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### Article

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**<https://orcid.org/0000-0001-6763-1489> (2022) Individualized therapy in statin intolerance: the key to success. European Heart Journal. ISSN 0195-668X**

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**Individualized therapy in statin intolerance: the key to success**

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endorsed by the *International Lipid Expert Panel* (ILEP)

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Statins are a widely available, cheap, safe and extremely effective means to reduce the cardiovascular disease (CVD) risk<sup>1</sup>, and it is therefore a tragedy that these life-saving medicines are under-used<sup>2</sup>. Non-adherence to statin therapy reaches up to 60% after two years, and cessation is associated with a significant increase in the risk of CVD events<sup>3</sup>. Much of this discontinuation of therapy is driven by frequent and noisy negative denouncements of statins in the lay press, and more recently in social media<sup>4</sup>. This fosters the perception that treatment with this drug class is often associated with treatment-limiting adverse effects, even when overwhelming evidence suggests that the vast majority of patients can take statins safely<sup>1,5</sup>.

In 2022, with the knowledge and lipid-lowering therapy (LLT) possibilities we have, a patient-centred approach is particularly important, especially in patients with statin intolerance (SI). In this context, we must always have at the forefront of our mind the central tenet of low-density cholesterol (LDL-C), that *'lower is better for longer'*<sup>6</sup> and our aim should be to achieve treatment targets. However, we should not forget that *'any (dose/drug) is better than none'*, and whichever (evidence-based) lipid-lowering drugs (statins or non-statins) our patients are willing to take, and any reduction in LDL-C they achieve, will afford them some benefit in reducing the risk of CVD.

We can consider four different scenarios when a patient presents with adverse effects that they perceive to be due to statin therapy, each requiring a different approach: (1) The adverse effect may be entirely unrelated to statin therapy. This can occur when a physical skeletal muscle injury is misattributed as having resulted from treatment. Alternatively, the adverse effect may have no discernible organic cause, and may have resulted entirely from the expectation that it would occur (the nocebo/drucebo effect<sup>7</sup>). (2) The adverse effect may have a reversible secondary cause, such as a comorbidity, or a drug-drug interaction. (3) The patient may experience adverse effects only with particular statins, or at high doses (partial statin intolerance). (4) In about 9% of the time, a patient may not be able to tolerate any statin at any

dose (complete statin intolerance). In this scenario we need also to include patients that are not willing to take statins (regardless of the side effects), which is recently also an increasing healthcare problem (even every 15-20<sup>th</sup> patient) (**Figure 1**).

Recent recommendations from the International Lipid Expert Panel (ILEP)<sup>8</sup> provide a firm basis for the patient centric approach to these situations. It is essential to listen to the patients' concern and to take a detailed history, to determine the appropriate diagnosis and course of action, and exclude very rare but serious adverse events. The use of tools, such as the MEDS approach (Minimise disruption to LLT, Education and counselling, Diet, lifestyle and nutraceuticals and Symptoms and biomarkers) may be helpful<sup>8</sup> in addition to validated tools such as the statin associated muscle symptoms clinical index (SAMS-CI)<sup>9</sup> patients. Reversible causes of statin intolerance should be addressed (e.g., by optimal treating comorbidities or resolving drug-drug interactions). Re-introducing lipid-lowering therapies when patients have experienced adverse event clearly requires a sensitive and patient-centric discussion, however, the SLAP algorithm (Switch statins, Lower dose, Alternate day therapy, and Polypharmacy/combotherapy with non-statin therapy)<sup>8</sup> summarises available options, which may help.

In the case of confirmed SI, use of non-statin drugs will be necessary to achieve therapeutic targets. In the case of partial intolerance, statins may be used at lower doses, in combination with other drugs (preferably as fixed dose combination [FDC]). In complete SI monotherapy or combination therapy with alternative drugs is indicated. The selection of treatment regimen can be made on an individualised basis (also based on the drug availability<sup>10</sup>), considering the patient's predicted risk of CVD and their measured circulating concentrations of LDL-C (and in the consequence the expected reduction of baseline LDL-C)<sup>3,8,10</sup>. The availability of very large datasets from observational studies and clinical trials of LLTs enables the maximum reduction of LDL-C by any given treatment regimen to be predicted with reasonably accuracy.

