Benign Prostatic Hyperplasia (BPH)
Important Papers / Landmark Studies

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Landmark Studies

• MTOPS & CombAT
• PLESS
• SMART
• ALTESS
• ALF-ONE
• VA
• PREDICT
• EPICS
MTOPS

- **Medical Therapy of Prostatic Symptoms**
- **NEJM 2003**
- **Objective** → to determine if therapy with α-blocker doxazosin or the 5α-reductase inhibitor finasteride, alone or in combination, would delay or prevent clinical progression of BPH
MTOPS

- Multi-centre randomized double blind placebo controlled study
- 3047 patients
- Duration → 4.5 years
MTOPS

• Inclusion
  - age ≥ 50 years
  - AUA-SI of 8 – 30
  - $Q_{\text{max}}$ 4 – 15 ml/s
  - Voided volume ≥ 125 ml

• Exclusion
  - prior medical / surgical intervention for BPH
  - BP < 90/70 mm Hg (supine)
  - Serum PSA > 10 ng/ml
MTOPS - Outcomes

• Primary (Overall clinical progression)
  - first occurrence of AUA-SI increase $\geq 4$ point
  - AUR
  - recurrent UTI
  - renal insufficiency
  - urinary incontinence

• Secondary
  - changes over time of AUA score
  - changes in $Q_{\text{max}}$
  - cumulative incidence of invasive treatment for BPH
  - changes over time of PSA and prostate volume
MTOPS

• Overall clinical progression
  → combi tx (vs Placebo) significantly reduces risk by 66% cf. Doxa 39% cf. Finas 34%
  → AUA sx score significantly reduced in combi tx
  → urinary incontinence and recurrent UTI
  → small numbers
  → no cases of renal insufficiency
MTOPS

• Risk of AUR
  → Combi therapy OR 5 αRI (finasteride) both significantly reduce risk (81% and 68% respectively)
  → Doxazosin delays but DOES NOT reduce risk

• Need for Invasive Therapy
  → Combi therapy OR 5 αRI (finasteride) both significantly reduce risk (67% and 64% respectively)
MTOPS

• Safe to use
• Minimal s/effects
• Combination therapy has slightly more side effects
MTOPS (Number needed to Treat)

• To prevent clinical progression in 1 ptt
  - Combi tx (8.4), if PSA > 4 (4.7), if PV > 40 (4.9)
  - Doxazosin (13.7)
  - Finasteride (15.0), if PSA > 4 or if PV > 40 (7.2)

• To prevent BPH related surgery in 1 ptt
  - Combi tx (25.9); if PSA > 4 (23.1), if PV > 40 (15.9)
    - Doxazosin (60.1)
    - Finasteride (29.0)
CombAT

- Combination of Avodart and Tamsulosin study
- European Urology 2010 (Roehrborn)
- Objective → To investigate if combination therapy is more effective than either monotherapy in reducing the RR for AUR, BPH related surgery, and BPH clinical progression over 4 years in men at increased risk of progression
CombAT

• Multi-national, multi-centre, double blind randomized study
• 4 year duration
• 4844 men randomized but 3195 men completed 4 year follow-up (66%)
CombAT (Inclusion / Exclusion Criteria)

- Almost similar with MTOPS
- Difference
  - Inclusion criteria – prostate volume $\geq 30 \text{ cm}^3$ by TRUS
    - total se. PSA $\geq 1.5 \text{ ng/ml}$
CombAT (Outcomes)

- Results similar to MTOPS
  - Combi tx significantly reduces risk of clinical progression
  - IPSS significantly reduced in combination tx
  - Combi therapy OR 5 αRI (dutasteride) both significantly reduce risk of AUR
  - Combi therapy OR 5 αRI (dutasteride) both significantly reduce risk of need for invasive surgery (for BPH)
- Additionally looked at prostate volume at end of 4 years
  - Prostate volume significantly increased with tamsulosin alone by 4.6%
# CombAT Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Combination Therapy</th>
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<tbody>
<tr>
<td></td>
<td>Vs. Tamsulosin</td>
<td>Vs. Dutasteride</td>
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<tr>
<td>Relative risk of AUR</td>
<td>↓ 67.6%*</td>
<td>↓ 18.3%</td>
<td></td>
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<tr>
<td>Relative risk of BPH related surgery</td>
<td>↓ 70.6%*</td>
<td>↓ 31.1%</td>
<td></td>
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<tr>
<td>Relative risk of clinical progression</td>
<td>↓ 44.1%*</td>
<td>↓ 31.2%*</td>
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*P < 0.001
CombAT (Adverse Events)

