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hypertensive drugs, such as calcium-channel blockers.<sup>1</sup>

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Since publication of their article, the authors report no further potential conflict of interest.

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## Dutasteride and Prostate Cancer

**TO THE EDITOR:** In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, Andriole et al. (April 1 issue)<sup>1</sup> found that there was a reduction in low-grade prostate cancer among high-risk men after dutasteride treatment — similar to the results with finasteride therapy among low-risk men in the Prostate Cancer Prevention Trial.<sup>2</sup> However, there was a slightly increased risk of high-grade tumors in the dutasteride group at the end of the study. The authors speculate that this was caused by the more frequent early detection of low-grade tumors in the placebo group. Some of these might have progressed to higher grades if left untreated. But if so, wouldn't this counterbalance the beneficial lower rate of biopsies for cause in the dutasteride group?

The end-of-study cumulative risk of prostate cancer among participants in the placebo group in both studies was extremely high (24 to 25%). With the use of data from the Surveillance, Epidemiology and End Results (SEER) program, one can calculate that participants in the Prostate Cancer Prevention Trial would have had a 7-year cumulative risk of only 6% if they had not participated in the trial. Participants in the REDUCE trial would have had a 4-year cumulative risk of 8 to 10% in the absence of protocol-driven biopsies, on the basis of data from the European Randomized Study of Screening for Prostate Cancer (Current Controlled Trials number, ISRCTN49127736).<sup>3</sup> Thus, the protocol-directed interim and end-of-study biopsies make it impossible to directly translate the results to public health or clinical practice.

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No potential conflict of interest relevant to this letter was reported.

1. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010; 362:1192-202.

2. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:215-24.

3. Schröder FH, van den Bergh RCN, Wolters T, et al. Eleven-year outcome of patients with prostate cancers diagnosed during screening after initial negative sextant biopsies. *Eur Urol* 2010; 57:256-66.

**TO THE EDITOR:** The long-expected results of the REDUCE trial show that among men 50 to 75 years of age who have prostate-specific antigen (PSA) levels of 2.5 to 10.0 ng per milliliter and who have previously undergone biopsies, the 5 $\alpha$ -reductase inhibitor dutasteride significantly reduces the rate of positive biopsies by 23%. The 24.9% rate of positive biopsy results among men who underwent at least two biopsies is consistent with the expressed purpose of the organizers to study a population that had a relatively high risk of prostate cancer. Protocol-mandated biopsies were carried out at year 2 and year 4 during the study. This procedure is in line with clinical practice.

Unfortunately, the authors do not address the possibility of avoiding at least some of the 82.8% of negative biopsies. Although the difference in positive biopsies must be considered a very preliminary end point, the possibility that the use of dutasteride avoids unnecessary biopsies must be explored. It has great relevance in a clinical environment, in which the overdiagnosis and overtreatment of prostate cancer are considered to be a major health care problem.

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**TO THE EDITOR:** In the editorial accompanying the article by Andriole et al., Walsh<sup>1</sup> convincingly disproves the conclusion of the REDUCE study, stating that dutasteride does not prevent prostate cancer but merely shrinks tumors. According to Walsh, this holds true for finasteride as well. However, this view cannot provide a post hoc justification for the use of placebo instead of finasteride as a control in the trial of dutasteride therapy. The REDUCE trial was based on the alleged evidence that made finasteride the current standard of treatment — that is, the reported 25% reduction in the risk of prostate cancer<sup>2</sup> — and aimed at showing that dutasteride did as well and possibly better by avoiding the 27% increase with finasteride in less well differentiated tumors that are more likely to be lethal. These expectations were possibly fueled by the fact that, unlike finasteride, dutasteride inhibits both type 1 and type 2 5 $\alpha$ -reductase.

How could all this have been proved without a comparison with finasteride? This comparison would have addressed the best interest of patients and national health services but might also have threatened the commercial prospects of dutasteride, which its manufacturer hopes will replace the older but cheaper generic finasteride.

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No potential conflict of interest relevant to this letter was reported.

1. Walsh PC. Chemoprevention of prostate cancer. *N Engl J Med* 2010;362:1237-8.
2. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:215-24.

**TO THE EDITOR:** Walsh dismisses the value of a reduction in moderately well-differentiated prostate tumors (tumors with a Gleason score of 5 or 6) in the REDUCE trial, suggesting that “many of the tumors were likely to have been clinically insignificant.” A diagnosis of cancer, even indolent cancer, is important for the patient. Cancers acquire major clinical significance if they drive radical intervention. And in the United States, 92% of patients who have prostate cancer with a

favorable risk receive radical intervention with its attendant complications and effects on quality of life.<sup>1</sup> Even patients who elect the approach of active surveillance acquire the “survivor” label and must deal with the psychological effects of a cancer diagnosis, repeated biopsies, and anxiety about the natural history of their cancer.<sup>2,3</sup>

Modeling of data from the Prostate Cancer Prevention Trial has suggested that the rate of both high-grade and low-grade cancers is reduced by treatment with a 5 $\alpha$ -reductase inhibitor.<sup>4</sup> Whether one accepts this or not, the REDUCE study showed that dutasteride therapy, when used as a prevention strategy, will reduce overdiagnosis and hence overtreatment. This is of real value to patients.

