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# The impact of the nocebo effect on discontinuation of statin therapy due to myopathy in patients with cardiovascular disease – a review

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## Abstract

**Introduction and purpose of review:** Statins are widely used drugs in the prevention of cardiovascular diseases, yet many patients experience side effects of statin use, mainly muscle symptoms, such as myopathy, which often lead to discontinuation of treatment. The aim of this literature review is to assess the role of the nocebo effect in reported muscle symptoms and its impact on statin discontinuation in patients with cardiovascular diseases.

**Methods**: The review analysed the results of several studies, including key publications such as the N-of-1 trial by Wood et al. [1] and the work of Collins et al. [2] on the safety and efficacy of statin therapy. The review covered articles published between 2000 and 2023 that examined the impact of the nocebo effect on statin discontinuation [3-10].

**Results**: The collected data indicate that the nocebo effect plays a significant role in the reported muscle symptoms during statin use. The study by Wood et al. [1] showed no significant differences in reported symptoms between the groups taking statins, placebo, or receiving no treatment, suggesting that a substantial portion of the symptoms results from the nocebo effect. Similar findings were obtained in the study conducted by the StatinWISE group [4], where

patients taking statins and placebo reported a comparable frequency of muscle symptoms . An analysis conducted by Collins et al. [2] indicates that the actual incidence of myopathy associated with statin therapy is much lower than commonly reported.

**Conclusions**: The nocebo effect significantly influences the perceived adverse effects of statins, which may lead to the unjustified discontinuation of these drugs by patients with cardiovascular diseases. Further research is needed to better understand the psychological mechanisms affecting statin tolerance and to develop educational and clinical strategies aimed at minimizing the nocebo effect and improving long-term adherence to therapy.

**Keywords**: statins, nocebo effect, myopathy, cardiovascular diseases, dyslipidemia, hypercholesterolemia, literature review, drug discontinuation.

## Background

Statins are a class of pharmacological agents that play a pivotal role in lowering blood cholesterol levels, which is crucial for the prevention of cardiovascular diseases. Their mechanism of action is based on the competitive inhibition of the enzyme HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase), a key enzyme in the cholesterol biosynthesis pathway in the liver. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol synthesis. The inhibition of this enzyme by statins results in a reduction of intracellular cholesterol production.

In response to the decreased intracellular cholesterol levels within hepatocytes, there is an upregulation of low-density lipoprotein receptors (LDLR) on the surface of these liver cells. The increased number of LDL receptors enhances the clearance of LDL-C (low-density lipoprotein cholesterol) from the bloodstream. Consequently, there is a reduction in circulating LDL-C levels, as well as other apolipoprotein B-containing lipoproteins, including triglyceride-rich lipoproteins (TG) [11].

The use of statins may reduce the risk of atherosclerotic cardiovascular diseases up to 55% [11, 12]. Adverse effects of drugs are very difficult to assess and identify. The interpretation of some side effects of statins is incorrect, and the adverse effects attributed to them are related to the occurrence of separate diseases, risk factors, the use of other drugs, or

the patient's clinical condition [13]. Potential side effects associated with the use of statins are still the main reason for non-compliance with recommendations or discontinuation of their use [10, 14, 15, Praca]. Non-adherence to statin treatment may be as high as 60% after 24 months of treatment and is associated with a 70% increase in the risk of cardiovascular events [16].

When taking statins, patients especially complain of myopathies [2]. Patients' knowledge of side effects of medications makes them susceptible to the nocebo effect —a psychological phenomenon in which the patient experiences negative side effects that are not actually related to the medication, but rather to their expectations [1].

Studies on the impact of the nocebo effect on statin therapy have shown that many symptoms of myopathy reported by patients may be associated with their expectations and beliefs about potential side effects, rather than with the treatment itself [1, 17]. A study conducted by Wood et al. [1] demonstrated that patients receiving statins, placebo, or no treatment reported similar symptoms, suggesting a significant influence of the nocebo effect on patient experiences. Similar findings were observed in the StatinWISE trial, where muscle symptoms were reported with suchlike frequency in both the statin and placebo groups [5].

