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Reply to: “Misinterpretation of Comparative Safety of Testosterone Dosage Forms”

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Letter

We appreciate the point of view expressed by Dr. Schooling and agree that given widespread use of testosterone products, a thorough investigation of its cardiovascular safety is crucial. Understanding whether testosterone treatment (in any form) contributes to an increased risk of cardiovascular events, stroke, and death is of great interest to multiple stakeholders, including patients, physicians, and regulators. The letter author is correct to point out that our recently-published study did not attempt to answer that question. Assessing the safety of testosterone relative to non-use is methodologically challenging in a non-experimental study, but is a line of research that is being actively pursued by our group and others.

In our current study, we sought to compare the cardiovascular safety of different testosterone dosage forms, not testosterone as a class versus no testosterone treatment. While Dr. Schooling's primary criticism appears to be with others' interpretation of our study, we disagree that our results are difficult to interpret. “Which testosterone form should I use?” is a different question than “should I use testosterone?”, but they are both important questions. Recent regulatory action in the US¹ has more narrowly-defined the indications for testosterone use, limiting the number of potential users: however, determining the safest treatment option in those men where testosterone use is deemed appropriate is critical. Across multiple data sources and populations, we observed a consistently increased cardiovascular risk associated with injection versus topical formulations, even after accounting for differences in patient characteristics. Although this association may be subject to some residual confounding by unobserved patient characteristics, our study clearly raises concerns about the safety of injection testosterone relative to other dosage forms, and it motivates further research on both the risk and benefits of different testosterone therapy modalities in older men. We did not see a difference in venous thromboembolism occurrence between dosage forms, but this would not contradict previously-established evidence that testosterone as a class increases venous thromboembolism risk—only that we did not detect risks which vary substantially by dosage form.

Recent trial data² have suggested that testosterone treatment does not alter atherosclerosis progression, while other trial data³ and non-randomized studies^{4,5} have reported an

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increased risk of cardiovascular events in older men and those at higher cardiovascular risk taking testosterone. Amid continued uncertainty, these safety signals need to be evaluated, and continued investigation of testosterone should examine multiple aspects of testosterone use, clearly differentiating between endogenous testosterone levels and exogenous testosterone supplementation, to fully understand the complex relationship between testosterone and cardiovascular risk.

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