BPH progression:
The disease continuum & evidence-based learnings

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Contents

• Natural history of LUTS/BPH - progression
• What evidences teach?
  – Olmsted County study
  – MTOPS study
  – ALTESS study
• Risk factors of BPH progression
• Conclusions
Introduction

- LUTS/BPH is a prevalent condition in ageing men
- Not a life-threatening → many patients even some physicians ignore the significance of this condition
- But, substantial number of men have a progressive disease
BPH progression

- Deterioration of symptoms and HRQoL
- Decreased Qmax
- Increased prostate size
- Unfavorable outcomes
  - AUR
  - BPH-related surgery
How can we know the fact?

• Longitudinal community-based studies
  – Olmsted county study
• Placebo arms of controlled studies
  (limitation due to selection criteria)
  – MTOPS study
  – ALTESS study
Olmsted County study
Olmsted County study

• Study subjects
  – Male residents of Olmsted County 40-79 years old on Jan 1, 1990
  – A 16% stratified random sample
  – Screen for prostatectomy, CaP, other medical conditions interfering with voiding function (=3,658 men potentially eligible)
  – 2,115 men (55%) completed study protocol
  – Followed for 12 years
### TABLE 1 Changes in IPSS, peak flow rate, prostate size and cumulative incidence of serious outcomes in the Olmsted County study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age, years</th>
<th>Overall</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>≥70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td></td>
<td>2115</td>
<td>839</td>
<td>587</td>
<td>434</td>
<td>252</td>
</tr>
<tr>
<td>IPSS [F]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline IPSS</td>
<td></td>
<td>0.18 (1.22)</td>
<td>0.05 (1.06)</td>
<td>0.18 (1.19)</td>
<td>0.44 (1.35)</td>
<td>0.14 (1.43)</td>
</tr>
<tr>
<td>Mean (sd) change/year</td>
<td></td>
<td>-2.1</td>
<td>-1.1</td>
<td>-2.7</td>
<td>-2.3</td>
<td>-6.2</td>
</tr>
<tr>
<td>Median change/year, %</td>
<td></td>
<td>-2.1</td>
<td>-1.1</td>
<td>-2.7</td>
<td>-2.3</td>
<td>-6.2</td>
</tr>
<tr>
<td>Peak flow rate [4]</td>
<td></td>
<td>-2.1</td>
<td>-1.1</td>
<td>-2.7</td>
<td>-2.3</td>
<td>-6.2</td>
</tr>
<tr>
<td>Median change/year, %</td>
<td></td>
<td>-2.1</td>
<td>-1.1</td>
<td>-2.7</td>
<td>-2.3</td>
<td>-6.2</td>
</tr>
<tr>
<td>Prostate volume [6]</td>
<td></td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Median growth per year, %</td>
<td></td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Cumulative incidence of surgical procedures over 6 years [8], n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TURP</td>
<td></td>
<td>45 (2.1)</td>
<td>1 (0.1)</td>
<td>5 (0.9)</td>
<td>21 (4.8)</td>
<td>18 (7.1)</td>
</tr>
<tr>
<td>MIST</td>
<td></td>
<td>19 (0.9)</td>
<td>0</td>
<td>6 (1.0)</td>
<td>7 (1.6)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>64 (3.0)</td>
<td>1 (0.1)</td>
<td>11 (1.9)</td>
<td>28 (6.5)</td>
<td>24 (9.5)</td>
</tr>
</tbody>
</table>

*MIST, minimally invasive surgical therapies.
Evidences-OCS

- A slow but measurable progression in urinary symptom severity among community dwelling men for 42 months f-u (Jacobsen et al, 1996 J Urol)
- During the 8,344 person-years f-u, 57 men had a first episode of AUR (6.8/1,000 person-yrs) (Jacobsen et al, 1997 J Urol)
- During 10,000 person-years f-u, 167 men were treated (16.0/1,000 person-yrs) (Jacobsen et al, 1999 J Urol)
• Prostate **volume** appears to increase steadily at about **1.6% per year** in randomly selected community men (*Rhodes et al, 1999 J Urol*)

• Median **Qmax** slope was **-2.1% per year**. **Qmax** declined more rapidly with ↓baseline rate, ↑baseline age, prostate volume, symptom severity (*Roberts et al, 2000 J Urol*)
Controlled studies

• Information can be collected from placebo arms of controlled studies in men with symptomatic BPH

• Strict inclusion criteria introduce a bias in the analysis of outcomes

• PLESS, MTOPS, ALTESS
MTOPS study
MTOPS (Medical Therapy Of Prostatic Symptoms)

Double-blind, placebo-controlled, multicenter, randomized
Average follow-up: 4.5 years