Knowledge about the possibility of myopathy in patients taking statins causes some patients to discontinue treatment, which inevitably leads to cardiovascular complications. Recent papers shows that myopathies do not affect many patients [1, 18]. In last years, some studies have completely denied the existence of a link between myopathy and statin use [5, 18, 19].

Analyses conducted by Collins et al. [2] and Thavendiranathan et al. [6] indicate that the actual incidence of statin-induced myopathy is significantly lower than suggested by patients' reports. In fact, many of these symptoms may result from the nocebo effect rather than the pharmacological action of the drug itself [10]. Studies on the risks and benefits of statin therapy, such as those by Kashani et al. [7] and Zhang et al. [9], have noted that misconceptions about risk can affect adherence to therapy and its effectiveness [7, 9].

In the context of global research on statin therapy, understanding the role of the nocebo effect and developing strategies to minimize its impact, are crucial for improving treatment adherence and achieving better health outcomes [8,13]. Therefore, further research is needed to explore the psychological mechanisms influencing statin tolerance and to develop effective clinical interventions.

**Review of selected original publications**

The study conducted by Wood FA, Howard JP, Finegold JA, and Nowbar AN [1], examined whether statin-induced myopathy is a nocebo effect. The study involved 60 patients

(from June 2016 to March 2019) who discontinued statins use due to side effects occurring after 2 weeks of taking the drug. Patients were enrolled in a randomized, double-blind study (n-of-1 trials) to see whether their symptoms would be induced by a statin or a placebo. Participants were given 12 1- month bottles: four bottles of atorvastatin 20 mg, four bottles of placebo and four empty bottles. Each bottle was intended to be used for a period of 1 month in random order. Patients rated the severity of side effects daily on a scale from 0 (no symptoms) to 100 (worst imaginable symptoms), including muscle pain. They used a smartphone application for this purpose. If the patient experienced very severe side effects, he could stop taking the tablets for a month. The analysis of the primary endpoint showed a nocebo ratio of 2.2 (95% confidence interval [CI], -62.3 to 66.7). This value was high and had a wide confidence interval because in some patients the difference in symptom severity scores with statins and symptom severity scores without statins or placebo was unexpectedly small or negative. The mean symptom intensity among all 60 patients, was 8,0 for no-tablet months (95% CI, 4,7 to 11,3), 15,4 for placebo months (95% CI, 12,1 to 18,7; P<0,001when comparing with no-tablet months) and 16,3 for statin months (95% CI, 13,0 to 19,6; p<0,001 when comparing with no-tablet months and P=0.39 when comparing with placebo months) [1].

Six months after the end of the study, 30 patients (50%) had successfully resumed taking statins, 4 planned to do so, and 1 could not be contacted. The remaining 25 patients were not receiving statins and did not plan to be re-treated with statins for the following reasons: side effects in 18, spontaneous improvement in cholesterol in 4 (patients no longer believed that statins caused side effects), recall that their cholesterol was not lowered by statins in 1, new diagnosis of progressive neurodegenerative disorder in 1, the feeling of being "too old" in 1. In patients who discontinued statin therapy due to side effects, 90% of the severity of symptoms induced by statin challenge was also elicited by placebo [1].

A series of randomized, double-blind studies by Emily Herrett, Elizabeth Williamson, Kieran Brack et al. [4] examined the overall effect of atorvastatin on muscle symptoms. The study was carried out in 50 general practitioners centers in the UK between December 2016 and April 2018. The study included 200 participants who had recently stopped or were considering stopping statin treatment due to muscle symptoms.

The study lasted for 12 months. Participants were randomly assigned to six two-month study periods. Three of the two-month periods, consisted of treatment with atorvastatin 20 mg. During other months, participants were given a placebo. Both parts of the study were double-blind. Patients and researchers did not know when the participant was receiving a statin. At the end

of each treatment period, participants rated their muscle symptoms on a visual analog scale (from 0 to 10). The analysis compared symptom scores during the statin and placebo periods. 151 participants provided symptom scores for at least one statin period and one placebo period, and were included in the analysis (Table 1).

| | No (%) of participants | |
|---|---|---|
| | Statin periods | Placebo periods |
| **Muscle symptoms** | 248/397 (62.5) | 239/388 (61.6) |
| **Muscle symptoms, not attributed to other causes** | 216/397 (54.4) | 200/388 (51.6) |

Table 1. Estimated effects for secondary outcomes comparing statin with placebo periods (from participant questionnaire; n=152) - table based on [4].