This enables the treatment regimen to be matched to the patients' needs at the outset, potentially commencing therapy with more than one drug, rather than starting the patient on a single drug, which could not conceivably enable them to reach treatment targets.

In partial statin intolerance, a 50-60% reduction of LDL-C can be achieved by using the combination of 10 mg daily dose of ezetimibe and atorvastatin 10-20 mg (achieving the same expected reduction in LDL-C as 80 mg atorvastatin, but with a smaller likelihood of adverse effects). Adding bempedoic acid 180 mg/day to the regimen would be expected to result in a total of 60-80% reduction, which would be necessary for a patient at very high risk of CVD<sup>2</sup>. In patients who cannot tolerate any statin non-statin regimens will be required. Fixed-dose combination therapy with bempedoic acid 180 mg and ezetimibe 10 mg/day can achieve a 40% LDL-C reduction. The PCSK9 inhibitors (alirocumab and evolocumab), and the anti-PCSK9 siRNA, inclisiran are the most effective drugs in LDL-C (50-60% reduction), although these drugs are expensive and may not be available in all jurisdictions. Consideration at the outset of the patients baseline risk, LDL-C and willingness to take (and in some cases pay for) LLTs increases the likelihood of a successful therapeutic regimen at the outset of therapy. The guidance on the individual statin intolerance approach is presented on **Figure 2**.

Clearly, patient participation in decision making with the continuous education is critical to therapeutic success (=overcome the placebo effect, increase of therapy adherence). The ILEP have suggested the use of a Personalised Lipid Intervention Plan (PLIP)<sup>8</sup>. This includes lifestyle advice and records the individual's current 10-year risk of CVD with and without statin therapy and provides an explanation of the likelihood of adverse effects. Clear details of the individual's lipid-lowering regimen are included alongside their personal LDL-C target. This provides a useful summary of care, potentially preventing therapeutic inertia and improving long-term compliance.

In summary, individualised and patient-centric care is essential in the effective management of statin intolerance to enable the patient to initiate a therapy which they are willing to take, and which will allow them to reach (as far as possible) risk-reduction targets for CVD. This requires careful history taking, and careful selection from the ever-widening range of evidence-based lipid-lowering therapies to meet the patients' needs. If we are successful, we may have most of the SI patients on LDL-C target.

### **Declarations of Interest**

*MB*: speakers bureau: Amgen, Daichii Sankyo, KRKA, Polpharma, Novartis, Pfizer, Sanofi, Teva, Viartis, Zentiva; consultant to: Adamed, Amgen, Daichii Sankyo, Esperion, NewAmsterdam, Novartis, Sanofi, Viartis; Grants from Amgen, Sanofi, and Viartis; CMO at Nomi Biotech Corporations; *CPC* (2020-2022): Research Grants from: Amgen, Better Therapeutics, Boehringer-Ingelheim (BI), Bristol-Myers Squibb (BMS), Daiichi Sankyo, Janssen, Merck, Novo Nordisk, Pfizer; Consulting fees from Aegerion/Amryt, Alnylam, Amarin, Amgen, Applied Therapeutics, Ascendia, BI, BMS, Eli Lilly, Janssen, Lexicon, Merck, Pfizer, Rhoshan, Sanofi; he serves on Data and Safety Monitoring Boards for the Veteran's Administration, Applied Therapeutics and NovoNordisk; *PEP*: 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. No stocks, shares, and regular paid employment by a company with a stake in the content of the manuscript.

