The Prostate Cancer Prevention Trial and Its Implications for Clinical Practice: A European Consensus

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1. Introduction

The landmark Prostate Cancer Prevention Trial (PCPT) is the largest completed and published study conducted in the urologic community and reported for the first time that medical intervention reduced the incidence of diagnosed prostate cancer to a clinically meaningful extent. Although the data clearly demonstrate a reduction in the incidence of prostate cancer in men treated with finasteride, controversy surrounds the incidence of tumours of Gleason grades 7–10 in the active treatment group. New data have been generated that aim to clarify this issue and the focus should now be on how information from the PCPT should be translated into clinical practice and shared with patients.

To this end, a European consensus meeting endorsed by the European Association of Urology was held in Paris, France on 19 December 2005. The invited group of experts included 10 panelists plus 41 participants from 13 European countries. The objective of the meeting was to produce a consensus
statement based on the most up-to-date and robust data set and analyses from the PCPT with a view to providing clear recommendations on its clinical implications. At the meeting, clinical findings in key areas were presented by the panelists. Each presentation was followed by audience discussion and, ultimately, the generation of consensus statements on each area. This paper presents the consensus statements plus brief summaries of the background to the topics discussed.

2. PCPT update

2.1. Background

An overview of findings from the PCPT (Akduman and Crawford [1]) was presented and formed the basis of discussion. In summary, finasteride significantly reduced the 7-yr period-prevalence of prostate cancer by 24.8% compared with men receiving placebo ($p < 0.001$) [2]. There was, however, an increased prevalence of tumours of Gleason scores 7–10 in the finasteride arm compared with placebo (6.4% vs. 5.1%; $p < 0.001$). The increase in high-grade tumours has been investigated and found to be explained, at least in part, by the effects of finasteride on prostate gland size [3]. Median prostate volume was 24% lower in patients with high-grade tumours in the finasteride arm compared with placebo, that is, 25.5 versus 33.6 ml. This reduction in size meant that a relatively larger proportion of the prostate was biopsied and evaluated histologically, increasing the chances of detecting tumours of Gleason grades 7–10 in the finasteride arm. More recently, receiver operating characteristic (ROC) analyses have been conducted on the biomarker prostate-specific antigen (PSA). Area under the curve (AUC) values for placebo and finasteride-tested patients indicated that PSA performed better in terms of overall detection of prostate cancer, including high-grade cancers [4] in finasteride-treated patients than those receiving placebo.

2.2. Consensus statement

The following consensus statement on the PCPT was prepared:

1. To date, the PCPT is the largest study ever reported in the urologic community and reported for the first time that medical intervention may reduce the prevalence of prostate cancer to a clinically meaningful extent (level 1b evidence). This study was funded by the United States government through the National Cancer Institute (NCI) and administered by the Southwest Oncology Group (SWOG) at 221 centres across the United States.

2. The results showed that finasteride reduced the risk of developing prostate cancer by 25% compared with placebo (24.4% placebo vs. 18.4% finasteride).

3. However, the finasteride-treated group had a higher prevalence of tumours with Gleason grades 7–10 (6.4%) compared with the placebo group (5.1%).

4. Subsequent analyses have concluded that this increased prevalence was probably due to a detection bias caused largely by the reduction in prostate volume in patients taking finasteride compared with patients receiving placebo. This improved detection of high-grade cancer at biopsy in the finasteride group is further enhanced by an improved performance of PSA in the finasteride arm relative to placebo.

3. Prostate cancer prevention

3.1. Background

Prostate cancer is a leading cause of cancer death, with high rates of incidence, prevalence, and death documented in North European countries, such as Germany, France, and the United Kingdom (Table 1)