There were few participants who withdrew from the study due to health complications. Eighteen of two hundred participants (9%) withdrew during the statin treatment period and 13 (7%) withdrew during the placebo period. A small group of participants in this study had previously experienced side effects from taking statins that were severe enough for them to discontinue treatment. Therefore, they knew the side effects of statins and may have been susceptible to the nocebo effect [1, 17]. Researchers found no differences in the frequency or severity of muscle symptoms between the periods of satin and placebo. In this series of studies, discontinuations due to symptom intolerance were rare and the excess compared with ststins and placebo was 2%. Of those who participated in the study, almost two-thirds reported that they intended to resume statin treatment. The researchers emphasize the consistency of their study with the ODYSSEY ALTERNATIVE study [20] and the GAUSS-3 study [21], which proved that only a small proportion of statin-intolerant patients developed intolerable muscle symptoms while taking statins compared to placebo. Observational studies have shown a negative effect of statins on muscles [2, 22] and the occurrence of muscle symptoms during therapy with these drugs in clinical practice often prompts patients to discontinue treatment [9, 10, 14, 15]. Various explanations have been proposed for this phenomenon, including the nocebo effect, in which waiting for the occurrence of side effects may cause patients to attribute muscle ailments to the statins they are taking [9, 10, 23]. Additionally, muscle pain is a common symptom in the elderly population, which often takes statins, which may lead to these ailments being wrongly attributed to the use of statins [13, 3]. The lack of randomization and blinding in observational

studies means that in the case of subjective symptoms, such as muscle pain, the association with statins may not be causal [8, 13]. The significant proportion of participants in our studies who intended to resume statin therapy after study completion is consistent with observational data suggesting that reinitiation of statin therapy is tolerable in most patients [24 , 25].

An article by Gupta et al. published in the Lancet in 2017 is an important study on the side effects of statins [3]. The aim of the study was to determine the true incidence of statin-related adverse events, including myopathy (Table 2).

| | Empty Cell Blinded randomised phase (ASCOT-LLA) | | Non-blinded non-randomised phase | |
|---|---|---|---|---|
| | Empty Cell Placebo (n=5079) | Atorvastatin (n=5101) | Atorvastatin non-user (n=3490) | Atorvastatin user (n=6409) |
| Muscle related | | | | |
| Patients (n) | 283 | 298 | 124 | 161 |
| AE rate (% per annum) | 2·00% | 2·03% | 1·00% | 1·26% |
| HR (95% CI) | 1 | 1·03 (0·88–1·21) | 1 | 1·41 (1·10–1·79) |
| p value | .. | 0·72 | .. | 0·006 |

Table 2. Risk of adverse events of interest - table based on [3].

Study participants of the Lipid-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA) [3], were recruited from various clinics and hospitals, which ensured population diversity and increased the representativeness of the results.

The subjects had not previously taken statins or fibrates. Patients were assigned to atorvastatin 10 mg daily or placebo, respectively. Investigators compared the reporting rate of adverse events during statin treatment in the blinded, randomized, and unblinded, nonrandomized phases (Table 3).

| In the blinded randomised phase | | | | | |
|---|---|---|---|---|---|
| | Rate (% per annum) | | HR (95 % Cl) | | P value |
| | Placebo | Atorvastatin | | | |
| Musculoskeletal and connective tissue disorders | 6·91% | 7·19% | 1·04 1·11) | (0·96– | 0·33 |
| In the non-blinded non-randomised phase | | | | | |
| | Rate (% per annum) | | HR (95 % Cl) | | P value |
| | Atorvastatin non-user | Atorvastatin user | | | |
| Musculoskeletal and connective tissue disorders. | 7·45% | 8·69% | 1·17 1·29) | (1·06– | 0·001 |

Table 3. Rates of all adverse events, in the blinded randomised phase nad in the non-blinded non-randomised phase - table based on [3].