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No potential conflict of interest relevant to this letter was reported.

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2. Burnet KL, Parker C, Dearnaley D, Brewin CR, Watson M. Does active surveillance for men with localized prostate cancer carry psychological morbidity? *BJU Int* 2007;100:540-3.
3. Fang F, Keating NL, Mucci LA, et al. Immediate risk of suicide and cardiovascular death after a prostate cancer diagnosis: cohort study in the United States. *J Natl Cancer Inst* 2010;102:307-14.
4. Redman MW, Tangen CM, Goodman PJ, Lucia MS, Coltman CA Jr, Thompson IM. Finasteride does not increase the risk of high-grade prostate cancer: a bias-adjusted modeling approach. *Cancer Prev Res (Phila Pa)* 2008;1:174-81.

**THE AUTHORS REPLY:** We agree with Kiemeny and Bosland that the results of the REDUCE trial cannot be directly translated to a clinical situation in which biopsies are performed only “for cause” and that the near elimination of high-grade tumors in the placebo group during years 3 and 4 may have been due to the fact that protocol-mandated biopsies were performed during years 1 and 2. Dutasteride may have inhibited the growth of low-grade and some high-grade tumors during years 1 and 2; hence, more remained to be detected during years 3 and 4. The rates of prostate cancer in the placebo group exceeded general estimates, as expected, since a population that was at increased risk for prostate cancer (on the basis of PSA levels) was selected for evaluation.

Schröder and Roobol ask whether dutasteride can help avoid biopsies among men who do not

have prostate cancer. A large proportion of the negative biopsies in the REDUCE trial were protocol-mandated biopsies; in clinical practice, dutasteride should result in the need for fewer biopsies because it suppresses PSA production from benign tissue (and indolent prostate cancers), as seen in two previous studies.<sup>1,2</sup> Data from the REDUCE trial showed that although rising PSA levels were a poor predictor of overall cancer and of high-grade cancer in the placebo group (perhaps since many placebo-treated men had rising PSA levels as a result of benign prostatic hyperplasia), rising PSA levels were a strong predictor of tumors with Gleason scores of 7 to 10 in the dutasteride group. The effect of dutasteride on the usefulness of PSA level for the diagnosis of prostate cancer would be the subject of a separate article.

Garattini and Bertele' question why placebo (rather than finasteride) was chosen for comparison with dutasteride and whether the data from the REDUCE trial can help determine whether inhibition of both isoforms of 5 $\alpha$ -reductase by dutasteride is superior to the inhibition of only one isoform by finasteride (as studied in the Prostate Cancer Prevention Trial). Finasteride was not used in the REDUCE trial for three main reasons: finasteride is not an approved therapy for reducing the risk of prostate cancer, the REDUCE trial was initiated before the results of the Prostate Cancer Prevention Trial were reported, and the reduction in the risk of prostate cancer with finasteride has never been tested in the population studied in the REDUCE trial (men with elevated PSA levels). Increased type 1 5 $\alpha$ -reductase in prostate tumors, especially in high-grade tumors, provides a biologically based rationale for the use of a dual inhibitor of 5 $\alpha$ -reductase to achieve a reduction in the risk of prostate cancer<sup>3</sup>; however, the REDUCE trial was not designed to test this hypothesis directly. In a prespecified analysis of data from the REDUCE trial in which baseline predictors of prostate cancer and post-baseline prostate volume at the time of biopsy were incorporated into the model (see the Supplementary Appendix, available with the full text of the article at NEJM.org), the odds ratio for prostate cancer, detected on biopsy, with dutasteride as compared with placebo was 0.60 for all tumors (95% confidence interval [CI], 0.52 to 0.68; P<0.001) and 0.62 for tumors with Gleason scores of 7 to 10 (95% CI, 0.49 to 0.79; P=0.001).

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Since publication of their article, the authors report no further potential conflict of interest.

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2. Roehrborn CG, Tubaro A, Barkin J, et al. Effect of dutasteride on the detection of prostate cancer in men with benign prostatic hyperplasia in the Combination of Avodart and Tamsulosin (CombAT) trial. Presented at the 2010 Genitourinary Cancers Symposium, San Francisco, March 5-7, 2010.
3. Thomas LN, Douglas RC, Lazier CB, et al. Levels of 5 $\alpha$ -reductase type 1 and type 2 are increased in localized high grade compared to low grade prostate cancer. *J Urol* 2008;179:147-51.

