Impact of 5α-Reductase Inhibitors and Alpha-Blockers on Prostate Cancer Incidence and Mortality

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5-ARIs may be used to prevent progression of LUTS secondary to BPH and to reduce the risk of urinary retention and future prostate-related surgery.
Impact of 5ARIs on Prostate Cancer: Evidence from BPH Clinical Trials

- 40% relative risk reduction of PC diagnosis in the CombAT RCT [1]

- Similar findings in other BPH RCTs
  - 34% risk reduction in a meta-analysis [2]

1. Roehrborn et al. 2011
2. Monga et al. 2013
Evidence from Prostate Cancer Prevention Trials

- Landmark RCTs examining 5α-reductase inhibitors (5ARIs), finasteride among healthy [PCPT, 1,2] and dutasteride among high-risk men [REDUCE, 3,4]

- 25% lower incidence of diagnosed PC among men randomized to 5ARIs

- Risk reduction substantiated by 2010 systematic review [5]
  1. Thompson et al. 2003
  2. Thompson et al. 2013
  3. Andriole et al. 2010
  4. Grubb et al. 2013
  5. Wilt et al. 2010
The Grade Issue

An increase in rate of diagnosis of Gleason 8-10

Both an absolute and a relative increase

- **PCPT:** 280 vs. 237, i.e., 43 more cases on finasteride out of 4368 men biopsied, an increase of 1%

- **REDUCE:** 29 vs. 19 cases, i.e., 10 more cases on dutasteride out of 6706 biopsies, an increase of 0.3%.
  - On re-analysis of the REDUCE cases using the modified Gleason criteria, Gleason 8-10 cancers increased from 0.5 to 1.0%, an absolute increase of 0.5%
Critical issue for urologists managing BPH

• 5 ARIs are used successfully in the management of BPH
  – The grade issue is a dilemma

WHAT DO WE TELL OUR BPH PATIENTS?
Is it a Sampling artifact? Does Evidence from Epidemiological Studies support increased PC mortality?

- A clear lack of association in relation to PC mortality for 5ARI therapy is relatively consistent [1-5] in epidemiological studies.
- But many limitations to such conclusions.

1. Thompson et al. 2013
2. Preston et al. 2014
3. Azoulay et al. 2015
5. Murtola et 2016
Acknowledgement

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## Risk of Prostate Cancer Outcomes among 5α-Reductase Inhibitor 5ARI (n=4,571) Users, α-Blocker Users (n=7,764), and Non-Users (n=11,677) with BPH

<table>
<thead>
<tr>
<th></th>
<th>No. of Events</th>
<th>Age-Adjusted HR (95% CI)</th>
<th>P value</th>
<th>Fully-Adjusted HR (95% CI)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5ARI Users vs. Non-users</strong></td>
<td></td>
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</tr>
<tr>
<td>Total prostate cancer</td>
<td>1551</td>
<td>0.60 (0.52-0.68)</td>
<td>&lt;0.0001</td>
<td>0.61 (0.53-0.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metastatic prostate cancer</td>
<td>199</td>
<td>1.13 (0.79-1.62)</td>
<td>0.50</td>
<td>1.12 (0.78-1.61)</td>
<td>0.54</td>
</tr>
<tr>
<td>Gleason score 8-10 cancer</td>
<td>298</td>
<td>1.51 (1.14-2.00)</td>
<td>0.005</td>
<td>1.37 (1.03-1.82)</td>
<td>0.03</td>
</tr>
<tr>
<td>Prostate cancer mortality</td>
<td>310</td>
<td>1.13 (0.83-1.53)</td>
<td>0.44</td>
<td>1.11 (0.82-1.50)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>5ARI Users vs. AB Users</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Total prostate cancer</td>
<td>1146</td>
<td>0.56 (0.49-0.65)</td>
<td>&lt;0.0001</td>
<td>0.63 (0.54-0.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metastatic prostate cancer</td>
<td>150</td>
<td>1.09 (0.76-1.57)</td>
<td>0.63</td>
<td>0.89 (0.61-1.30)</td>
<td>0.54</td>
</tr>
<tr>
<td>Gleason score 8-10 cancer</td>
<td>205</td>
<td>1.32 (0.98-1.76)</td>
<td>0.06</td>
<td>1.00 (0.75-1.35)</td>
<td>0.98</td>
</tr>
<tr>
<td>Prostate cancer mortality</td>
<td>241</td>
<td>0.94 (0.69-1.28)</td>
<td>0.69</td>
<td>0.84 (0.61-1.14)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