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
<th>Age-standardised rate (per 100,000)</th>
<th>Deaths</th>
<th>Age-standardised rate (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Union</td>
<td>144,504</td>
<td>67.55</td>
<td>56,035</td>
<td>25.55</td>
</tr>
<tr>
<td>Denmark</td>
<td>1,627</td>
<td>53.89</td>
<td>1,009</td>
<td>32.11</td>
</tr>
<tr>
<td>France</td>
<td>28,135</td>
<td>87.10</td>
<td>9,239</td>
<td>27.08</td>
</tr>
<tr>
<td>Germany</td>
<td>30,911</td>
<td>77.21</td>
<td>11,417</td>
<td>26.65</td>
</tr>
<tr>
<td>Italy</td>
<td>19,258</td>
<td>52.78</td>
<td>7,109</td>
<td>19.12</td>
</tr>
<tr>
<td>Spain</td>
<td>10,659</td>
<td>45.33</td>
<td>5,742</td>
<td>23.76</td>
</tr>
<tr>
<td>Sweden</td>
<td>6,610</td>
<td>114.95</td>
<td>2,480</td>
<td>37.71</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>21,056</td>
<td>60.97</td>
<td>9,470</td>
<td>26.41</td>
</tr>
</tbody>
</table>
This high prevalence points to the magnitude of the human cost of the disease and the potential benefit of a successful preventive strategy. Dietary modification as a means of preventing prostate cancer has been explored for some considerable time and a wealth of literature on the subject is available [6]. More defined strategies might target three possible stages in prostate cancer development: initiation, promotion, and progression. The impact of the reduction in incidence of prostate cancer using finasteride has been explored in a hypothetical model based on the findings from the PCPT [7]. The authors assumed that a 24.8% reduction in the incidence of prostate cancer for 5 yr among US men aged ≥55 yr would lead to an estimated saving of 316,760 person-years due to finasteride. Even allowing for an absolute increase of 6.9% in the proportion of men with high-grade tumours (corresponding to the difference between the rates on the placebo and finasteride arms of the PCPT), the number of person-years saved would only be reduced to 262,567. The authors of the report estimate that for each absolute increase of 5% in the proportion of patients with high-grade tumours, the number of person-years saved would be reduced by approximately 39,000. They concluded that the results of the PCPT would have a major impact on population mortality from prostate cancer if they were applied clinically. The potentially detrimental effects of an increased rate of patients with prostate cancer with high-grade Gleason scores would be outweighed by a reduction in overall incidence.

Risk factors for the development of prostate cancer have been well documented [8,9]. A sub-analysis of the PCPT showed that the relative risk of developing prostate cancer in men treated with finasteride was reduced in all subgroups analysed, including age, race or ethnic group, family history, and baseline PSA level (Table 2) [2]. In terms of the cost of prostate cancer prevention using finasteride, it has been estimated that 6 life-years would be gained per 1000 men treated at a cost of $1,660,000 per life-year gained [10]. It was also estimated that it would cost $200,000 to gain one additional quality-adjusted life-year (QALY). The authors of the report concluded that to achieve an incremental cost below $100,000 per QALY gained, the cost of finasteride would have to be reduced by 50% from its current average wholesale price.

One open question regarding prostate cancer prevention is whether such prevention decreases prostate cancer mortality. A reduction in the development of symptomatic disease or prostate cancer mortality needs to be demonstrated in clinical trials. Incidence-based statistical models, although useful, are not sufficient in this setting.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Finasteride (n = 4368)</th>
<th>Placebo (n = 4692)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–59</td>
<td>15</td>
<td>21</td>
<td>0.72</td>
</tr>
<tr>
<td>60–64</td>
<td>18</td>
<td>24</td>
<td>0.73</td>
</tr>
<tr>
<td>≥65</td>
<td>22</td>
<td>28</td>
<td>0.80</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>18</td>
<td>24</td>
<td>0.75</td>
</tr>
<tr>
<td>African American</td>
<td>27</td>
<td>34</td>
<td>0.79</td>
</tr>
<tr>
<td>Hispanic</td>
<td>16</td>
<td>20</td>
<td>0.80</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>16</td>
<td>0.60</td>
</tr>
<tr>
<td>Prostate cancer in first-degree relative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25</td>
<td>30</td>
<td>0.81</td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>23</td>
<td>0.74</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1.0</td>
<td>11</td>
<td>16</td>
<td>0.66</td>
</tr>
<tr>
<td>1.1–2.0</td>
<td>21</td>
<td>28</td>
<td>0.77</td>
</tr>
<tr>
<td>2.1–3.0</td>
<td>32</td>
<td>39</td>
<td>0.81</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen.

3.2. Consensus statement

The following consensus statement on prostate cancer prevention was prepared:

1. Prostate cancer is one of the leading causes of cancer death in Europe.
2. The PCPT showed that finasteride significantly reduces the prevalence of histologically proven prostate cancer.
3. For men who are concerned about prostate cancer (e.g., familial disease, abnormal PSA, increased PSA velocity/doubling time), it may be appropriate to discuss chemoprevention with finasteride.
4. In so doing, it is important to highlight both the benefits and potential side-effects associated with long-term treatment.
5. Further data on health economic analyses are required before recommending widespread chemoprevention with finasteride.