The study found that in the blinded phase, when participants did not know whether they were taking statins, there were no excess reports of muscle problems. However, after it was revealed that patients were taking statins in the unblinded phase, reports of such problems increased significantly. This observation suggests a nocebo effect [17].

Gupta A et al., draw attention to non-randomized observational studies on the use of statins in everyday health care, where every fifth patient reports that they do not tolerate statins [26, 27]. However, these studies, unlike the study by Gupta et al., are not blinded. Both the patient and the doctor know what drug is being used for therapy and that the treatment has specific side effects. The ASCOT-LLA example illustrates how lack of blinding can lead to overreporting of adverse events. This article is an important source of knowledge on the impact of statin therapy on patient safety and provides a starting point for further analysis, especially in the context of the nocebo effect.

In 2008, a JUPITER study was published, in which 17,802 people without hyperlipemia were selected. It was randomized, double-blind, placebo-controlled, multicenter study, conducted in 1,315 centers in 26 countries [28]. During the study, the number of reported adverse events was similar in the group receiving rosuvastatin 20 mg and placebo. The number of patients reporting muscle symptoms (muscle weakness, stiffness, or pain) was 1,421 for rosuvastatin group and 1,375 for placebo group (Table 4). There were no significant differences between the two study groups in terms of adverse events on muscles during the study.

| Event | Rosuvastatin (N=8091) | Placebo (N=8901) | P Value |
|---|---|---|---|
| Muscular weakness, stiffess, or pain – no. (%) | 1421 (16.0) | 1375 (15.4) | 0.34 |
| Myoparthy – no. (%) | 10 (0.1) | 9 (0.1) | 0.82 |
| Rhabdomyolysis – no. (%) | 1 (<0.1) | 0 | - |
| Creatinine, >100% increase from baseline – no. (%) | 16 (0.2) | 10 (0.1) | 0.24 |

Table 4. Monitored Adverse Events Reported Events of Interest during the Follow-up Period. Tabela na podstawie badania; „Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein - table based on [28].

.An increase in adverse events with long-term statin use cannot be excluded. The median follow-up time for patients was 1.9 years. However, there was no increase in adverse events in the analysis of participants who continued treatment for 4 or more years. The rates of first major cardiovascular event and all-cause death were significantly lower in participants receiving rosuvastatin than in those receiving placebo. There were 142 major cardiovascular events in the rosuvastatin group and 251 in the placebo group.

This study showed that rosuvastatin therapy significantly reduced the number of cardiovascular events. The study was double-blind, meaning that neither patients nor investigators knew which treatment was assigned to each participant. This method helps eliminate the influence of patient

and investigator expectations on the results, allowing for more reliable data on the efficacy and safety of the treatment.

In a study conducted as part of the Integrated Systematic Care for Older Persons (ISCOPE) study in the Netherlands [29], patients with a well-documented medical history and a history of statin treatment were selected. The screening questionnaire asked: “What health problems currently limit you most in your daily life?” [30, 31]. No muscle-related adverse events were suggested.

The study included a representative group of 4355 patients. During the observation period, there was no difference in the frequency of muscle-related complaints in statin users (3.3%) and non-users (2.5%)(p=0.18) (Fig.1).