**THE EDITORIALIST REPLIES:** Garattini and Bertele' argue that a direct comparison is necessary to determine whether dutasteride is equivalent to finasteride. I believe that such a study is unlikely to show any difference, because inhibition of the type 1 5 $\alpha$ -reductase isoform does not appear to provide significant additional benefit. The relative reduction in the risk of a positive biopsy with either agent is 23 to 25%, and among men who underwent random biopsies without a cause, there was neither a decrease nor an increase in the risk of prostate tumors with Gleason scores of 7 to 10.

Klotz misunderstands the clinical implications of the study. All the participants underwent random biopsies. However, dutasteride reduced the risk of cancer only in men who would never have known that they had cancer and who would not have received treatment because in a clinical setting they would never have undergone a biopsy. These were men with one or two previous negative biopsies who had been screened for more than 2 to 4 years and had no clinical indication for a biopsy. In contrast, among men with an indication for a biopsy (abnormal digital rectal examination or PSA level corrected for the effect of the drug), treatment with dutasteride failed to decrease the risk of cancer. Because treatment with dutasteride produces a marked reduction in PSA levels, men may be lulled into a false sense of security. They will interpret this reduction as they understand the effect of statins in lowering cholesterol ("My PSA is down by 50%; now I don't have to worry about prostate cancer") without

understanding that the decrease in PSA level is only the result of shrinkage of benign prostatic tissue. For this reason, dutasteride may delay the diagnosis of prostate cancer until a patient has high-grade disease that may be difficult to cure. As was concluded in another publication, “in clinical practice taking dutasteride would probably decrease the number of prostate biopsies and subsequent radiation treatments and prostatectomies, but it might also increase the number of deaths from the disease.”<sup>1</sup> Rather than advising

the use of a drug that could be dangerous and costs \$1,500 per year, if Dr. Klotz wishes to reduce the overdiagnosis and overtreatment of prostate cancer, why not simply discourage PSA testing?

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Since publication of his article, the author reports no further potential conflict of interest.

1. Dutasteride (Avodart) for prevention of prostate cancer. *Med Lett Drugs Ther* 2010;52:29.

## Ultrasound-Guided Internal Jugular Vein Cannulation

**TO THE EDITOR:** We wish that Ortega et al. (April 22 issue)<sup>1</sup> had demonstrated the use of the needle-guide technique in their video of internal jugular vein cannulation. As noted in the video, it can be difficult to determine the location of the tip of the needle, which may be either in front of or behind the narrow cross-sectional plane of the ultrasound image. With the use of a needle guide, the operator can direct the needle tip such that it intersects the middle of the image on the screen at the depth prescribed by the guide. This technique has been shown to be superior to the free-hand technique in successfully cannulating the internal jugular vein.<sup>2</sup>

We believe that the use of ultrasonography without a needle guide may give the operator a false sense of security, especially if the person doing the procedure lacks experience. Although imaging alone may help to identify the target vein, a needle guide allows for direct, real-time visualization of vessel puncture.

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No potential conflict of interest relevant to this letter was reported.

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2. Augoustides JG, Horak J, Ochroch AE, et al. A randomized controlled clinical trial of real-time needle-guided ultrasound for internal jugular venous cannulation in a large university anesthesia department. *J Cardiothorac Vasc Anesth* 2005;19:310-5.

**TO THE EDITOR:** In their video, Ortega et al. failed to mention the use of the micropuncture tech-

nique for additional safety. A micropuncture needle is a very small, 22-gauge needle that can enter the jugular vein with little discomfort to the patient. Accidental puncture of the carotid artery with this small needle generally does not lead to major bleeding. The micropuncture technique is particularly helpful in children, in patients taking an anticoagulant, and in situations requiring immediate access. Unintentional penetration of the posterior wall of the internal jugular vein during placement of a central catheter occurs frequently, despite the use of ultrasound guidance.<sup>1</sup> Use of the micropuncture needle can help to prevent the creation of a large posterior hole in the vein, thus reducing the likelihood of bleeding. In the cardiac catheterization laboratory at our institution, my colleagues and I recently switched to the exclusive use of the micropuncture technique to obtain any vascular access. We believe that use of this technique should become the standard of care in clinical practice.

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No potential conflict of interest relevant to this letter was reported.

1. Blaivas M, Adhikari S. An unseen danger: frequency of posterior vessel wall penetration by needles during attempts to place internal jugular vein central catheters using ultrasound guidance. *Crit Care Med* 2009;37:2345-9.

**THE AUTHORS REPLY:** Despite the 18-minute duration of our video, the multitude of techniques and approaches that can be used for internal jugular vein cannulation made it necessary for us to carefully decide which points to include and