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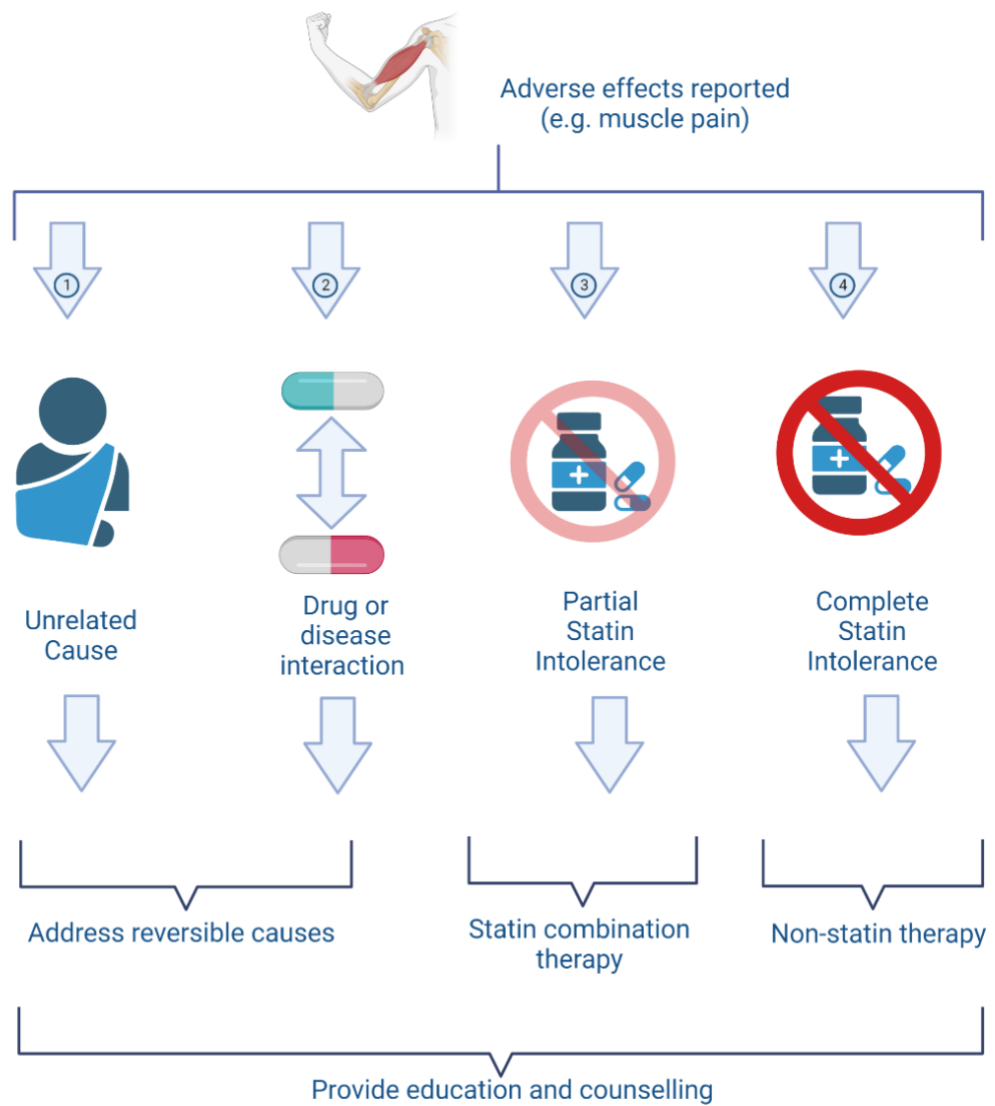
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**Figure 1:** Individual approach to the management of statin intolerance. Produced using Biorender.com.



**Figure 2.** The guidance on how to effectively diagnose and treat statin intolerance. *STEP 1:* The guidance on how to keep even 98% of the patients on statin therapy (assuming only about 2% of patients with complete statin intolerance) and effectively achieve LDL-C goals. *STEP 2:* The individual guidance on how to achieve LDL-C goal in even 95% of statin intolerant patients based on the baseline CVD risk and LDL-C level. \*Based on the available data the risk of SAMS with pitavastatin is similar to placebo [3]; #with low-to moderate intensity statin therapy; \$ moderate intensity statin therapy for partial SI patients; \*\*preferably with ezetimibe. *Abbreviations:* EZE – ezetimibe, BA- bempedoic acid; for the definitions of other abbreviations, see the main text. PLIP, MEDS and SLAP algorithms are available here: <https://onlinelibrary.wiley.com/doi/10.1002/jcsm.12960>