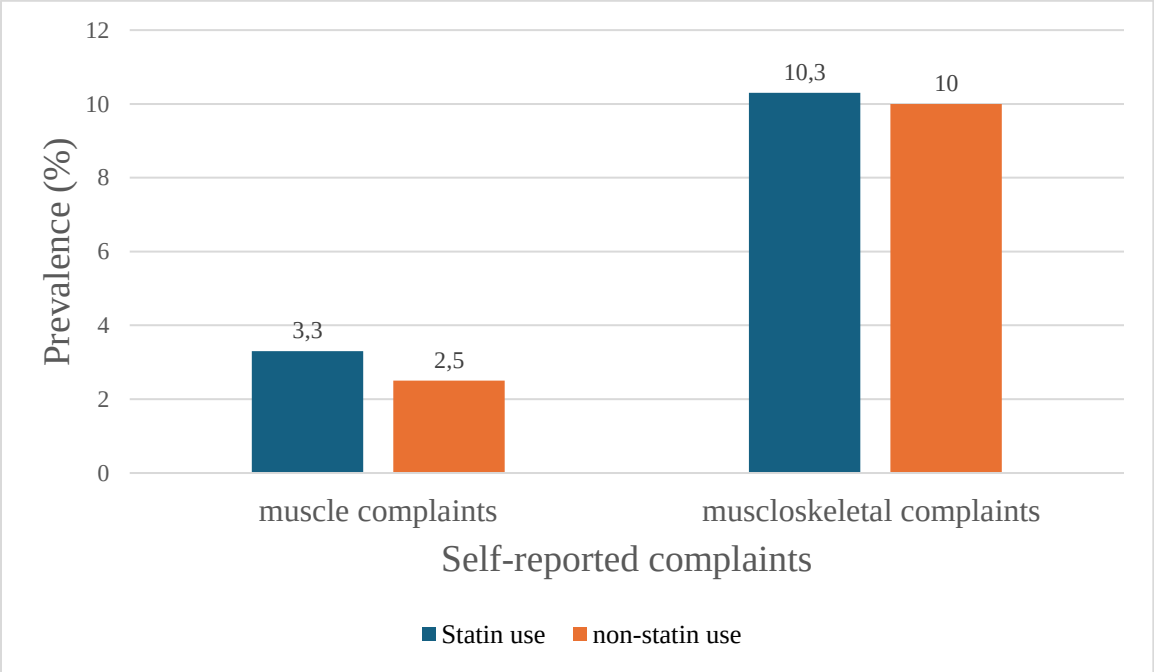


Fig 1. Prevalence of self-reported complaints according to statin use and non-statin use - chart based on [29].

The study examined whether the use of statins is associated with self-reported muscle symptoms that impair daily living. No significant difference was found in the frequency of self-reported muscle symptoms between individuals using statins and those not using statins [10, 32]. The researchers draw attention to the frequently discussed topic in public discourse regarding muscle symptoms related to statin use, which may lead to negative patient expectations towards statins. The unpleasant effects experienced are not always necessarily a result of statin use [23, 33]. Furthermore, physicians may be inclined to incorrectly attribute muscle symptoms to statin therapy [5].

The Heart Protection Study is one of the largest clinical trials evaluating the effect of statins on the prevention of cardiovascular disease [34]. The primary objective of the study was to determine whether the use of statins can reduce the risk of death and cardiovascular events in patients at various risk of cardiovascular disease, regardless of baseline cholesterol levels. A total of 20,536 patients took part in the study, the average duration of follow-up was 5 years.

At each follow-up, approximately 6% of participants reported unexplained muscle pain or weakness, but there was no significant difference between the simvastatin and placebo groups. These symptoms occurred at least once in 32.9% of participants taking simvastatin and 33.2% of participants taking placebo. Similarly, there was no significant difference in the number of participants who discontinued treatment because of muscle symptoms (49 in the statin group vs. 50 in the placebo group). Creatine kinase levels were measured in every participant who reported muscle symptoms. Only a few patients taking a statin had elevated creatinine levels (Table 5).

| | Simvastatin-allocated (n=10269) | Placebo-allocated (n=10267) |
|---|---|---|
| Elevated CK | | |
| 4−10×ULN | 19 (0·19%) | 13 (0·13%) |
| >10×ULN* | 11 (0·11%) | 6 (0·06%) |
| Myopathy | | |
| No rhabdomyolysis | 5 (0·05%) | 1 (0·01%) |
| Rhabdomyolysis | 5 (0·05%) | 3 (0·03%) |

CK=creatine kinase; ULN=upper limit of normal for laboratory.

*

Among those with CK >10×ULN, 1 *vs*2 were asymptomatic.

Table 5. Numbers of participants with elevated liver or muscle enzymes during follow-up - based on [34].

Myopathy, defined as the occurrence of muscle symptoms and a creatine kinase increase of more than 10 times the upper limit of normal (ULN), was diagnosed in a small number of participants taking simvastatin, but the difference was not statistically significant (p=0.2).