4. BPH management

4.1. Background

The efficacy of 5α-reductase inhibitors has been established in a number of randomised controlled clinical trials and studies also show that these agents are most effective in men with enlarged prostates (>30–40 ml) [11,12]. Two 5α-reductase
inhibitors are currently marketed: finasteride, which inhibits type 2 5α-reductase, and dutasteride, which inhibits type 1 and type 2 5α-reductase. Type 2 is the predominant isoenzyme found in the prostate. Although dutasteride can reduce serum dihydrotestosterone (DHT) levels to a greater degree than finasteride (95% vs. 71%) [13], this effect has not been shown to translate into superior intraprostatic DHT reduction [14,15] or, more importantly, additional clinical benefit; both therapies produce similar improvements in symptoms, flow rates, and prostate volume reduction [11,12]. The Medical Therapy of Prostatic Symptoms (MTOPS) Study has gone further to demonstrate that the combination of a 5α-reductase inhibitor plus an α1-blocker provides greater benefits than either agent as monotherapy [16] (also see Marberger [17]). Recent analyses of the MTOPS Study indicate that patients with prostates ≥25 ml may benefit from combination therapy, whereas those with a baseline prostate volume ≥31 ml are at significantly greater risk of progression. Combination therapy for this latter patient group represents optimal therapy for benign prostatic hyperplasia (BPH).

The PCPT also demonstrated the positive effects of finasteride in regard to genitourinary symptoms (Fig. 1), with a significantly (p < 0.01) lower incidence of BPH, prostatitis, urinary tract infection for urgency/frequency, urinary retention, and transurethral resection of the prostate procedures compared with patients receiving placebo [2]. These, along with the additional benefit of the reduced risk of developing prostate cancer, have to be balanced against an increase in typical 5α-reductase inhibitor side-effects, such as reduced ejaculate volume, decreased libido, and erectile dysfunction, which were as expected in this study. A risk-benefit analysis on data from the PCPT has been conducted and shows areas where finasteride provides a benefit over placebo (Table 3) [18].

The use of finasteride to treat men with BPH does not preclude the use of PSA in detecting prostate cancer. Studies have shown that finasteride decreases PSA by approximately 50% during the first 12 mo of use [19] and a similar reduction was seen in the PCPT over the same time period. Recent analysis of the ROC of PSA in the PCPT shows that PSA performs better in detecting all grades of cancer, as well as high-grade cancers in men treated with finasteride compared with placebo.

4.2. Consensus statement

The following consensus statement on BPH management was prepared:

1. Randomised, placebo-controlled trials have demonstrated the benefit of 5α-reductase inhibitors over placebo in men with clinically enlarged prostates above 30–40 ml secondary to BPH (level 1 grade A).
2. The efficacy of combination therapy with 5α-reductase inhibitors and α1-adrenoceptor antagonists is greater than either agent alone (level 1 grade B).
3. The clinical utility of this combination therapy should consider the balance between efficacy and additional side-effects (level 1 grade B).
4. If one assumes a class effect:
   • All combinations of an α1-adrenoceptor antagonists and a 5α-reductase inhibitor would be equally effective.
   • The combination of doxazosin and finasteride is the best tested regarding safety and efficacy.
5. The evidence currently available from the PCPT provides additional support for the use of

<table>
<thead>
<tr>
<th>Table 3 – Risks and benefits of finasteride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit/risk</td>
</tr>
<tr>
<td>Prostate cancer diagnosis</td>
</tr>
<tr>
<td>Genitourinary symptoms and complications</td>
</tr>
<tr>
<td>Sexual dysfunction or endocrine symptoms</td>
</tr>
<tr>
<td>High-grade cancer diagnosis</td>
</tr>
</tbody>
</table>

Reproduced with permission from [18].
finasteride in the management of men with LUTSs/BPH.

6. Based on current knowledge, a conversion factor of 2 for PSA is accurate for patients taking finasteride. Further analysis of the PCPT data would suggest that finasteride therapy may enhance detection of high-grade disease.

7. It is recommended that prostate management guidelines [20] be updated to include the results from both the PCPT and the MTOPS Study.

