Impact of bariatric surgery on circulating PCSK9 levels as a marker of cardiovascular disease risk: a meta-analysis

Tannaz Jamialahmadi[1,2], Maciej Banach[3,4], Wael Almahmeed[5], Prashant Kesharwani[6], Amirhossein Sahebkar[1,7,8,9]

[1]Applied Biomedical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Department of Preventive Cardiology and Lipidology, Medical University of Lodz, Lodz, Poland
[4]Cardiovascular Research Centre, University of Zielona Gora, Zielona Gora, Poland
[5]Heart and Vascular Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
[6]Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, India
[7]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[8]School of Medicine, The University of Western Australia, Perth, Australia
[9]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Corresponding author:
Prof. Amirhossein Sahebkar
Applied Biomedical Research Center
Pharmaceutical Technology Institute
Mashhad University of Medical Sciences
Mashhad, Iran
E-mail: amir_saheb2000@yahoo.com; sahebkara@mums.ac.ir

Submitted: 11 July 2022; **Accepted:** 19 July 2022
Online publication: 8 August 2022

Arch Med Sci 2022; 18 (5): 1372–1377
DOI: https//doi.org/10.5114/aoms/152685

Abstract

Introduction: This systematic review and meta-analysis focuses on PCSK9 changes in obese patients following bariatric surgery.
Methods: A systematic literature search in four databases was performed. Comprehensive Meta-Analysis (CMA) V2 software used to conduct the meta-analysis. Studies were evaluated regarding heterogeneity in design, populations under investigation, and treatment duration using a random-effects model and the generic inverse variance weighting approach. A random-effect meta-regression approach was used to investigate the association with the estimated effect size.
Results: The results of the meta-analysis on 4 trials including 260 individuals demonstrated a remarkable decline of PCSK9 after bariatric surgery (WMD = –57.34 ng/ml, 95% CI: –87.97, –26.71, $p < 0.001$; $I^2 = 96.25\%$). Consistently, a significant decrease of LDL-C after bariatric surgery (WMD = –22.57 mg/dl, 95% CI: –27.5, –17.574, $p < 0.001$; $I^2 = 86.35\%$) was observed.
Conclusions: PCSK9 is reduced significantly after bariatric surgery. The decrease of PCSK9 might be utilized as an independent surrogate marker of improvement of atherosclerotic cardiovascular disease risk after bariatric surgery.

Key words: bariatric surgery, low-density lipoprotein-cholesterol, obesity, meta-analysis, PCSK9.

Obesity is an increasing morbid condition with epidemic features associated with cardiovascular risk factors [1]. Currently, bariatric surgery for severely obese patients has proven to be the most effective treatment option, with the number of procedures performed increasing on a global scale [2]. The Swedish Obese Subjects (SOS) study [3] discovered that patients with obesity who underwent bariatric surgery had a 53% lower risk of mortality from cardiovascular disease when compared to patients who did not have the procedure. One mechanism by which this reduction may occur is through alteration of lipid profiles of patients. Dyslipidemia is improved following bariatric surgery and the extent of improvement varies depending on the surgical approach utilized [4].

PCSK9 is a key regulator of low-density lipoprotein-cholesterol (LDL-C) via enhancing LDL receptor internalization and endosomal degradation. PCSK9 plasma levels have been demonstrated to predict cardiovascular (CVD) risk [5–8]. Interestingly, some studies have found a correlation between PCSK9 concentrations and fat mass [9]. Although caloric restriction lowers PCSK9 concentration in adults [10], bariatric surgery has recently been found to lower plasma LDL-C as well as PCSK9 levels simultaneously [11]. However, the magnitude of such a reduction is not known and there has been no meta-analysis evaluating the effects of bariatric procedures on plasma PCSK9 concentrations. This meta-analysis focuses on PCSK9 changes in obese patients following bariatric surgery.