\*HR adjusted for age at index, index year, baseline use of lipid-lowering drugs (statins and/or non-statin lipid-lowering medications), and baseline cardiometabolic conditions (diagnosed diabetes, hypertension, heart disease, and/or hyperlipidemia).
Objective: to investigate the use of 5ARIs (and α blockers) among BPH-diagnosed men in relation to PC incidence, severity, and mortality

- Retrospective 20-year cohort study in Saskatchewan, Canada male patients aged 40-89 years between 1995 and 2014

- Cox proportional hazards regression compared incidence of a PC diagnosis, metastatic PC, Gleason score 8-10 PC, and PC mortality among 5ARI users (n=4,571), α blocker users (n=7,764), and non-users (n=11,677) with a BPH-coded medical claim
Kaplan-Meier Curves for Prostate Cancer Incidence among 5ARI (n=4,571) Users, α-Blocker Users (n=7,764), and Non-users (n=11,677) with BPH

(A) 5ARI users vs. non-users HR 0.61 (95% CI: 0.53-0.70), \( P<0.0001 \)

(B) α-blocker users vs. non-users HR 0.89 (95% CI: 0.81-0.97), \( P=0.01 \)

(C) 5ARI users vs. α-blocker users HR 0.63 (95% CI: 0.54-0.73), \( P<0.0001 \)
Kaplan-Meier Curves for Prostate Cancer Mortality among Male New Users of 5ARIs (n=4,571), α-blockers (n=7,764), and Non-users (11,677) Diagnosed with Benign Prostatic Hyperplasia

(A) 5ARI users vs. non-users HR 1.11 (95% CI: 0.82-1.50), P=0.49
(B) α-blocker users vs. non-users HR 1.18 (95% CI: 0.97-1.44) P=0.10
(C) 5ARI users vs. α-blocker users HR 0.84 (95% CI: 0.61-1.14), P=0.26.
Earlier index years – presumably longer duration of use – were inversely correlated with prostate cancer outcomes
Summary

• In comparison with both non-users and α blocker users, 5ARI users had >35% lower risk of a PC diagnosis
  – α blocker users had 11% lower risk of a PC diagnosis compared with non-users

• Approximately 30% higher risk of Gleason score 8-10 cancer compared with non-users (for both 5ARI and α blocker users)

• Overall, no significant increase in metastatic PC or PC mortality among 5ARI and α blocker users (P>0.05 for both drugs)
2019 a BIG year for 5ARI and PCa

• Impact of 5α-reductase inhibitor and α-blocker therapy for benign prostatic hyperplasia on prostate cancer incidence and mortality
  – BJUInt, 2019; 123:511-518
2019 a BIG year for 5ARI and PCa

- Impact of 5α-reductase inhibitor and α-blocker therapy for benign prostatic hyperplasia on prostate cancer incidence and mortality
  - BJUInt, 2019; 123:511-518

- 5-alpha-reductase inhibitors delay prostate cancer diagnosis, worsen outcomes
  - JAMA Intern Med, 2019

- Long-Term Effects of Finasteride on Prostate Cancer Mortality
Prior treatment with 5-ARIs were more likely to have a clinical stage of T3 or higher (4.7% vs. 2.9%; \( P < .001 \)) and have node-positive (3.3% vs. 1.7%; \( P < .001 \)) and metastatic (6.7% vs. 2.9%; \( P < .001 \)) disease than patients who did not use 5-ARIs.

A multivariable regression showed 5-ARIs prior to prostate cancer diagnosis had a higher rate of prostate cancer-specific (subdistribution HR = 1.39; 95% CI, 1.27-1.52) mortality.

“Although these results are hypothesis generating, they
Long-Term Effects of Finasteride on Prostate Cancer Mortality

• With 296,842 person-years of follow-up and a median follow-up of 18.4 years, of 9423 men randomized to finasteride, there were 3048 deaths of which 42 were due to prostate cancer; of 9457 randomized to placebo, there were 2979 deaths, 56 due to prostate cancer.

• With the small number of deaths due to prostate cancer, the 25% lower risk of death from prostate cancer with finasteride was not statistically significant.
Why is our study important?

• Database of over 200,000 men – linked de-identified administrative health claims data, electronic prescription records, and cancer registry data for an entire Canadian province

• Long follow-up time (up to 20 years)

• Relatively large numbers of events for the main outcomes of interest

• Community-based sample provides more generalizable findings

• Universal health care (decreased socioeconomic bias)
Message for urologists managing BPH

• 5ARI use was associated with lower risk of a PC diagnosis

• Risk of high-grade PC was higher among both 5ARI users and α blocker users compared with non-users

• This high grade issue did not translate into higher risk of PC mortality

• There is a continued need to be aware of 5-ARI–induced PSA suppression
Message for urologists managing BPH

Reassuring for BPH patients

This data cannot be used to recommend a formal 5ARI cancer prevention strategy