Unlike other areas of medicine, such as cardiology and diabetology, urology has often been slow to embrace strategies for risk reduction. Currently, urologists prefer to treat the disease at the stage they encounter it, rather than approaching the problem with a preventative frame of mind. However, a recent publication evaluating the effect of dutasteride on prostate cancer\(^1\) calls this view into question. The current lifetime risk of prostate cancer in the USA is estimated at 16.7 per cent.\(^2\) As the disease is both extremely common and generally slow to progress, potentially it provides a prime target for chemoprevention.\(^3\)

The first chemopreventative strategy to be evaluated in a randomised controlled trial was the combination of selenium and vitamin E in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) study. Notable results of SELECT after a median follow-up of 5.5 years can be summarised as follows:\(^4\)

- Hazard ratios and 99 per cent confidence intervals (CI) for developing prostate cancer were 1.04 for selenium (CI 0.87–1.24), 1.13 for vitamin E (0.95–1.35) and 1.05 for the combination of selenium and vitamin E (0.88–1.25) when compared with placebo.
- There were no significant differences in other pre-specified cancer endpoints.
- There was a statistically non-significant increase in risk of prostate cancer for vitamin E.
- There was a statistically non-significant increase in risk of type 2 diabetes for selenium.

These data provide compelling evidence that neither vitamin E nor selenium are capable of significantly reducing a man’s risk of prostate cancer. Indeed, the slight increase in risk of prostate cancer with vitamin E is of concern. The mild increase in risk of diabetes with selenium has been previously reported, and adds to growing concerns regarding the safety of dietary supplements in the absence of large-scale trials that prove efficacy and safety.\(^5\)

Another landmark study of chemoprevention of prostate cancer is the Prostate Cancer Prevention Trial (PCPT).\(^6\) In the PCPT, an endpoint (prostate cancer diagnosis or end-of-study biopsy) was available in 59.6 per cent of the finasteride group and 63 per cent of the placebo group. Of the 9060 men who constituted the final analysis, prostate cancer was confirmed in 803/4368 (18.4 per cent) of the finasteride group and in 1147/4692 (24.4 per cent) of the placebo group. The relative risk reduction was 24.8 per cent (\(p<0.001\)). When subjects were stratified by age, race/ethnicity, family history and entry prostate-specific antigen (PSA) level, prostate cancer was reduced with finasteride by a similar degree in all groups. Rates of acceptance of biopsy recommendations differed slightly between study groups. Biopsy recommendation was given to 2122/9423 (22.5 per cent) in the finasteride group and to 2348/9457 (24.8 per cent) of the placebo group. However, there was no significant difference in the rates of acceptance of biopsy in the two groups. About half of biopsies were prompted by abnormal digital rectal examination (DRE) and half by PSA level. The mean PSA level at biopsy was approximately 2.5ng/ml in both arms (using an adjusted PSA value in the finasteride group). Study drug discontinuation at any time during the study for reasons other than death or prostate cancer was 36.8 per cent in the finasteride arm and 28.9 per cent in the placebo arm. Participants who temporarily discontinued the drug were allowed to restart the study medication later and, regardless of whether or not they were taking the study drug, were still eligible for the end-of-study biopsy. The annual rate of prostate cancer diagnosis was 0.5 per cent.

Thompson et al.\(^7\) found that finasteride significantly enhanced the ability of PSA level to detect both prostate cancer and high-grade prostate cancer.

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drug discontinuation dropped from 10 per cent and 6.3 per cent (respectively for finasteride/placebo) in the first year to 3.6 per cent and 3.4 per cent in the fifth year. Side-effects were the primary reason for temporary discontinuation, which occurred in 18.3 per cent in the finasteride group and 9.8 per cent of the placebo group.

A secondary objective of the study was measuring Gleason score. In spite of a 24.8 per cent reduction in risk of cancer overall, there was a small increased risk, both absolute and relative, of high-grade disease. Gleason 7–10 tumours constituted 280/757 graded tumours (37 per cent) in the finasteride group as opposed to 237/1068 in the placebo group (22.2 per cent). This excess of 43 cancers could be seen to be primarily caused by the excess Gleason 7–10 tumours in the for-cause biopsies (excess of 40) compared with end-of-study biopsies (excess of three). The cause for this has been the subject of much debate, but it is now widely accepted that the 5-reductase inhibitor (5ARI) finasteride affected the PSA detection rate of prostate cancer. Studying 5112 and 4579 men in the placebo and finasteride groups, respectively, all of whom had a prostate biopsy and associated PSA level, Thompson et al.7 found that finasteride significantly enhanced the ability of PSA level to detect both prostate cancer and high-grade prostate cancer.

Over the course of the four-year study period [of the REDUCE trial], dutasteride reduced the risk of incident prostate cancer detected on biopsy and improved the outcomes related to BPH

Redman et al.8 performed a comprehensive analysis, taking into account those factors that affected cancer detection in the two groups of the study, including the lower biopsy rate in the finasteride group as well as the group of factors related to cancer detection. Examining only biopsy itself, the bias-adjusted rates of prostate cancer in the groups were 21.1 per cent (4.2 per cent high grade) in placebo versus 14.7 per cent (4.8 per cent high grade) in the finasteride group, a highly significant 30 per cent reduction of risk of cancer and a statistically non-significant 14 per cent increase in high-grade disease. When the grade change between biopsy and prostatectomy (understanding that ‘true’ Gleason grade is best determined at radical prostatectomy when the entire prostate is available for analysis rather than the biopsy that is affected by sampling error) was incorporated, the analysis found that the true rates of high-grade disease in the groups were 8.2 per cent in the placebo and 6.0 per cent in the finasteride group, a 27 per cent risk reduction (p=0.02). Pinsky et al.9 from the National Cancer Institute, using a different analysis methodology and conducting an independent analysis, arrived at a similar conclusion that the rate of true high-grade disease may have been lower in the finasteride group compared with the placebo group.

