation of inclisiran therapy in Slovakia. The ORION-1 study indicated that the average LDL-C reduction was approximately 50 % after 2 months and 45 % after 3 months of inclisiran administration. Given the pharmacokinetics and effect of inclisiran, it is assumed that the most relevant data point is the LDL-C value after the third administration of therapy, as observed in the ORION studies. Additionally, the aforementioned British study had a higher percentage of patients with statin co-medication compared to the study by Mulder et al. (18) (53 % vs. 37 %), which may also have played a role, as demonstrated in other studies with PCSK9-mAbs (mAb – monoclonal antibodies), and which we also demonstrated in our study in the group with maximum doses of high intensity statins (18).

The cohort of most real-world studies is highly heterogeneous regarding accompanying lipid-lowering therapy. In our study, we found that patients treated with statins, especially at maximum doses, had significantly greater LDL-C reduction than patients not using statins. This finding is consistent with previous publications evaluating inclisiran in a real-world clinical practice cohort.

It is well known that statins induce the expression of the sterol regulatory element – binding protein 2 (SREBP-2), a process leading to increased transcription of LDL-R mRNA, as well as PCSK9, and thus to increased concentrations of PCSK9 in plasma (19). Previous studies have also shown that a greater reduction in LDL-C in response to statins is positively associated with plasma levels of PCSK9 (20). Moreover, the relationship between statin treatment and plasma concentrations of PCSK9 may explain variations in LDL-C response to statin therapy and subsequently to inclisiran response (21, 22).

Interindividual differences were also observed in the HEYMANS registry focusing on the real analysis of evolocumab PCSK9-mAb, which demonstrated substantial interindividual variability in LDL-C reduction (23). In addition to biochemical and molecular characteristics, there are also other possible factors explaining these differences. In controlled clinical studies, patients exhibit greater adherence to prescribed medications compared to observational studies due to more thorough supervision, regular monitoring, and a higher level of engagement. Furthermore, patients admitted to special lipid clinics are characterized by multiple drug intolerances. Thus, the cohort of observational studies with real clinical data may differ from clinical studies (24).

Some studies also described a slight increase in LDL-C levels after switching from PCSK9-mAb administration to inclisiran (25). In our cohort, we did not monitor the effect of this transition; however, it is known that the inhibition of PCSK9-mAb increases plasma concentrations of PCSK9 during the first 3 months after the injection of PCSK9-mAb due to delayed plasma clearance of PCSK9 induced by the PCSK9-mAb complex. This could be a potential reason why pre-treatment with PCSK9-mAb was associated with a less pronounced reduction in LDL-C. To what extent this may influence the magnitude of LDL-C reduction in response to inclisiran and what other pathways may contribute to the relationship between PCSK9 protein and LDL-C reduction is not fully known; however, it is assumed that after switching to inclisiran and stabilizing levels, any increase in LDL-C should not be significant.

Large clinical studies have demonstrated a reduction in Lp(a) levels of up to 30 % of