Randomized
N=3047

Entry Criteria
• Men $\geq 50$ years of age
• AUA symptom score 8–30
• $Q_{\text{max}}$ 4–15 ml/sec
• Voided volume $\geq 125$ ml

Doxazosin (n=756)
PROSCAR® (n=768)
PROSCAR + doxazosin (n=786)
Placebo (n=737)

McConnell et al, N ENGL J Med 2003
Impact on clinical progression of BPH

Cumulative incidence of BPH progression

- Placebo (n=737)
- PROSCAR® (n=768)
- Doxazosin (n=756)
- Combination (n=786)

McConnell et al, N ENGL J Med 2003
Impact on Symptom Control

Cumulative incidence of ≥4-point increase in symptom score

McConnell et al, N ENGL J Med 2003
Effect on Prostate Volume

Change from baseline in prostate volume

-16%* (Combination, n=786)
-13%* (PROSCAR®, n=768)
+18% (Doxazosin, n=756)
+18% (Placebo, n=737)

Median % change from baseline

McConnell et al, N ENGL J Med 2003
Impact on the Risk of AUR

Cumulative incidence of AUR

- Placebo (n=737)
- PROSCAR® (n=768)
- Doxazosin (n=756)
- Combination (n=786)

McConnell et al, N ENGL J Med 2003
Impact on the Need for BPH-Related Surgery

Cumulative incidence of BPH-related surgery

- Placebo (n=737)
- PROSCAR® (n=768)
- Doxazosin (n=756)
- Combination (n=786)

McConnell et al, N ENGL J Med 2003
In the placebo arms,

- The cumulative incidence of overall clinical progression was **16.6%** (122/737) over 5 years.
- **Symptom** deterioration (IPSS worsening by ≥4 points) was the main contributor (97/122, 79.5%) with a cumulative incidence of **14%** over 5 years.
- **AUR** was uncommon (18/122, 14.8%) with a cumulative incidence of **2%**.
- BPH-related surgery (2° endpoint) was required in 5% of men (37/737) over 5 years.
Placebo effects

• Positive effect on LUTS and Qmax
  • Median improvement of 4 points and 1.4mL/s
• No effect on volume and PSA
  • Volume increased by a median of 24%
  • Serum PSA level: a 15% increase
• Placebo arms ≒ but, ≠ natural history
ALTESS
ALTESS

- Alfuzosin 10mg once daily long-term efficacy and safety study
- Study (duration: 2 years)
  - Men enrolled: at high risk of developing LUTS/BPH progression events
    - $\geq 55$ years
    - moderate to severe symptoms
    - $Q_{\text{max}}=5-12\text{mL/s}$
    - Size(DRE) $\geq 30\text{g}$
    - Baseline s-PSA: 1.4-10ng/mL
• 167/775 (placebo arm) = 22.1% had at least one BPH progression event
• Main event was symptom worsening of ≥ 4 points (16.8%)
• AUR = 2.2%
• BPH related surgery = 6.5% (49/757)
## ALTESS & MTOPS

<table>
<thead>
<tr>
<th>Variable</th>
<th>ALTESS (2 years)</th>
<th>MTOPS* (4 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N placebo-treated patients</td>
<td>757</td>
<td>737</td>
</tr>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPSS worsening of ≥4 points</td>
<td>127 (16.8)</td>
<td>97 (14.0)</td>
</tr>
<tr>
<td>AUR</td>
<td>14 (1.8)</td>
<td>18 (2.0)</td>
</tr>
<tr>
<td>BPH-related surgery</td>
<td>49 (6.5)</td>
<td>37 (5.0)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>ND</td>
<td>6 (0.8)</td>
</tr>
<tr>
<td>UTI or urosepsis</td>
<td>ND</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

*patients having a progression event were censored in other progression-event analyses; ND, not done.
Risk factors: BPH progression

- PSA
- Large prostate
  - Old age
  - Severe LUTS
  - Low Qmax
  - Increased PVR
Study for Asian?

- Retrospective cohort study
- Inclusion: 2 measurements of PV & IPSS
- Exclusion: hormone therapy, CaP, surgery
- 67 patients were eligible
- alpha blockers only? Or watchful waiting?

Change in International Prostate Symptom Score, prostate-specific antigen and prostate volume in patients with benign prostatic hyperplasia followed longitudinally

Prostate volume increase

• PV increased in 46(70%) men, remained the same in 10 and decreased in 11
• Rather small sized study
• The only Asian study appeared in PubMed
Summary

- There is evidence from longitudinal studies and in some extent from the placebo arms of the large controlled studies, that **BPH is a progressive disease**
- **Symptom worsening** is the most frequently occurring event
- **Risk factors** of BPH progression should be considered to optimize the management of individual patient
- Maybe, we need to have Asian data
Thank you very much!