The REDuction by DUtasteride of prostate Cancer Events (REDUCE) trial is a multicentre, international study; subjects were randomised to receive either the dual 5ARI dutasteride or placebo for a study period of four years. Eligibility criteria include PSA level between 2.5 and 10 ng/ml and a previous negative prostate biopsy within six months of randomisation. Biopsies were performed after two and four years of follow-up. Because of the advantage of REDUCE over the PCPT (with its ‘for-cause’ prostate biopsies performed frequently for PSA levels that can be affected differentially by 5ARIs), there were few additional PSA level-prompted biopsies beyond those dictated by the protocol. The results have recently been reported by Andriole et al.1 Among 6729 men who underwent a biopsy or prostate surgery, cancer was detected in 659 of the 3305 men in the dutasteride group, as compared with 858 of the 3424 men in the placebo group, representing a relative risk reduction with dutasteride of 22.8 per cent (95 per cent CI 15.2–29.8) over the four-year study period (p<0.001).

Overall, in the first year through to the fourth year, among the 6706 men who underwent a needle biopsy, there were 220 (6.7 per cent) tumours with a Gleason score of 7–10 among 3299 men in the dutasteride group and 233 among 3407 men in the placebo group (6.8 per cent) (p=0.81). Dutasteride therapy, as compared with placebo, resulted in a reduction in the rate of acute urinary retention (1.6 per cent versus 6.7 per cent, a 77.3 per cent relative reduction). The incidence of adverse events was similar to that in studies of dutasteride therapy for benign prostatic hyperplasia (BPH), except that in this study, as compared with previous studies, the relative incidence of the composite category of cardiac failure was higher in the dutasteride group than in the placebo group (0.7 per cent [30 men] versus 0.4 per cent [16 men], p=0.03). It was concluded that over the course of the four-year study period, dutasteride reduced the risk of incident prostate cancer detected on biopsy and improved the outcomes related to BPH.

In a recent editorial, Dr Patrick Walsh10 reviewed these results, arguing that reduction of cancer diagnosed based on a biopsy driven by PSA level rises or alteration of the consistency of the prostate on palpation was more clinically relevant than a reduction in cancer detected by protocol-driven biopsy. Although he makes a relevant point, it is difficult to conceive how one could design a convincing trial to assess the impact of 5ARIs on the risk of developing
biopsy-detectable prostate cancer without using a protocol-driven biopsy regimen. Because this class of drug is well documented as having a significant impact on the sensitivity and specificity of both PSA level and DRE in prostate cancer diagnosis, any trial relying on PSA level or DRE-triggered biopsies would fail to distinguish between the impact of these drugs on the risk of developing prostate cancer versus their impact on the likelihood of detecting a tumour. Dr Walsh also questions the relevance of the reduction in incidence of lower Gleason score cancers, which possess a much lower tendency to progress or result in death compared with higher score cancers. However, from a clinical viewpoint, Gleason pattern 6 cancers are the most problematic, as it is often difficult to decide whether active treatment or active surveillance is the best treatment strategy, and patients are often perturbed by this uncertainty. In addition, it may be the case that, if left undetected, some of the Gleason 6 tumours identified in the study would have progressed to represent clinically significant disease. He also argued that the deployment of a 5ARI in a chemopreventative setting carries the potential risk of delaying the diagnosis of more poorly differentiated cancers. However, this is at variance with publications,\textsuperscript{11,12} which suggests that both finasteride and dutasteride in fact improve the sensitivity and specificity of PSA level and DRE in the detection of prostate cancer. Moreover, all other endpoints of prostate cancer risk, namely the incidence of prostate intraepithelial neoplasia, atypical small acinar proliferation and tumour volume, were all improved in the 5ARI arm compared with placebo.

It is relevant in this context to compare the design of the PCPT study and the REDUCE trial. The key differences lie in the patient selection; men recruited in the REDUCE study were potentially at higher risk of developing prostate cancer and arguably a more clinically relevant group to evaluate.

The follow-up protocol was also considerably more rigorous in the REDUCE study with >70 per cent of patients in both the active treatment and placebo completing the biopsy protocol, which adds credibility to the results.

In conclusion, the USA Food and Drug Administration and European regulatory authorities will doubtless come to their own conclusions about the safety and efficacy of dutasteride as a chemopreventative agent in prostate cancer, and will do so in view of a more complete analysis of the data than is possible simply from a review of the publication in the New England Journal of Medicine,\textsuperscript{1} which is inevitably a summary of a very large volume of material. In the interim, urologists seem certain to face questions from their patients about the advisability of the use of these agents in a chemopreventative setting. Recent developments in molecular genetics are beginning to allow us to identify a subgroup of patients with an especially high risk of developing prostate cancer.\textsuperscript{13} These highly susceptible men and their families are precisely those who might be expected to benefit from effective chemoprevention for this disease. In the interim, clinicians must decide for themselves which patients are most likely to benefit from these medications.

Declaration of interests
John M. Fitzpatrick was a member of the REDUCE study group.

REFERENCES