The Heart Protection Study found no significant difference in the incidence of unexplained muscle pain or weakness between simvastatin and placebo. The study results suggest that statin therapy provides a clear health benefit that may prevent serious vascular events in about 70 to 100 people per 1,000 treated for 5 years, even with a moderate incidence of muscle-related side

effects. Long-term statin therapy appears to be valuable for many high-risk patients, especially because the therapy is well tolerated and safe.

**Conclusions**

This review discusses issues related to statin therapy, particularly with regard to the incidence of adverse events and the impact of the nocebo effect on reported symptoms [35]. Recent studies suggest that the true incidence of statin-related myopathy is much lower than that reported by patients [2,6, 28, 29, 34]. That is why it is important to understand the role of the nocebo effect and develop strategies to minimize its impact on treatment.. The results of the studies by Wood et al. [1] and Herrett et al. [4] indicate a significant influence of the nocebo effect on the reported muscle symptoms in patients taking statins. Both studies used randomized, double-blind, placebo-controlled protocols, which allowed for the assessment of the true association between statin use and the occurrence of symptoms. The results of these studies indicate that patient-reported symptoms were as common in the placebo group as in the statin group, strongly suggesting that the nocebo effect plays a significant role in the perception of adverse effects by patients. Similar conclusions can be drawn from the study by Gupta et al. [3], which showed that there was no excess reporting of muscle problems during the blinded phase, but after revealing that patients were taking statins, the number of such reports increased significantly. This observation also suggests the influence of the nocebo effect on the subjective experiences of patients. Observational studies have shown that patients taking statins are more likely to report muscle symptoms, which often leads to treatment discontinuation [9, 10, 14, 15]. However, the lack of randomization and blinding in these studies means that the association between statin use and muscle symptoms may not be causal [8, 13]. The evidence confirms that the actual incidence of statin-induced myopathy is significantly lower than suggested by patient reports [2, 28, 29, 34, 36, 37]. These data underscore the importance of the nocebo effect in statin therapy. Patients who are aware of the potential side effects may be more susceptible to the nocebo effect, which may lead to higher adverse event reporting rates and more frequent discontinuation of therapy. Unfortunately this may lead to worse health outcomes, as statins play a key role in preventing cardiovascular disease [38, 39, 40].

**Disclosure**

**Author's contribution**

Conceptualization: Jakub Stanek and Patrycja Sornek; Methodology: Wiktoria Izdebska; Software: Klaudia Perkowska; Check: Anna Kaźmierczak; Formal analysis: Jakub Stanek; Investigation: Jakub Stanek, Patrycja Sornek; Resources: Radosław Ciesielski; Data curation: Igor Pawlak and Wiktoria Izdebska; Writing- rough preparation: Agata Borkowska;

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## References

1. Wood FA, Howard JP, Finegold JA, et al. "N-of-1 trial of a statin, placebo, or no treatment to assess side effects." *New England Journal of Medicine*. 2020; 383:2182-2184.
2. Collins R, Armitage J, Parish S, et al. "Interpretation of the evidence for the efficacy and safety of statin therapy." *Lancet*. 2016; 388(10059):2532-2561.
3. Gupta A, Thompson D, Whitehouse A, et al.ASCOT Investigators . Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. *Lancet* 2017;389:2473-81. 10.1016/S0140-6736(17)31075-9
4. Herrett E, Williamson E, Brack K, et al. "Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials." *BMJ*. 2021; 372.
5. Finegold JA, Manisty CH, Goldacre B, et al. "What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug?" *European Journal of Preventive Cardiology*. 2014; 21(4):464-474.
6. Thavendiranathan P, Bagai A, Brookhart MA, et al. "Primary prevention of cardiovascular diseases with statin therapy: A meta-analysis of randomized controlled trials." *Archives of Internal Medicine*. 2006; 166(21):2307-2313.