Methods. PubMed, Scopus, Embase, and Web of Science were searched from inception to June 1st, 2021 using the following keywords in titles and abstracts (also when used with MESH terms): ("bariatric surgery" OR gastroplast* OR "gastric bypass" OR "Roux-en-Y" OR "gastric band" OR "biliopancreatic diversion" OR gastrectom* OR "duodenal switch" OR "weight loss surgery" OR "gastrointestinal diversion" OR gastroenterostom* OR "jejunoileal bypass" OR "obesity surgery" OR "weight-loss surgery" OR "bariatric procedure" OR "sleeve surgery" OR "metabolic surgery") AND (PCSK9 OR PCSK-9 OR "proprotein convertase subtilisin kexin type 9" OR "proprotein convertase subtilisin/kexin type 9" OR NARC-1 OR "neuronal apoptosis regulated convertase-1"). Only peer-reviewed original papers written in English were considered for inclusion. All forms of bariatric surgery were considered in the study. Papers must have documented PCSK9 before and after surgery to be considered for inclusion.

Quality assessment. The Newcastle-Ottawa Scale (NOS) was utilized to estimate the quality of the studies included in this meta-analysis [12, 13]. Three aspects of each qualified study are considered for this scale: (1) the selection of the patients in the studies (4 items), (2) the comparability of the studied populations (one item) and (3) the outcome of interest (3 items).

Quantitative data synthesis. The meta-analysis was conducted by Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [14]. The weighted mean differences (WMDs) with relevant CIs were determined for continuous outcomes. From each group sample sizes, means, and standard deviations were obtained for each relevant outcome to calculate WMDs. Overall estimate of effect size was measured by a random effects meta-analysis. To account for the heterogeneity of studies with regard to study design, characteristics of the populations under investigation and treatment duration, a random-effects model (using the DerSimonian-Laird method) and the generic inverse variance weighting approach were utilized [15]. A sensitivity analysis employing the leave-one-out

Table I. Characteristics of studies measuring PCSK9

Study, year	Study design	Follow-up	Treatment	Control	Clinical result		Patients	No. of patients
					PCSK9	*P*-value		
Zenti *et al.*, 2020 [16]	Non-randomized interventional study	6 months	Bariatric surgery	Nonobese healthy controls	Significant decrease in PCSK9 values	< 0.003	Morbidly obese subjects	20
Blanchard *et al.*, 2020 [9]	Prospective study	6 months	SG/RYGB	–	Significant change in PCSK9 values	< 0.0001	Morbidly obese subjects	156
Ghanim *et al.*, 2018 [5]	Prospective study	6 months	RYGB	–	Significant change in PCSK9 values	Not mentioned	Morbidly obese subjects	15
Boyer *et al.*, 2015 [11]	Randomized interventional study	24 h 5 days 6 months 12 months	BPD-DS	Severely obese patients	Significant decrease in PCSK9 values	< 0.005	Morbidly obese subjects	69

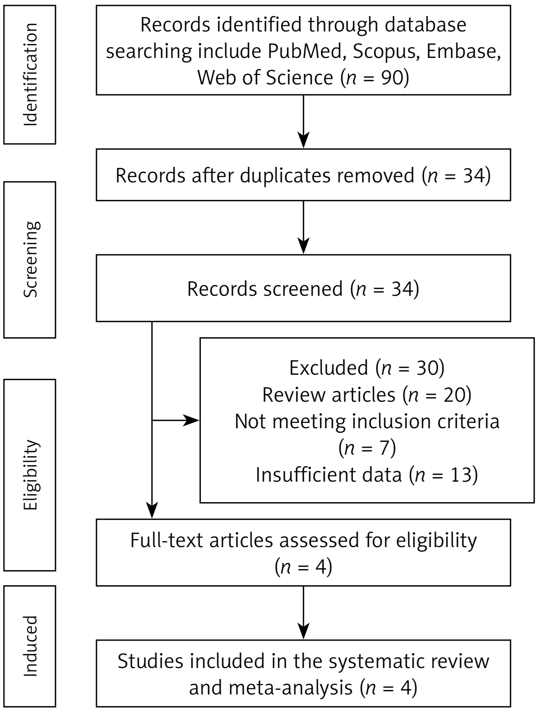


Figure 1. Flow diagram of study selection process for meta-analysis

approach (i.e., deleting one study each time and repeating the analysis) was applied to analyze the effect of each study on the overall effect size.

