

25.11.16

This is a follow-up comment on the draft of the ezetimibe review, which I have just seen, further to my initial 15 points submitted 1 year ago on 05.11.15 (attached).

1. Personally I would recommend ezetimibe remaining 2<sup>nd</sup> line because of enormous amount of statin data c/f ezetimibe and informing most international guidelines. Whilst the evidence (from GWAS and clinical outcome studies) for blocking the NPC1L receptor is very powerful, statins clearly remain the 1<sup>st</sup> line therapy.
2. Perceived statin intolerance is far more common than alluded to in the report.
  - a. Firstly, the overwhelming “meme” from patient-initiated internet searches overwhelms the careful explanation of professionals. Clinicians like myself find this a major day-to-day issue.
  - b. Randomised clinical trial patients are highly selected and most have not prospectively collected specific data on myalgia – therefore not really relevant. Eg. HPS (Lancet 2002) with 4 weeks run-in placebo followed by 4-6 weeks run-in active simvastatin 40mg before randomisation.
  - c. The rates of
  - d. The STOMP study (Parker BA, Circulation 2013) of statin-naïve patients used a very tight definition of statin myalgia (within 2 weeks of starting, resolving within 2 weeks of stopping, and returning within 4 weeks of rechallenge). In spite of using this tight definition, 10% of patients had “definite” myalgia on atorvastatin 80mg (about double the rate of placebo).
  - e. Muscle symptoms (pain, stiffness or weakness) were found in 16% of patients in JUPITER (albeit the same in both rosuvastatin and PBO groups).
  - f. Only a minority of those with myalgia have elevated muscle enzymes. Although the proportion with elevated CK is small – perhaps only 5% of those who have been previously “demonstrated” to be statin intolerant (Odyssey Alternative Trial) - muscle symptoms remain high (about 25% in these patients who have previously experienced muscle side-effects).
  - g. Statin intolerance has many aspects that range from demonstrable skeletal muscle pathology to typical myalgia to atypical symptoms to primarily psychosocial issues. However, the clinical outcome for the patient – progressive atherosclerotic CV disease – will be the same for whatever reason the statin is not taken.
  - h. Thus it is the “perception” of the patient that is clinically important – and the determinant of patient adherence to therapy, not any specific “diagnostic” definition of muscle intolerance.
  - i. **Realistically the rates of statin myalgia are generally at least 10% (as in STOMP 2013) and closer to 20% when less tight definitions of intolerance are used (as is the case in usual clinical practice), the perception of the patient being the actual “truth” in this setting – because it is the patient perception that determines the adherence to therapy.**
3. I would favour leaving the general statement unchanged – and continuing to educate the profession as to the importance of lower LDL levels - although it could be good to facilitate the easier prescription of ezetimibe eg. coming off authority – but still remaining 2<sup>nd</sup> line.

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