

Response to: 'The association between osteoporosis and statins therapy' by Lai

We read with interest the correspondence of Lai.¹ Whether statin therapy impacts the risk of osteoporosis is still a matter of debate. We have recently shown that there is a dose-dependent relationship between statins and diagnosis of osteoporosis; while low-dose statin treatment was related to an underrepresentation of diagnosed osteoporosis when compared with non-statin-treated patients, we found in patients on higher dosages of statins an overrepresentation of diagnosed osteoporosis in the general Austrian population.² Although osteoporosis is often underdiagnosed until incident fractures, our data are based on diagnoses derived from in-patient treatment. Even though there are data available suggesting that some statins could have protective effects on osteoporosis,³ in the JUPITER trial, an international, randomised, double-blind and placebo-controlled study in which 17 802 patients were investigated, it has been shown that high-potency statin treatment did not reduce the risk of fractures.⁴ The fact that statin treatment might not only have positive effects on bone health has also been demonstrated in a Women's Health Initiative Observational Study in which 93 716 postmenopausal women with simvastatin and atorvastatin treatment showed an HR of 1.42 (0.79–2.57) for hip fracture and did not show improved bone mineral density (BMD) when compared with controls. Interestingly, in this study, statins of higher potency were related to a higher risk of hip fracture when compared with statins with lower potency such as pravastatin, fluvastatin and lovastatin.⁵ A study by Lin *et al* also showed not only positive effects on new-onset osteoporotic fractures, but also demonstrated a trend for a higher risk under lovastatin treatment.³ A comparison of our results to previous findings is problematic due to other studies not considering the detailed different dosages of the respective statins.³ It is indeed a well-known statistical phenomenon that a trend that appears in different groups of data (eg, groups of statins) may disappear or even reverse after combining the groups, the so-called Simpson's paradox.⁶ A recently published study by Cheng *et al* investigating 7464 patients with newly diagnosed hip fractures showed that a statin treatment with a dosage higher than 15 mg (OR: 0.71, CI 0.61 to 0.82), as well as lower than 15 mg (OR: 0.75, CI 0.65 to 0.88) was related to a lower risk of hip fractures in comparison to non-statin-treated patients, but they did not investigate the different kinds of statins and their exact dosages in detail.⁷ Despite limited comparability to the study by Cheng *et al*, we, for instance, also found an underrepresentation for doses of up to 20 mg of fluvastatin in our recently published study. In addition, dosages of >10–20 mg of the most potent statin, rosuvastatin, also showed a tendency towards an underrepresentation of osteoporosis; however, these results were not statistically significant in our study.² We do not agree with the argument of Lai *et al* that when the treatment goal of blood lipids is achieved, the dose of statins can be decreased. Guidelines do not recommend reducing statin dosage when the treatment goal is achieved; on the contrary, the current credo is 'the lower the better' for low density lipoprotein (LDL) cholesterol mirrored in recently published European Society of Cardiology/European Atherosclerosis Society guidelines on the management of dyslipidemias recommending lowering LDL cholesterol levels <55 mg/dL in high-risk patients.⁸ This goal is very difficult to achieve with a reduction in the statin dose. The cardiovascular advantage of low LDL cholesterol

levels in patients of high cardiovascular risk is also evidenced by recent studies on PCSK9 inhibitors which even achieve lower cholesterol levels but without impact on sex hormones.⁹

However, especially the discrepancies in the currently existing data regarding the relationship between statins and osteoporosis and the sparse data about the different kinds of statins and their exact dosages was one of the major reasons for the present study to investigate this relevant topic in more detail. Thus, one has to keep in mind that cholesterol is the basic substance for vital hormones such as estrogens, testosterone, cortisol or aldosterone and several studies have shown that, for example, statins can lower the levels of sex hormones.^{10–14} These vital hormones are closely related to several diseases. Hence, especially the relationship between high-dosage statin treatment and the different potencies and potentially related diseases such as osteoporosis or cancer should be investigated in prospective clinical studies and randomised controlled trials.

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