Results. Among 90 published studies identified in the systematic database search, 34 were directly related to the topic of this study. Among them, 30 studies were excluded after careful evaluation (20 studies were reviews, 7 studies did not match the inclusion criteria and 3 studies did not report sufficient data). Therefore, 4 studies which evaluated PCSK9 after bariatric surgery were included (Table I) [16]. Figure 1 depicts the process of study selection.

Quality assessment of included studies. All the selected studies showed representativeness of the exposed cohorts, but most of them were distinguished by a lack of selection of the non-exposed cohort. Given that most of the studies did not include a non-exposed group, they were not assessed for comparability and adequacy of follow-up of cohorts. Finally, all included studies met the assessment of outcome. Quality assessment of the selected studies is presented in Table II.

Effect of bariatric surgery on PCSK9 and LDL-C. The random-effects meta-analysis of 4 studies including 260 subjects demonstrated a significant decrease of plasma PCSK9 levels after bariatric surgery (WMD = –57.341 ng/ml, 95% CI: –87.969, –26.714, $p < 0.001$; $I^2 = 96.25\%$) (Figure 2 A). The reduction in PCSK9 was robust in the leave-one-out sensitivity analysis. Consistently, a significant decrease of LDL-C after bariatric surgery (WMD = –22.573 mg/dl, 95% CI: –27.571, –17.574, $p < 0.001$; $I^2 = 86.35\%$) was observed (Figure 2 B). The reductions in PCSK9 and LDL-C were robust in the leave-one-out sensitivity analysis (Figures 3 A, B).

Meta-regression. Random-effects meta-regression was used to analyze the association between baseline BMI and the PCSK9-reducing effect of bariatric surgery. The results suggested a significant association between the changes in PCSK9 and baseline BMI (slope: 8.232; 95% CI: 5.622, 10.842; $p < 0.001$). The results must be interpreted with caution owing to the limited number of included studies.

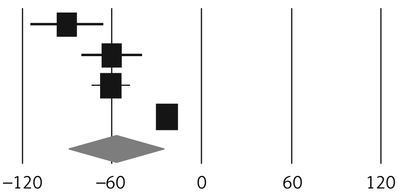
Publication bias. Evaluation for bias using Egger's test (intercept = –5.206, standard error = 0.858; 95% CI = –8.899, –1.513, $t = 6.066$, d$f = 2$, two-tailed $p = 0.026$) suggested publication bias, while Begg's test (Kendall's tau with continuity correction = –0.166, $z = 0.339$, two-tailed p-value = 0.734) suggested that there was no publication bias in the meta-analysis demonstrating bariatric surgery's impact on PCSK9. Trim and fill correction identified one potentially "missing" study. In accordance with the "fail-safe N" test, 2961 missing

Table II. Quality assessment of included studies

Study	Selection				Comparability†	Outcome		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstrate that the focal outcome was not existent at the start	Comparability of cohorts	Assessment of outcome	Long enough follow-up	Adequacy of follow-up
Zenti *et al.* 2020	*	*	*	*	–	*	*	–
Blanchard *et al.* 2020	*	–	*	*	–	*	*	–
Ghanim *et al.* 2018	*	–	*	*	–	*	*	–
Boyer *et al.* 2015	*	*	*	*	*	*	*	*

A

Study name	Statistics for each study						
	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*P*-value
Zenti *et al.* 2020	–90.000	12.118	146.846	–113.751	–66.249	–7.427	< 0.001
Blanchard *et al.* 2020	–60.000	10.531	110.904	–80.641	–39.359	–5.697	< 0.001
Ghanim *et al.* 2018	–61.000	6.105	37.267	–72.965	–49.035	–9.992	< 0.001
Boyer *et al.* 2015	–23.350	0.279	0.078	–23.897	–22.803	–83.603	< 0.001
	–57.341	15.627	244.190	–87.969	–26.714	–3.669	< 0.001