• Higher with combination therapy
• Mainly ejaculatory disorders
• Increase in cardiac failure (caution)
• No floppy iris
• No breast cancers
• Prostate cancer similar across groups
• Serum PSA \(\downarrow\) by 56\% in combi tx and dutasteride group
CombAT

• No placebo
• Large baseline prostate volume (55g)
• Only 1 point superior sx reduction (IPSS) vs Dutasteride alone → is it worth it? Steven A. Kaplan (Eur. Urol 2010)
MTOPS vs CombAT

• CombAT no placebo control
• CombAT had additional inclusion criteria of prostate volume $\geq 30 \text{ cm}^3$ AND PSA $\geq 1.5 \text{ ng/ml}$
• In MTOPS, on average ptts prostate volume smaller (baseline $< 25 \text{ cm}^3$), in CombAT (avg 55g)
  $\rightarrow$ sub-studies of MTOPS reveal no improvement in clinical progression even with combi. tx in this group
PLESS

- **Proscar Long Term Efficacy and Safety Study**
- NEJM 1998 (McConnell)
- Objective → to evaluate the long term effects of finasteride on sx of BPH and on incidence of important outcomes such as AUR and need for surgery
PLESS

- 4 year randomized double blind placebo-control
- 3040 men with
  - moderate to severe LUTS
  - $Q_{\text{max}} < 15 \text{ ml/s} \ (\text{Voided} \geq 150 \text{ ml})$
  - DRE $\rightarrow$ enlarged prostate
  - PSA $< 10 \text{ ng/ml} \ (\text{between 4 to 10} \rightarrow \text{biopsy to exclude PC})$
PLESS

• Primary end-point
  - Sx score (AUA)

• Secondary end-point
  - Surgery for BPH
  - Occurrence of AUR
PLESS Outcomes

• Finasteride vs. Placebo
• Withdrawal: 1157 subjects (Total; d/t worsening sx / adverse s.e. / loss to f.up
• Sx score decreased by 3.3 pts in finasteride vs 1.3 (placebo) → (P < 0.001)
• PV ↓ by 18% in finasteride vs 14% ↑ in placebo (P < 0.001)
• Q_{max} ↑ by 1.9 ml/s (finasteride) vs 0.2 ml/s (placebo) (P < 0.001)
PLESS Outcomes

- Finasteride ↓ risk of AUR and BPH related surgery (P < 0.001) vs placebo
- 15 men need to be treated for 4 years to prevent 1 event of AUR or BPH related surgery
PLESS Problems

• High rate of discontinuation
• Not all symptomatic men have enlarged prostates
VA Coop Trial

- Veteran Affairs Cooperative Studies BPH Study Group
- NEJM 1996 (Lepor)
- Compare safety & efficacy of placebo vs. terazosin vs. finasteride vs. combi tx (1 year looking at AUA-SI & Q_max)
- Outcomes
  - Terazosin and combi tx. improved AUA-SI and Q_max cf. finasteride / placebo
  - Finasteride alone did not improve AUA-SI and Q_max in this study (recruitment of men with smaller glands)
  - Terazosin better than finasteride for AUA-SI and Q_max (combi tx. no added benefit)
PREDICT

• Prospective European Doxazosin and Combination Therapy Trial
• Urology 2002 (Kirby)
• 1095 men (largest randomized trial in Europe)
• Outcomes (similar to VA Coop Study NEJM 1996)
  → Doxazosin AND Doxazosin + Finasteride (Combi tx) improved $Q_{\text{max}}$ and IPSS significantly
  → Finasteride alone did not show any improvement (possibly because duration of study 1 yr or in prostates $< 40\text{cm}^3$)
  → AUR & BPH related surgery uncommon
SMART

• **Symptom Management After Reducing Therapy**
• European Urology 2003 (Barkin)
• Objective → examine short-term combi. tx with an $\alpha_1$-blocker and dutasteride, followed by removal of the $\alpha_1$-blocker and continuation of dutasteride monotherapy
SMART

• Multicentre randomized trial (6 countries)
• Inclusion
  - men ≥ 45 years with
  - IPSS ≥ 12
  - Prostate volume (PV) ≥ 30ml on DRE
  - PSA 1.5 – 10 ng/ml
SMART

