Prevalence of statin intolerance: What is the current understanding?

Responses to audience questions were specially prepared for you by Prof. Maciej Banach and Prof. Christopher Cannon

Question: Prof. Banach how can you define the term "complete" SI in the Bytyci et al 2022 manuscript?

Answer: *Complete SI in the clinical practice as well as in the paper was defined as the lack of possibility of using any statin dose, having tried at least two, with the 2nd one used at the lowest available dose.*

Question: Prof. Banach could you be so kind to comment on the relationship between depression and statin intolerance, particularly for younger patients?

Answer: *There is no confirmed link between depression and SI. The association we observed in our meta-analysis on the protective role of depression against SI (12.2% reduced risk of SI in patients with depression) is now an issue of the independent analysis with the psychiatrists, however I would not be making far-reaching conclusions yet. The most important is to remember that all patients at the CVD risk should be effectively treated with statins, independently on concomitant diseases.*

Question: Could statins decrease high calcium?

Answer: *Statin therapy increases of dense calcium volume (SMD: +0.229, 95%CI: +0.008, +0.450; p=0.043) (see our analysis: BMC Med. 2015 Sep 18;13:229. doi: 10.1186/s12916-015-0459-4) and based on our recent data there is a small but significant negative interaction between CAC score and statin use for the prediction of CHD (p-value = 0.036) and CVD mortality (p-value = 0.025) (see: Atherosclerosis. 2021 Jan; 316:79-83. doi: 10.1016/j.atherosclerosis.2020.10.009.). However, the impact of statins on coronary artery calcium (CAC) predictive value is unclear and required further investigations.*

Question: Could statins decrease high calcium scoring of the coronary arteries and thereby prevent bypass surgery?

Answer*: See the response above. Statin therapy in patients after ACS, especially in those with MVCVD (defines now as those at the extremely high CVD risk: Eur Heart J. 2022 May 14;43(19):1784-1786. doi: 10.1093/eurheartj/ehab771) very effectively prevents recurrent CVD events (especially in the high intensive doses, and especially using the upfront double or triple LLT, and in the consequence the necessity for CABG. In very high-risk patients, I would not definitely look at CAC Score, and on the effective LLT according to the rules: the lower the better for longer and the earlier (on LDL-C target) the better.*

Imaging studies like the recent HUYGENS trial (Please refer to: https://ascvd-lipidology.knowledgehub.wiley.com/videos/; Peer to Peer Discussion: Novel Lipid-lowering therapies, Prof. Christopher Cannon and Prof. Kausik Ray) have found that the target of lipid lowering is the lipid core of the plaque – to decrease its size. It is replaced by fibrotic cells and sometimes more calcium. So, plaques can potentially have an increase in the calcium content as they remodel, but this is a good thing – that they become more stable and less prone to rupture.

Question: Tolerability of statin among patients with CKD

Answer: *CKD patients are a great challenge for cardiologists. Due to the metabolism of statins – both dual renal/hepatic plasma clearance (besides atorvastatin which only has hepatic plasma clearance), CKD patients are on the higher risk of statin intolerance (based on our meta-analysis it is 25.2% higher SI risk), therefore while optimizing renal function, we may decrease the risk of SI in this patient's group.*

Despite challenges, the benefit of statins and of all lipid lowering therapies is similar proportionally, but then actually greater in absolute terms because patients with CKD are higher risk.

Question: Is pitavastatin related AE predictable/dose dependent?

Answer: *Based on the data from the REAL-CAD study there was a significant increase of SAMS in patients treated with pitavastatin 1 vs 4 mg, but still the prevalence (0.7 vs 1.9%, respectively) was comparable to placebo.*

Question: What is an expected level of intolerance before you cease statin?

Answer: *It should be always individually assessed, that is why, after exclusion of nocebo/drucebo effect, we always ask about the tolerability of pain, measure CK, ALT, etc. We should try our best to avoid statin discontinuation. That is why we prefer even using*

one small dose of statin per week vs complete discontinuation. All the issues on the individual approach and all steps how to proceed with the SI patient you may find in the current ILEP 2022 recommendations on nocebo/drucebo effect and statin intolerance: https://onlinelibrary.wiley.com/doi/full/10.1002/jcsm.12960

Question: Epidemiology of 1) pitavastatin; 2) rosuvastatin and gene interaction and Adverse events- which one goes well with sacubitril/valsartan? pitavastatin/eze combo or rosuvastatin/eze combo? Is there benefit of ezetimibe alone?

Answer: *Briefly: (1) prevalence of SI after pitavastatin is usually about 2% (for SAMS) and about 4-4.5% for NOD; (2) it as rare as for the other statins (<0.05%); (3) no confirmed risk of drug-to-drug interactions between ARNI and statins, (4) great tolerability for both, the difference only with the maximal LDL-C reduction – for rosuva/eze it is even 65%, for pitava/exe it is usually 55%; (5) obviously for SI patients, eze should be administered immediately (see recommendations above) to ensure 15-20% LDL-C reduction, now however preferably with fixed combinations with bempedoic acid (even 40% reduction) or PCSK9 targeted approach therapy (>60% reduction).*