B

Study name	Statistics for each study						
	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*P*-value
Zenti *et al.* 2020	–16.700	8.171	66.766	–32.715	–0.685	–2.044	0.041
Blanchard *et al.* 2020	–15.000	2.726	7.429	–20.342	–9.658	–5.503	< 0.001
Ghanim *et al.* 2018	–25.000	1.549	2.400	–28.036	–21.964	–16.137	< 0.001
Boyer *et al.* 2015	–27.110	0.439	0.193	–27.971	–26.249	–61.697	< 0.001
	–22.573	2.550	6.504	–27.571	–17.574	–8.851	< 0.001

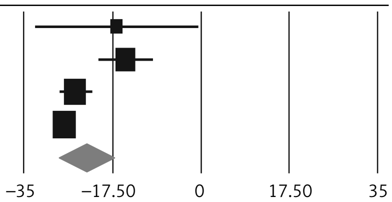
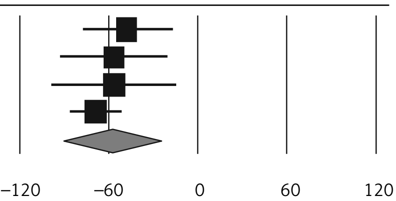


Figure 2. Forest plot indicating weighted mean difference (WMD) and 95% confidence interval (CI) for the effect of bariatric surgery on PCSK9 (**A**) and LDL (**B**)

A

Study name	Statistics with study removed						
	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*P*-value
Zenti *et al.* 2020	–47.275	15.466	239.210	–77.589	–16.962	–3.057	0.002
Blanchard *et al.* 2020	–56.621	18.643	347.545	–93.159	–20.082	–3.037	0.002
Ghanim *et al.* 2018	–56.540	21.275	452.605	–98.237	–14.842	–2.658	0.008
Boyer *et al.* 2015	–68.298	8.477	71.865	–84.913	–51.682	–8.057	< 0.001
	–57.341	15.627	244.190	–87.969	–26.714	–3.669	< 0.001



B

Study name	Statistics with study removed						
	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*P*-value
Zenti *et al.* 2020	–23.059	2.655	7.047	–28.262	–17.856	–8.686	< 0.001
Blanchard *et al.* 2020	–26.281	1.105	1.222	–28.448	–24.114	–23.774	< 0.001
Ghanim *et al.* 2018	–20.414	5.196	26.995	–30.597	–10.230	–3.929	< 0.001
Boyer *et al.* 2015	–19.682	4.222	17.822	–27.956	–11.408	–4.662	< 0.001
	–22.573	2.550	6.504	–27.571	–17.574	–8.851	< 0.001

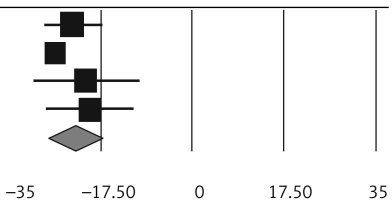


Figure 3. Leave-one-out sensitivity analyses for the effect of bariatric surgery on PCSK9 (**A**) LDL (**B**)

papers would be required to lower the effect size to a non-significant (p < 0.001) level. The results must be interpreted with caution owing to the limited number of included studies (Figure 4).