7. Kashani A, Phillips CO, Foody JM, et al. "Risks associated with statin therapy: A systematic overview of randomized clinical trials." *Circulation*. 2006; 114(25):2788-2797.
8. Taylor F, Huffman MD, Macedo AF, et al. "Statins for the primary prevention of cardiovascular disease." *Cochrane Database of Systematic Reviews*. 2013; (1).
9. Zhang H, Plutzky J, Skentzos S, et al. "Discontinuation of statins in routine care settings: A cohort study." *Annals of Internal Medicine*. 2013; 158(7):526-534.
10. Stroes ES, Thompson PD, Corsini A, et al. "Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel statement on assessment, aetiology, and management." *European Heart Journal*. 2015; 36(17):1012-1022.
11. Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. Cell. 2015 Mar 26;161(1):161-172. doi: 10.1016/j.cell.2015.01.036. PMID: 25815993; PMCID: PMC4525717.
12. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgözoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017 Aug 21;38(32):2459-2472. doi: 10.1093/eurheartj/ehx144. PMID: 28444290; PMCID: PMC5837225.
13. Banach M., Michailidis DP. Nietolerancja statyn: kilka praktycznych wskazówek . Cardiol Clin 2018; 36 :225–231 -LINK
14. Banach M, Stulc T, Dent R, Toth PP. Statin non-adherence and residual cardiovascular risk: There is need for substantial improvement. Int J Cardiol. 2016 Dec 15;225:184-196. doi: 10.1016/j.ijcard.2016.09.075.
15. Penson PE, Bruckert E, Marais D, Reiner Ž, Pirro M, Sahebkar A, Bajraktari G, Mirrakhimov E, Rizzo M, Mikhailidis DP, Sachinidis A, Gaita D, Latkovskis G, Mazidi M, Toth PP, Pella D, Alnouri F, Postadzhiyan A, Yeh HI, Mancini GBJ, von Haehling S, Banach M; International Lipid Expert Panel (ILEP). Step-by-step diagnosis and management of the nocebo/drucebo effect in statin-associated muscle symptoms

patients: a position paper from the International Lipid Expert Panel (ILEP). J Cachexia Sarcopenia Muscle. 2022 Jun;13(3):1596-1622. doi: 10.1002/jcsm.12960

16. Banach M, Burchardt P, Chlebus K, Dobrowolski P, Dudek D, Dyrbuś K, Gąsior M, Jankowski P, Jóźwiak J, Kłosiewicz-Latoszek L, Kowalska I, Małecki M, Prejbisz A, Rakowski M, Rysz J, Solnica B, Sitkiewicz D, Sygitowicz G, Sypniewska G, Tomasik T, Windak A, Zozulińska-Ziółkiewicz D, Cybulska B. PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021. Arch Med Sci. 2021 Nov 8;17(6):1447-1547. doi: 10.5114/aoms/141941.
17. Tobert JA, Newman CB. The nocebo effect in the context of statin intolerance. J Clin Lipidol. 2016 Jul-Aug;10(4):739-747. doi: 10.1016/j.jacl.2016.05.002. Epub 2016 May 13. PMID: 27578103.
18. Malcolm Law, Alicja R. Rudnicka. Statin Safety: A Systematic Review. Am J Cardiol. 2006; 97: 52C-60C.
19. Naci H, Brugts J, Ades T. Comparative tolerability and harms of individu - al statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. Circ Cardiovasc Qual Outcomes. 2013; 6: 390–399.
20. Moriarty PM, Jacobson TA, Bruckert E, Thompson PD, Guyton JR, Baccara-Dinet MT, Gipe D. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. J Clin Lipidol. 2014 Nov-Dec;8(6):554-561. doi: 10.1016/j.jacl.2014.09.007. Epub 2014 Sep 19. PMID: 25499937.
21. Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, Sattar N, Preiss D, Bruckert E, Ceška R, Lepor N, Ballantyne CM, Gouni-Berthold I, Elliott M, Brennan DM, Wasserman SM, Somaratne R, Scott R, Stein EA; GAUSS-3 Investigators. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. JAMA. 2016 Apr 19;315(15):1580-90. doi: 10.1001/jama.2016.3608. PMID: 27039291.
22. Macedo AF, Taylor FC, Casas JP, Adler A, Prieto-Merino D, Ebrahim S. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. *BMC Med* 2014;12:51. 10.1186/1741-7015-12-51
23. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002;287:622-7. 10.1001/jama.287.5.622

