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EDITORIAL
Coronary artery disease

Adherence to statin therapy: it seems we know everything, yet we do nothing

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Statin discontinuation is one of the most important reasons why such a small proportion of patients reach their LDL cholesterol (LDL-C) goal.[1] In the DaVinci study, only one-third of patients achieved their LDL-C target irrespective of their level of risk. Only 18% of those at very high cardiovascular risk reached targets.[2] The situation is even worse in the Central and Eastern European countries where only 24 and 13% of patients, respectively, from the groups mentioned above achieve lipid-lowering therapy (LLT) goals.[3] The most important reasons for statin discontinuation (and non-adherence) are statin-associated adverse effects (statin intolerance, SI) as well as anti-statin movements, fake news relating to statin therapy, and a lack of patient education resulting in a fear of adverse effects. Often, the blame for statin non-adherence is attributed to patients, without considering that physician inertia (relating to both general practitioners and cardiologists) is an equally important factor.[1]

It is worth mentioning that, based on the most current data, the prevalence of SI is <7% if diagnosed based on the approved definitions and as low as ≤2% when considering complete SI.[4] A recent analysis by the CTT Collaboration suggests that SI may be observed in only 1 of 15 patients, but we need to remember that these results were obtained in randomized controlled trials, in which patients with statin-associated muscle symptoms (SAMSs) or a history of SAMS were excluded at baseline or during the washout period. Additionally, several conditions that may increase the risk of SI would have made participants ineligible to participate in the trial, according to the exclusion criteria.[5]

The new analysis accepted for publication in the *European Heart Journal Open* adds a lot to the current knowledge on discontinuation of statins and non-statin drugs and non-adherence to these therapies, based on nationwide prescription data from Norway.[6] The prevalence of hypercholesterolaemia in the European population is estimated to be as 60%.[2,3,7] Therefore, it is somewhat surprising that in this study, only 10% of patients in Norway were on LLT in 2019 (with an increase of 1.1% since 2010). These data imply that the majority of patients are not aware that they have lipid disorders or are not treated despite a diagnosis. In fact, quite similar results were obtained based on the data from the NATPOL study in Poland, which was performed in 2011. In this study, we showed that amongst subjects with hypercholesterolaemia, almost 60% were not aware of their condition; 22.0% were aware but were not receiving treatment; and only 10.9% were being treated.[8] The authors again confirmed that combination therapy with statin and ezetimibe is highly underused, with only 11% of patients treated with ezetimibe.[6] These results, in fact, reflect the current situation in Europe and worldwide.[3,5,9] To address this problem, the International Lipid Expert Panel, for the first time in April 2021, suggested that treatment should be started with upfront combination therapy of a statin and ezetimibe (preferably in a fixed-dose combination preparation) for the selected group of patients at very high and extremely high cardiovascular risk.[10] These recommendations were subsequently approved in the national guidelines and in other expert opinion papers.[7,11,12] Engebretsen *et al.*[6] also clearly show substantial underutilization of innovative drugs such as PCSK9 inhibitors (PCSK9Is), which in 2019 were used in only 0.2% of patients. Finally, despite widespread educational initiatives on the necessity of intensive statin/LLT, the study showed a decreased proportion of patients on the highest doses of potent statins—a finding that is hard to understand or explain. This may reflect the unwelcome trend observed throughout the world, whereby the increasing proportion of patients being treated with a combination therapy of statin and ezetimibe (or triple LLT with statin, ezetimibe, and PCSK9Is) is associated with a simultaneous reduction of the dose of statin and discontinuation of ezetimibe while adding PCSK9Is. Unfortunately, such an approach (whilst still a small number of patients are treated with PCSK9Is) results in only a small improvement of patients being on LDL-C goal, when as many as 95% of patients could reach their LDL-C target if treated optimally.[13]

The study presents positively surprising data with respect to adherence to statin and ezetimibe therapy, with 72.2% adherence for ezetimibe, and even 84.9% for simvastatin.[6] However, it needs to be emphasized that adherence, in this context, does not take account of the dose of drug, because dose changing was not evaluated as part of the evaluation of non-adherence.[6] Disappointingly, the adherence to