Discussion. This meta-analysis indicated a significant decrease of circulating PCSK9 levels after bariatric surgery. This is the first meta-analysis evaluating the impacts of bariatric surgery on PCSK9 as a regulator of plasma cholesterol levels. This finding is consistent with other reports suggesting a positive impact of bariatric surgery on cardiovascular risk factors [17–20]. The observed drop in circulating PCSK9 levels could be attributed to long-term weight loss caused by the bariatric procedure as well as sustained decreases in total food intake [11]. Total weight loss after bariatric surgery was found to be inversely associated with PCSK9 alterations [9]. It suggests

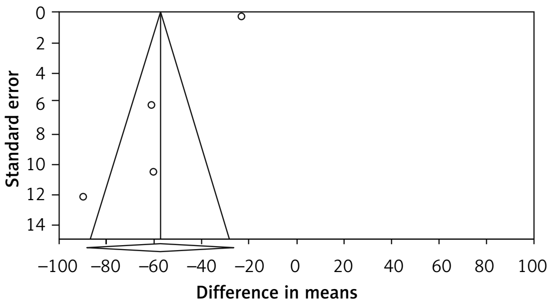


Figure 4. Funnel plot detailing publication bias in the publications describing the effect of bariatric surgery on PCSK9

that following bariatric surgery, PCSK9 levels were significantly decreased throughout chronic and significant weight loss. However, a recent study indicated that enhancing nutritional quality and physical activity did not result in reductions in circulating PCSK9 levels, implying that modest weight loss is not enough to reduce plasma PCSK9 concentration [21]. Furthermore, reduced PCSK9 levels in the chronic period may potentially be explained by better function and regulation of adipose tissue, as well as adipokine secretion following bariatric surgery. It was recently found that leptin and resistin may modulate PCSK9 and LDL-C levels [22]. Previous research also revealed that in response to bariatric surgery-induced weight loss and insulin sensitivity, adipose tissue plays an undetected role in PCSK9 homeostasis. Thus, it is feasible to speculate that physiological insulin levels may influence expression of hepatic PCSK9 and its circulating levels [16]. Alternatively, it is possible that the observed alterations in plasma PCSK9 levels are attributable to a change in metabolism of bile acids. Certainly, after Roux-en-Y gastric bypass (RYGB), bile acids in plasma have been shown to be significantly elevated in morbidly obese patients [23]. Increased bile acid concentrations can result in reduced PCSK9, as bile acids reduce hepatic mRNA and protein expression of PCSK9, an effect that is likely mediated by the activation of farnesoid X receptor [24].

Despite the novelty of this study, limitations include the small number of overall studies, restricting the generalizability of the findings. Moreover, in most of the studies there was no differentiation of free and total PCSK9. Finally, the included studies lacked control groups with other methods of weight loss to allow a direct comparison between different weight loss approaches with respect to their impact on plasma PCSK9 levels.

In conclusion, our findings imply that bariatric surgery is related to lower circulating levels of PCSK9. This finding may partly explain the improvement in lipid profile and cardiovascular risk that occurs following surgery. More research is needed to better understand the mechanisms underlying the influence of bariatric surgery on PCSK9 concentration, as well as to determine the clinical impact of the weight loss procedure on PCSK9 function [25–28].

Conflict of interest

The authors declare no conflict of interest.

References

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012; 307: 491-7.
2. Buchwald H, Oien DM. Metabolic/bariatric surgery worldwide 2011. Obesity Surg 2013; 23: 427-36.
3. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. JAMA 2012; 307: 56-65.
4. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA 2004; 292: 1724-37.
5. Ghanim H, Abuaysheh S, Monte S, Dandona P. Effect of restricted caloric intake and bariatric surgery on PCSK9 concentrations in plasma. Diabetes 2018; 67 Suppl 1: 2093-P.
6. Macchi C, Greco MF, Botta M, et al. Leptin, resistin, and proprotein convertase subtilisin/kexin type 9: the role of STAT3. Am J Pathol 2020; 190: 2226-36.
7. Ricci C, Ruscica M, Camera M, et al. PCSK9 induces a pro-inflammatory response in macrophages. Sci Rep 2018; 8: 2267.
8. Ruscica M, Ferri N, Fogacci F, et al. Circulating levels of proprotein convertase subtilisin/kexin type 9 and arterial stiffness in a large population sample: data from the Brisighella Heart Study. J Am Heart Assoc 2017; 6: e005764.
9. Blanchard C, Ledoux S, Verhaegen A, et al. Roux-en-Y gastric bypass, but not sleeve gastrectomy, decreases plasma PCSK9 levels in morbidly obese patients. Diabetes Metabol 2020; 46: 480-7.
10. Straniero S, Rosqvist F, Edholm D, et al. Acute caloric restriction counteracts hepatic bile acid and cholesterol deficiency in morbid obesity. J Intern Med 2017; 281: 507-17.
11. Boyer M, Piche ME, Auclair A, et al. Acute and chronic impact of bariatric surgery on plasma LDL cholesterol and PCSK9 levels in patients with severe obesity. J Clin Endocrinol Metabol 2017; 102: 4023-30.
12. Higgins JP. Cochrane handbook for systematic reviews of interventions version 5.0. 1. The Cochrane Collaboration. http://www cochrane-handbook org. 2008.
13. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford 2000.
14. Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive meta-analysis, version 2 Biostat. Englewood NJ. 2005.
15. Sutton AJ, Abrams KR, Jones DR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. Wiley, Chichester 2000.
16. Zenti MG, Lupo MG, De Martin S, et al. Impact of bariatric surgery-induced weight loss on circulating PCSK9