5. Communicating with patients

5.1. Background

In addition to some very good sites, a brief search on the Internet using any of the common search engines will bring up much spurious information on the subject of prostate cancer. Some of this “disinformation” is simply misleading, but other sites contain dangerously incorrect data [21]. Patients using the Internet to search for information on BPH and prostate cancer have the difficult task of distinguishing fact from fiction. Doctors can assist in communicating factual information on prostate cancer to their patients. Compliance with medication is another important issue that needs to be addressed by doctors with their patients. Urologists could potentially use the fact that finasteride has been shown to significantly reduce the incidence of prostate cancer as an added benefit to improve compliance among men taking finasteride for BPH. Uptake of health care provisions by men is another area that should be addressed. A household survey conducted in the United Kingdom in 1998–1999 indicates that men were less likely than women to consult their general practitioner about a medical problem [22]. This statistic appears to be borne out by data from the World Health Organization European “Health for All” database. Across a survey of 17 European countries in 2003, the incidence of melanoma in women was found to be higher than in men, yet more men die of the disease [23]. Clearly, patients, and in particular men, need to be better educated and provided with better literature on health issues to overcome these problems.

The urologist plays a key role in disseminating accurate information on the benefits of finasteride in not only BPH but also prostate cancer including providing reassurance over the high-grade tumour findings from the PCPT. They should understand the information, set the standard for counselling patients, and take charge of what has been learned from the PCPT. Urologists are well placed to be important sources of information for general practitioners and patients alike and in so doing have the potential to make a difference in the health of millions of men worldwide.

5.2. Consensus statement

The following consensus statement on communicating with patients on the findings of the PCPT was prepared:

1. Implications for patient information
   - Physicians should be aware of the findings from the PCPT.
   - This will allow physicians to appropriately counsel their patients about the potential benefits and side-effects of treatment with finasteride.
   - Patients entering a programme of chemoprevention should be closely followed up and monitored to ensure that they do not develop malignant prostate disease that is unrecognised.

2. Implications for education of medical community
   - This information needs to be discussed in the urologic and general health care community to allow a balanced opinion to be provided to patients.
   - Urologists are encouraged to disseminate these recommendations among other health care professionals, including general practitioners, who often play a significant role in the management of BPH/LUTSs.

6. Conclusions

The PCPT and MTOPS Study have provided information that should change the way urologists manage prostate disease. Clearly, the chemopreventive benefits of finasteride demonstrated in the PCPT provides additional support for the use of finasteride in the management of patients with BPH. The MTOPS Study established that combination therapy is indicated for patients most at risk of clinical progression, that is, with a baseline prostate volume >30 ml. There are other important implications of this new line of management both in terms of the potential for chemoprevention of prostate cancer and the need to ensure that the new paradigms are accessible to and followed by physicians in primary care. Management guidelines on prostate disease should be updated to reflect the findings from the PCPT and the MTOPS Study, so assisting physicians to adopt and embrace new management practices.
Appendix A. Consensus meeting panelists & participants

Panelists

Professor Pierre Teillac, France
Professor Per-Anders Abrahamsson, Sweden
Professor Clément-Claude Abbou, France
Professor Christopher Chapple, United Kingdom
Mr Adrian Joyce, United Kingdom
Professor Jean-Louis Misset, France
Professor Jørgen Nordling, Denmark
Dr Eduardo Solsona, Spain
Professor Andrea Tubaro, Italy
Professor Manfred Wirth, Germany

Panelists from left to right: Jørgen Nordling, Manfred Wirth, Pierre Teillac, Per-Anders Abrahamsson, David Crawford (key note speaker on the PCPT data), Christopher Chapple, Adrian Joyce, Clément-Claude Abbou, Jean-Louis Misset, Andrea Tubaro, Eduardo Solsona.

Participants

Professor Michael Marberger, Austria
Professor Stephan Madersbacher, Austria
Dr Wolfgang Loidl, Austria
Professor Fred Saad, Canada
Dr Laurence Klotz, Canada
Professor Ognjen Kraus, Croatia
Professor Benoît Feuillu, France
Professor Jean-Jacques Rambeaud, France
Professor Klaus Höfner, Germany
Professor Ulf Tunn, Germany
Dr Richard Berges, Germany
Professor Bernd Schmitz-Dräger, Germany
Mr Thanos Anastasios, Greece
Mr Gerasimos Alivizatos, Greece
Dr Tommaso Prayer-Galetti, Italy
Professor Roberto Mario Scarpa, Italy
Professor Domenico Prezioso, Italy
Professor Alessandro Sciarra, Italy
Dr Giario Conti, Italy
Professor Theo M. de Reijke, Netherlands
Dr Carlos Rabaca, Portugal
Dr Fernando Manuel Pinto Faria, Portugal
Dr Kutaiba El-Metwally, Saudi Arabia
Professor Bojan Trsinar, Slovenia
References