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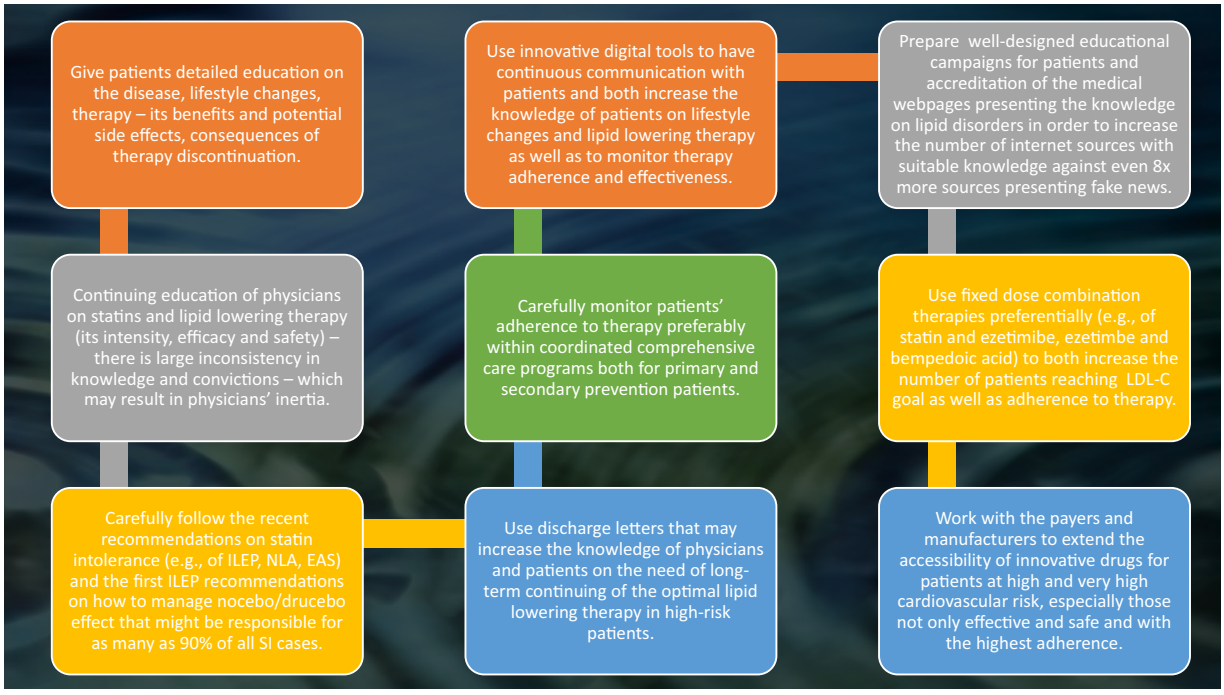

Figure 1 The summary of the different activities that might effectively improve statin adherence and avoid discontinuation.

evolocumab and alirocumab was between 72.6 and 79%.[6] The authors, however, used doses in this analysis instead of counting injections, and considering the multiple available doses for alirocumab (75 and 150 mg) and evolocumab (140 and 420 mg), this may have resulted in an underestimation of the adherence to PCSK9Is. By comparison, data from the ODYSSEY APPRISE study showed an adherence to PCSK9Is as high as 97%.[14] However, the most recent reports also suggest that non-adherence/discontinuation of PCSK9Is by as much as >20%,[15] which is hard to explain, may be due to the long-term prescription (90 days and longer); lack of patient education on the disease, treatment benefits, and risk associated with the discontinuation; lack of suitable monitoring; and consequent omission of some (auto)injections.

As it has been shown that the likelihood of statin non-adherence and SI may increase with age,[4] it is unfortunate that patients >80 years were excluded from the study, especially as the data on discontinuation in these patients are still inconsistent, and some studies suggest that elderly and very elderly patients might present better compliance and adherence in comparison with younger groups.[1,7] In fact, this study also confirmed this, as there was a significant difference in mean adherence across the age groups 0–59, 60–69, and 70+ with 77.8, 85.4, and 87.5%, respectively.[6] It is also difficult to agree with the authors' conclusion that the evidence supporting statin in the primary prevention group of patients >70–75 years of age is weak, especially in the light of large analyses published recently.[16] The exclusion of pitavastatin from the analysis was perhaps a missed opportunity, as the safety profile of this drug seems to be better than that for other statins—and this study could have been the first to evaluate its adherence and discontinuation ratio.[7] To the best of our knowledge, this study, for the first time, presents not only the discontinuation rate but also the ratio of patients with different times of discontinuation/gaps with statin therapy, suggesting that as many as 40% patients had gaps in statin treatment of 180 days or more—and almost 20% of 730 days or more. This implies that every fifth patient did not take any statin for over 2 years![6]

The study has some obvious limitations. The most important ones are associated with the lack of scope to investigate statin discontinuation and non-adherence separately in primary and secondary prevention, especially as previous studies have demonstrated differences between these groups.[1] This analysis also does not permit investigation of the most important factors that may have influenced the gaps/discontinuation and/or non-adherence, which certainly requires further investigation.

To conclude, we would like to congratulate the authors of these very important results, which again confirmed that our ineffectiveness is not only associated with a lack of suitable statin doses (mostly too low doses are used), but also results from an almost complete lack of the use of combination therapy of statin and ezetimibe, and definitely from over-restrictive criteria for the use of innovative therapies. The results highlight that, in particular, we significantly underutilize cheap and effective therapy with statins, alone or combined with ezetimibe (especially in the form of polypills). Such therapies have the potential (hypothetically assuming optimal administration) to achieve LDL-C targets in >70% of patients with atherosclerotic cardiovascular disease.[7] Therefore, we need to find ways to effectively educate our patients and to convince them to use statins/LLT. We should certainly monitor the therapy more effectively, preferably within coordinated comprehensive medical programmes, and using all the available e-tools. We should also effectively address SI and the nocebo/drucebo effect, and we must continuously educate physicians to avoid therapeutical inertia (*Figure 1*).

Conflict of interest: M.B.: speakers bureau: Amgen, Daichii Sankyo, KRKA, Polpharma, Novartis, Pfizer, Sanofi, Teva,Viatris, Zentiva; consultant to: Adamed, Amgen, Daichii Sankyo, Esperion, NewAmsterdam, Novartis, Sanofi, Viatris; Grants from Amgen,Sanofi, and Viatris; CMO at Nomi Biotech Corporations. P.E.P.: owns four shares in AstraZeneca PLC and has received honoraria and/ortravel reimbursement for events sponsored by AKCEA, Amgen, AMRYT, Link Medical, Mylan, Napp, Sanofi. No stocks,

shares, and regular paid employment by a company with a stake in the content of the manuscript.

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