levels in obese patients. Nutr Metabol Cardiovasc Dis 2020; 30: 2372-8.
17. Tang B, Zhang Y, Wang Y, Wang X, An Z, Yu X. Effect of bariatric surgery on long-term cardiovascular outcomes: a systematic review and meta-analysis of population-based cohort studies. Surg Obes Relat Dis 2022; 18: 1074-86.
18. Jamialahmadi T, Alidadi M, Atkin SL, et al. Effect of bariatric surgery on flow-mediated vasodilation as a measure of endothelial function: a systematic review and meta-analysis. J Clin Med 2022; 11: 4054.
19. Jamialahmadi T, Reiner Z, Alidadi M, et al. The effect of bariatric surgery on circulating levels of oxidized low-density lipoproteins is apparently independent of changes in body mass index: a systematic review and meta-analysis. Oxid Med Cell Longev 2021; 2021: 4136071.
20. Jamialahmadi T, Reiner Z, Alidadi M, et al. Impact of bariatric surgery on pulse wave velocity as a measure of arterial stiffness: a systematic review and meta-analysis. Obes Surg 2021; 31: 4461-9.
21. Arsenault BJ, Pelletier-Beaumont E, Alméras N, et al. PCSK9 levels in abdominally obese men: association with cardiometabolic risk profile and effects of a one-year lifestyle modification program. Atherosclerosis 2014; 236: 321-6.
22. Melone M, Wilsie L, Palyha O, Strack A, Rashid S. Discovery of a new role of human resistin in hepatocyte low-density lipoprotein receptor suppression mediated in part by proprotein convertase subtilisin/kexin type 9. J Am Coll Cardiol 2012; 59: 1697-705.
23. Patti ME, Houten SM, Bianco AC, et al. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. Obesity 2009; 17: 1671-7.
24. Langhi C, Le May C, Kourimate S, et al. Activation of the farnesoid X receptor represses PCSK9 expression in human hepatocytes. FEBS Lett 2008; 582: 949-55.
25. Banach M, Burchardt P, Chlebus K, et al. PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021. Arch Med Sci 2021; 17: 1447-547.
26. Momtazi-Borojeni AA, Jaafari MR, Afshar M, Banach M, Sahebkar A. PCSK9 immunization using nanoliposomes: preventive efficacy against hypercholesterolemia and atherosclerosis. Arch Med Sci 2021; 17: 1365-77.
27. Macchi C, Ferri N, Sirtori CR, Corsini A, Banach M, Ruscica M. Proprotein convertase subtilisin/kexin type 9: a view beyond the canonical cholesterol-lowering impact. Am J Pathol 2021; 191: 1385-97.
28. Banach M, Kaźmierczak J, Mitkowski P, et al. Which patients at risk of cardiovascular disease might benefit the most from inclisiran? Polish experts' opinion. The compromise between EBM and possibilities in healthcare. Arch Med Sci 2022; 18: 569-76.