Drucebo effect – the challenge we should all definitely face!

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Commentary on: N-of-1 trial of a statin, placebo, or no treatment to assess side effects (Wood et al. NEJM 2020; 383: 2182-4)

We would like to congratulate the authors of the N-of-1 Trial for the fact that they decided to face the assessment of the extremely difficult phenomenon, which is the so-called nocebo effect [1]. This is in fact the second attempt to approach this research question, after the *post-hoc* analysis of the Lipid-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA), in which the authors showed a 41% higher risk of statin intolerance in those on statin therapy in the non-blinded phase in comparison to blinded, what they attributed to the nocebo effect [2].

The Self-Assessment Method for Statin Side-effects Or Nocebo (SAMSON) investigators demonstrated that 50–57% of individuals who had discontinued statin therapy owing to adverse events (AEs) were able to resume (rechallenge) long-term treatment [1]. With careful application of diagnostic methods and patient-centered care, we believe this proportion can be further increased [3]. We should always remember about this critical step if only the symptoms (and/or creatine kinase levels) are relieved, as continuation of statin therapy (even at a reduced dose) is a critical means to avoid visit-to-visit variability in low density lipoprotein cholesterol (LDL-C) concentrations, increased risk of plaque instability, and the consequent risk of cardiovascular events and mortality [4–7]. That is why now there is an important discussion, and strong recommendations have been made to start non-statin therapy (ezetimibe, bempedoic acid, PCSK9 inhibitors, nutraceuticals and their combination) immediately in all those who required statin discontinuation, especially in patients with very high and extremely high cardiovascular risk [4–7].

The SAMSON trial included a 'no treatment' group in addition to statin and placebo [1]. This allowed the on-treatment AEs to be compared with the 'nocebo' effect (AE caused by expectation on consuming an inert substance). Arguably more relevant is the drucebo effect (AE caused by expectation on taking a drug), which we introduced in 2018 within the International Lipid Expert Panel (ILEP), which may account for up to 78% of muscle pain on statin therapy [8]. Objectivity of the symptoms might be another source of bias in this trial, potentially resulting in overestimation of the prevalence of the drucebo effect [1]. The first question we ask

patients with statin intolerance is about tolerability. After our attempts to exclude secondary causes and to provide information about the benefits of continued statin therapy (e.g. with information that statins might prolong their life, presenting them their heart age, etc.), many patients (including those who initially described their symptoms as 'intolerable') still agree to try continuing the treatment. This might involve using a lower dose of statin, combination therapy or alternative-day statin therapy [9–11]. This approach means that 95% of patients initially suffering muscle pain may be able to continue statin therapy, and only 3–5% experience complete statin intolerance [9–11].

One should ask why participation in the study was limited to patients who experienced AEs within 2 weeks of therapy, as the majority of AEs appear in first 4 (about 40%) to 8 weeks (> 60%) [3, 10, 11]. Although not causally confirmed, several modifiable risk factors associated with statin intolerance (thyroid disorders, vitamin-D deficiency, chronic kidney and liver diseases, and potential drug-drug interactions) should be addressed if statin-intolerance is suspected [9–11]. SAMSON did not appear to exclude such patients or address reversible causes [1]. The authors did not also recommend any age cut-off point, especially it has been confirmed many times that older age itself (> 65 years) might be associated with the risk of statin intolerance [9].

Moreover, patient reported adverse effects are subjective (recorded each day using a smartphone application to report symptom intensity) [1]. The degree to which symptoms are tolerated may depend on the extent to which the patient perceives and values treatment benefits. 17% of SAMSON participants had previously received ≥ 4 statins [1]. This is very unusual in real-life clinical practice [11–13]. That these individuals were still willing to participate in the trial suggests that their symptoms were not intolerable and may have responded better to patient-centered counselling than repeated drug switches [12, 13].

Finally, it is difficult to understand Section S4 in the trial presenting adverse events observed in the study (both serious and non-serious), because most of them were not related to statin-therapy [1]. Here we should strongly emphasize that there are only 3 statin-related adverse events with the confirmed causality: (1) myalgia/myopathy, (2) temporary elevation of aminotransferase alanine, and (3) new onset diabetes [9–11]. For all others it is extremely difficult to confirm the causality and in most cases it is possible to find another secondary clinical cause [9–13].

Irrespectively, the SAMSON investigators should be congratulated for their meticulous and clinically important findings which will greatly help the uptake of preventative medicine.

Conflict of interest

Peter E. Penson owns four shares in AstraZeneca PLC and has received honoraria and/or travel reimbursement for events sponsored by AKCEA, Amgen, AMRYT, Link Medical, Mylan, Napp, Sanofi; Maciej Banach – speakers bureau: Abbott/Mylan, Akcea, Amgen, Daichii Sankyo, KRKA, MSD, Novartis, Novo-Nordisk, Polpharma, Sanofi, Servier; consultant to Akcea, Amgen, Daichii Sankyo, Esperion, Freia Pharmaceuticals, MSD, Polfarmex, Resverlogix, Sanofi/Regeneron; Grants from Amgen, Mylan, Sanofi, and Valeant.

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