baseline values. The ORION-1 study showed a 15–19% reduction after 1 dose of inclisiran and a 19–25% reduction after 2 administrations over 150 days, but none of the reductions reached statistical significance. In the ORION-3 study, in the open-label continuation of ORION-1, the decrease was only by 6.3 % and 14.3 % in the group transitioning from PCSK9-mAbs (11). In the ORION-9 study monitoring patients with HeFH, the reduction was 17.2 % compared to placebo, but again, it was not significant (12). In contrast, the reduction in the ORION-10 studies was 25.6 % compared to placebo, while in the ORION-11 study, it was 18.6 %. All results were consistent with findings from studies involving PCSK9 antibodies, which also observed a similar decrease (13).

Monoclonal antibodies (mAbs) against PCSK9 reduce Lp(a) levels by approximately 20–30 % (16). In large clinical studies such as FOURIER with evolocumab and ODYSSEY OUTCOMES with alirocumab, a reduction of about 25 % in major adverse CV events (MACE) was noted (26, 27). In the ODYSSEY OUTCOMES study, patients with recent acute coronary syndrome had LDL-C levels close to 1.8 mmol/L and Lp(a) levels ≥ 13.7 mg/dL, which were associated with a significant clinical benefit from alirocumab therapy. In contrast, patients with LDL-C around 1.8 mmol/L but Lp(a) < 13.7 mg/dL showed no reduction in MACE with alirocumab, whereas patients with higher LDL-C levels consistently benefited from alirocumab treatment, regardless of Lp(a) levels (28).

In our study, we found a significant interindividual variation in Lp(a) reduction, ranging from 0 % to 58.33 %. In patients with elevated Lp(a) levels > 50 mg/dL (n = 5), the reduction in levels after adding inclisiran was more pronounced compared to patients with normal Lp(a) levels: 16.66 ± 5.7 % vs. 15.47 ± 5.4 %, which may explain and align with the findings from the aforementioned ODYSSEY OUTCOMES study. The exact mechanism by which PCSK9 inhibitors reduce Lp(a) levels remains unclear. Current hypotheses include increased clearance of Lp(a) particles through LDL receptors (LDL-R), increased clearance of Lp(a) via other receptors (LDL-R-related protein 1, cluster differentiation receptor 36, Toll-like receptor 2, scavenger receptor B1, and plasminogen receptors), as well as reduced production, secretion, or assembly of apo(a) (29).

hsCRP has been shown to be a reliable marker of underlying systemic inflammation, a strong and independent predictor of future CV events in individuals with and without established CV disease. Measurement of hsCRP can aid physicians in assessing CV risk and monitoring therapeutic interventions (30). Although PCSK9 inhibition does not reduce CRP levels in clinical studies, including ORION-1, -2, and -7, preclinical studies have provided substantial evidence for a relationship between PCSK9 and inflammation, as well as the impact of PCSK9 inhibition on the overall inflammatory process (31). In our study, we observed an average hsCRP reduction of 14.8 ± 8.7 %, but significant interindividual differences were present. Based on the sample size, it is difficult to predict the effect of inclisiran on hsCRP levels; we rather assume that it was influenced by the titrated statin levels or the interaction of the PCSK9 inhibition pathways themselves, but further studies are needed to demonstrate this effect.

In terms of side effects, our study showed slightly higher rates of local reactions compared to the clinical studies ORION-3, -9, -10, and -11 (14). When assessing adverse effects, we found that mild burning occurred in 38.23 % of total administrations during therapy. In studies ORION-3, -9, -10, and -11, the prevalence of injection site reactions was 3–17 % (15). The aforementioned UK real-world registry reported only 1 patient (1.3 %) with a moderate injection site reaction, while the German study reported 5 patients (3 %) (16,17). In our study, we did not observe any moderate or severe reactions. In studies ORION-9, -10, and -11, other types of reported side effects occurred with similar frequency in both groups (14). In real-world studies, fewer side effects (4–6 %) were reported, which were of a similar nature: myalgia, dizziness, headache, and fatigue, in addition to the previously mentioned mild injection site reaction (15). In our study, we monitored the above symptoms in 5.9 % of administrations, with a maximum duration of up to 24 hours. In the German study with PCSK9 mAbs, most side effects (74 %) were also reported in patients without concurrent lipid-lowering therapy. Although the etiology is not always known, for example, in the case of myalgia symptoms, it is important to listen to patients to arrive at an optimal tailored treatment plan to minimize individual ASCVD risk (17). Adherence to therapy was similar to that in clinical studies, and we observed therapy interruption in only 1 patient after the first dose of inclisiran, but not due to adverse effects. Furthermore, liver tests after starting treatment with inclisiran were comparable to baseline levels.

In conclusion, consistent with clinical trials and other studies in real clinical practice, our findings support that inclisiran has a favorable safety profile and can be an effective means of achieving LDL-C target values in patients at very high CV risk, which we achieved in 63.4 % of patients, compared to 0 % with LDL-C > 2.6 mmol/L based on inclusion criteria.

Limitations

This study has several limitations, most of which are characteristic of observational studies. The study is based on information reported by patients, and we did not measure drug (or metabolite) concentrations. Therefore, we cannot exclude the possibility that in some patients, the varying changes in LDL-C, particularly after the second and subsequent injections of inclisiran, may have been due to non-adherence to accompanying lipid-lowering therapy. The cohort was also highly heterogeneous and included patients with various diagnoses, albeit at very high CV risk, on different baseline lipid-lowering therapies. Finally, in this study, we did not distinguish between patients taking a statin and those receiving combination therapy with a statin and ezetimibe. This factor may have influenced the interpretation of the results, although the primary aim of this study was to highlight the fact that the addition of inclisiran to the initially initiated lipid-lowering therapy led to a more pronounced reduction in LDL-C and Lp(a). Despite the study's limitations, our data provide valuable insights into the effectiveness of inclisiran and the management of patients in real clinical practice in Slovakia.