- Study design
  - Initial phase → 4 weeks single blind placebo
  - 2\textsuperscript{nd} phase → 24 weeks single blind combi tx
  - 3\textsuperscript{rd} phase → double blind randomization into combi tx or dutasteride + placebo for 12 weeks
SMART

- Outcomes
  - Primary → Any difference in symptoms at 30 weeks (6 weeks after tamsulosin withdrawal)
  - Secondary → change in IPSS at similar follow-up
SMART (Primary Outcome)

- 6 weeks after stopping tamsulosin, symptom improvement (same or better) was at 77% vs combi tx (91%)

  **HOWEVER**

- 12 weeks after stopping tamsulosin, symptom improvement (same or better) was at 93% vs combi tx (96%)
SMART (Outcome)

• After stratifying sx, less ptts with more severe sx at baseline (IPSS ≥ 20) reported feeling better at 30 weeks vs moderate IPSS

• Ptts with > severe sx may benefit from combi tx longer than 24 weeks before tamsulosin withdrawal

• Improved / Identical IPSS score similar between gps (combi 61% vs withdrawal 56%) at week 24 and 30
SMART (Adverse Events)

- Similar to most combination studies
- Malaise and lethargy (tamsulosin)
- Retrograde ejaculation (tamsulosin)
- Decreased libido (dutasteride)
ALTESS

• **Alfuzosin Long-Term Efficacy and Safety Study**
• BJUI 2006 (Roehrborn)
• Objective ➔ Assess impact of alfuzosin on risk of BPH/LUTS progression
• 2 year study, 1515 ptts
ALTESS

• On average → older men
  → higher IPSS
  → larger prostate than MTOPS

• Endpoints → 1\textsuperscript{st} occurrence of AUR (primary)
  → need for BPH-related surgery
ALTESS

• Findings
  - similar to MTOPS
  - Alfuzosin significantly reduced risk of BPH progression (IPSS improved by ≥ 4 points)
  - Alfuzosin did not significantly reduce risk of AUR or BPH-related surgery
ALF-ONE

- **Alfuzosin Once Daily**
- BJUI (Vallencien)
- Objective → Evaluate long-term efficacy and tolerability of alfuzosin 10mg od in clinical practice
- 29 countries, open-label study, 6523 men
ALF-ONE

- Failure to respond to alfuzosin 10mg od
  - lack of symptom relief
    ±
  - persistent high degree of bother
    identified as a powerful predictor of AUR and BPH-related surgery at short term (6 mths) and at long term (3 yrs)
- Thus → First line treatment with alfuzosin may help select pts at risk of BPH progression in order to optimize their management...
EPICS

- Enlarged Prostate International Comparator Study (Comparison of dutasteride vs finasteride in tx of BPH)
- BJUI 2011 (Nickel)
- Only prospective randomized trial comparing finasteride vs dutasteride – looking at efficacy & safety over 1 year
EPICS

• Outcomes
  → both dutasteride and finasteride reduced PV (no sig. difference)
  → AUA-SI reduction / improvement of $Q_{\text{max}}$ was similar in both grps (no sig. difference)
  → PSA reduction was between 47 to 50% at 1 yr f/up from baseline in both grps
  → Similar rates of adverse events

• Problems
  → Only 1 year (may see > improvement if longer)
  → PV may not correlate with clinical efficacy (PREDICT & VA)
THANK YOU
Health Cost Implications

• US Agency for Health Care Policy and Research (AHCPR) 1994 and Lowe et al
  - surgical tx for BPH cost 5x as much as medical tx (α-blockers = finasteride)

BUT THIS IS SHORT TERM OVER 2 YEARS ONLY
Health Cost Implications

• Chirikos & Stanford
  - Medical tx (finasteride or terazosin) < cost effective cf. TURP (if medical tx started on pts's age < 70 yrs old)

• Canadian Coordinating Office for Health Technology Assessment (15 year assessment)
  - mild sx → WW appropriate
  - mod to severe sx → surgery more economical for greater life expectancy
Health Cost Implications

- DiSantostefano et al (2008) WW vs α-blockers vs 5α-reductase inhibitors vs combi tx vs TUMT vs TURP (over 20 years)
  - annual cost of WW steady
  - TURP highest cost at 5 years; TUMT highest at 7 years
  - After 9 years combi tx cost > surgery
  - TUMT cost effective for mod sx
  - TURP most cost effective for severe sx
Health Cost Implications

• Lasers??
• Stovsky et al
  - Total cost of PVP expected to be lower than ALL OTHER THERAPIES