Making Sense of the Statin–Prostate Cancer Relationship: Is It Time for a Randomized Controlled Trial?

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The relationship between statin medications and prostate cancer (PCa) has received considerable attention over the past 15 yr. It is not because of the blockbuster prospective randomized trial data supporting their use. In fact, the sum of evidence, mostly retrospective in nature, is generally conflicting. Why then the fascination? Is it the fact that statin use is so prevalent? Chances are that you or a very close friend or family member take a statin. Is it the allure of the possibility of a cheap, safe, commonly used medication that could slow or prevent the risk of PCa death? Or is it simply intuitive that a steroid hormone–dependent cancer that becomes addicted to cholesterol-mediated signaling pathways is susceptible to cholesterol-lowering medication?

The fact remains, in the face of the conflicting evidence, the story supporting statin use continues to build. The scientific understanding also continues to shed light on the potential patients and scenarios in which statins may be most efficacious.

In this month’s issue of European Urology Focus, Murtola and colleagues performed a secondary analysis of a population-based randomized controlled trial (RCT) of prostate-specific antigen screening nested within the Finnish population registries [1]. Among the 80 000 men randomized to screening versus usual care, 6537 PCa cases were identified. Murtola et al used the Finnish national prescription database to capture statin use before and after PCa diagnosis. They observed that statin use before PCa diagnosis was not significantly associated with a reduced risk of PCa-specific death (hazard ratio [HR]: 0.92; 95% confidence interval [CI], 0.75 – 1.12), whereas statin use after diagnosis was associated with 20% risk reduction (HR: 0.80; 95% CI, 0.65 – 0.98).

The common criticism of any nonrandomized study of statin use versus nonuse is that statin users are different than nonusers. This truth is inescapable. Statin users differ significantly in measurable ways. One glance at any “Table 1,” including the one in this study [1], bears this out. Multivariable and propensity methods attempt to adjust for these measurable differences, but the unknown immeasurable differences threaten the validity of results due to residual confounding. What strengthens this study is that even after controlling for the measurable differences between users and nonusers, a significant dose-, duration-, and intensity-dependent effect was seen. More statin use meant less likelihood of dying from PCa. The exquisite ability to capture drug dispensing through a national prescription database is a clear strength of this study.

At first glance, there are some confusing elements to this study’s findings [1]. The most obvious is the subgroup analysis showing that only statins appeared to be associated with benefit in patients undergoing primary androgen deprivation therapy (ADT). While a small subset of PCa patients in North America [2], this group represented >40% of the cohort in this study (as shown in Table 1 and Supplementary Table 1 by Murtola et al [1]); however, a rationale exists to believe that statins may have synergy with ADT. In a secondary analysis of a randomized trial of intermittent versus continuous ADT, we observed that statin use was associated with improved overall and PCa-specific survival [3]. Harshman et al observed an identical association among men starting ADT for biochemical
recurrence or de novo metastases: Statin use significantly prolonged time to progression [4]. Their in vitro correlative studies uncovered a potential mechanism for this synergy. Statins compete with the transporter SLCO2B1 for dehydroepiandrosterone, a precursor to dihydrotestosterone. In the setting of ADT, the limited extracelullar androgen availability may be unable to overcome this competition, whereas in hormone-naive conditions, the plentiful androgens minimize the significance of the transporter competition.

Moreover, with evidence of intracellular androgen synthesis in castrate PCa, combined with the recent data suggesting serum cholesterol levels correlate with intratumoral androgen levels [5], it is conceivable that statins lower intraprostatic androgen levels by lowering intraprostatic cholesterol levels. This effect would be most pronounced during ADT, when extratumoral androgen concentrations are lowest.

It is possible that the conflicting evidence for statin use and PCa risk and outcomes is due to the heterogeneity of study scenarios, patients, drugs, and durations. Before launching an RCT, it would be prudent to sort out (1) the scenario or clinical state in which statins are most effective; (2) the germline genetic signature most susceptible to statin antineoplastic efficacy; (3) the tumor somatic signature that is vulnerable to statin inhibition; and (4) the correct drug, dose, and duration.

We are gaining evidence toward these goals. The current study by Murtnola et al [1] adds to data from meta-analyses suggesting that statins may be most efficacious in advanced settings and perhaps in combination with ADT [6,7]. Several studies have identified germline genetic signatures that predict lipid, cardioprotective, and adverse effect responses to statins [8]; although not reported in PCa, a germline genetic signature has been identified (but not validated) as predicting the statin chemopreventive efficacy in colorectal cancer [9]. Similarly, looking at tumor gene expression profiling—although no signature has been identified in PCa—a 10-gene messenger RNA panel reliably predicted statin vulnerability in breast cancer cell lines [10]. This too has yet to be validated or studied in vivo, but the concept should be pursued. Finally, not all statins are created equal; they differ in cholesterol-lowering ability and propensity to cross cell membranes. This could affect their antineoplastic properties and clearly needs further study [11].

Perhaps asking statins to work effectively as cancer monotherapy is asking too much of a drug class designed to lower cholesterol. Evidence is emerging that combining statins with metformin [12], nonsteroidal anti-inflammatory drugs [13], or other drugs that block steroid feedback loops could enhance statin efficacy [14]. More work is needed to identify which combinations may be best to push forward to trial.

In summary, evidence continues to build in support of statins’ chemopreventive properties, and this work by Murtnola and colleagues [1] adds to that mounting evidence. Before launching a clinical trial, we need to learn more about the right clinical state or scenario to study, the mechanisms to identify a germline or somatic signature predicting statin susceptibility, and the drug and dose that is best. Until that time, I fear trial evidence will mirror the observational studies—conflicting.

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References


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