24. Zhang H, Plutzky J, Shubina M, Turchin A. Continued statin prescriptions after adverse reactions and patient outcomes: a cohort study. *Ann Intern Med* 2017;167:221-7. 10.7326/M16-0838
25. Mampuya WM, Frid D, Rocco M, et al.. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. *Am Heart J* 2013;166:597-603. 10.1016/j.ahj.2013.06.004
26. Abramson JD, Rosenberg HG, Jewell N, Wright JM. Should people at low risk of cardiovascular disease take a statin? BMJ 2013; 347: f6123.
27. Armitage J. The safety of statins in clinical practice. Lancet. 2007 Nov 24;370(9601):1781-90. doi: 10.1016/S0140-6736(07)60716-8. PMID: 17559928.
28. *Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008 Nov 20;359(21):2195-207. doi: 10.1056/NEJMoa0807646. Epub 2008 Nov 9. PMID: 18997196*
29. *Blom J, den Elzen W, van Houwelingen AH, Heijmans M, Stijnen T, Van den Hout W, Gussekloo J. Effectiveness and cost-effectiveness of a proactive, goal-oriented, integrated care model in general practice for older people. A cluster randomised controlled trial: Integrated Systematic Care for older People--the ISCOPE study. Age Ageing. 2016 Jan;45(1):30-41. doi: 10.1093/ageing/afv174. PMID: 26764392; PMCID: PMC4711660.*
30. van der Ploeg MA, Poortvliet RK, van Blijswijk SC, den Elzen WP, van Peet PG, de Ruijter W, Blom JW, Gussekloo J. Statin Use and Self-Reported Hindering Muscle Complaints in Older Persons: A Population Based Study. PLoS One. 2016 Dec 2;11(12):e0166857. doi: 10.1371/journal.pone.0166857. Erratum in: PLoS One. 2021 Jan 22;16(1):e0245997. doi: 10.1371/journal.pone.0245997. PMID: 27911918; PMCID: PMC5135075.
31. van Blijswijk SC, Chan OY, van Houwelingen AH, Gussekloo J, den Elzen WP, Blom JW. Self-Reported Hindering Health Complaints of Community-Dwelling Older Persons: A Cross-Sectional Study. PLoS One. 2015 Nov 16;10(11):e0142416. doi: 10.1371/journal.pone.0142416. PMID: 26571233; PMCID: PMC4646486.
32. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO

study. Cardiovasc Drugs Ther. 2005 Dec;19(6):403-14. doi: 10.1007/s10557-005-5686-z. PMID: 16453090.

33. Colloca L, Finniss D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. JAMA. 2012 Feb 8;307(6):567-8. doi: 10.1001/jama.2012.115. PMID: 22318275; PMCID: PMC6909539.
34. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.
35. Rosenbaum D, Dallongeville J, Sabouret P, Bruckert E. Discontinuation of statin therapy due to muscular side effects: a survey in real life. Nutr Metab Cardiovasc Dis. 2013 Sep;23(9):871-5. doi: 10.1016/j.numecd.2012.04.012. Epub 2012 Jun 29. PMID: 22748604.
36. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994 Nov 19;344(8934):1383-9. PMID: 7968073.
37. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998 Nov 5;339(19):1349-57. doi: 10.1056/NEJM199811053391902. PMID: 9841303.
38. Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med. 1997 Jan 16;336(3):153-62. doi: 10.1056/NEJM199701163360301. Erratum in: N Engl J Med 1997 Dec 18;337(25):1859. PMID: 8992351
39. Cai T, Abel L, Langford O, Monaghan G, Aronson JK, Stevens RJ, Lay-Flurrie S, Koshiaris C, McManus RJ, Hobbs FDR, Sheppard JP. Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. BMJ. 2021 Jul 14;374:n1537. doi: 10.1136/bmj.n1537. PMID: 34261627; PMCID: PMC8279037.
40. Ramkumar S, Raghunath A, Raghunath S. Statin Therapy: Review of Safety and Potential Side Effects. Acta Cardiol Sin. 2016 Nov;32(6):631-639. doi: 10.6515/acs20160611a. PMID: 27899849; PMCID: PMC5126440.