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Letter to the Editor

Reply to Jae Heon Kim and Benjamin I. Chung's Letter to the Editor re: Teemu J. Murtola, Heimo Syvälä, Teemu Tolonen, et al. Atorvastatin Versus Placebo for Prostate Cancer Before Radical Prostatectomy—A Randomized, Double-blind, Placebo-controlled Clinical Trial. Eur Urol 2018;74:697–701

We thank Drs. Kim and Chung for their insightful comments on the role of testosterone as a possible mechanism mediating the effect of statins in prostate cancer in response to our article [1]. We agree that androgen metabolism probably has an important role, as cholesterol is the common precursor for synthesis of all steroid hormones. The role of statins in androgen metabolism is supported by recent in vitro observations demonstrating that simvastatin enhanced the effects of the androgen signaling inhibitor enzalutamide against prostate cancer cell growth [2]. The additive effects of statins and androgen-targeted therapy are also supported by recent epidemiological evidence of better relapse-free survival among statin users starting androgen deprivation therapy (ADT) for hormone-sensitive prostate cancer [3,4] and among men using enzalutamide or abiraterone for castration-resistant disease [5] as compared to men not using statins.

Our randomized trial demonstrated that short-term high-dose intervention with atorvastatin did not significantly affect the prostate cancer proliferation marker Ki-67 overall compared to placebo over a median exposure time of 27 d, but proliferation decreased in correlation with the atorvastatin exposure duration, with a significant difference observed after minimum exposure of 28 d [1]. The study recruited men scheduled for radical prostatectomy as the primary treatment, and none of the participants were on ADT. Thus, the study demonstrates that atorvastatin also affects the prostate without androgen deprivation.

Nevertheless, the notions put forward by Drs. Kim and Chung together with the above-mentioned recent studies suggest that the greatest clinical benefits of statins among men with prostate cancer could be in combination with ADT. In accordance with this scenario, several epidemiological studies have reported better prostate cancer-specific survival among men using statins [6]. ADT is almost invariably used before prostate cancer death. In epidemiological studies the survival benefit associated with statin use appears to be most often observed for men treated with ADT or radiation therapy, which is frequently combined with ADT [6,7].

Therefore, a crucial question for future studies to address is to clarify the effects of statins on androgen signaling in the prostate in both the castration-sensitive and castration-resistant phases. The clinically relevant question will be whether it is possible to extend the effects of ADT and androgen-targeted therapy such as androgen signaling inhibitors by combining them with statins. Given the adverse association between ADT and cardiovascular morbidity [8] this would be likely to lead to improvements in overall survival and, as suggested by recent studies, possibly to better disease-specific survival.

Conflicts of interest: Teemu J. Murtola reports grants from the Finnish Cancer Society, the Finnish Cultural Foundation, and the Expert Responsibility Area of Tampere University Hospital during the conduct of the study; personal fees from Astellas and Janssen; and other fees from Astellas and Bayer, outside the scope of the submitted work. Jarno Riikonen reports nonfinancial support from Astellas and Ferring, and personal fees from Astellas, Ferring, Bayer, Myovant, and Pfizer outside the scope of the submitted work. Heimo Syvälä has nothing to disclose.

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