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

- **M**edical **T**herapy of **P**rostatic **S**ymptoms
- 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_{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 ≥ 4 point
  - AUR
  - recurrent UTI
  - renal insufficiency
  - urinary incontinence
- Secondary
  - changes over time of AUA score
  - changes in Q_{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

- **C**ombination of **A**vodart and **T**amsulosin 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 ≥ 30 cm^3 by TRUS

  - total se. PSA ≥ 1.5 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

	Combination Therapy	
	Vs. Tamsulosin	Vs. Dutasteride
Relative risk of AUR	↓ 67.6%*	↓ 18.3%
Relative risk of BPH related surgery	↓ 70.6%*	↓ 31.1%
Relative risk of clinical progression	↓ 44.1%*	↓ 31.2%*

*$P < 0.001$

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 ↓ 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 ≥ 30 cm^3 **AND** PSA ≥ 1.5 ng/ml
- In MTOPS, on average ptts prostate volume smaller (baseline < 25 cm^3), in CombAT (avg 55g)

  → sub-studies of MTOPS reveal no improvement in clinical progression even with combi. tx in this group

PLESS

- **P**roscar **L**ong Term **E**fficacy and **S**afety **S**tudy
- 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_{max} < 15 ml/s (Voided ≥ 150 ml)
  - DRE → enlarged prostate
  - PSA < 10 ng/ml (between 4 to 10 → 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_{max} and IPSS significantly

  → Finasteride alone did not show any improvement (*possibly because duration of study 1 yr or in prostates < 40cm^3)*

  → AUR & BPH related surgery uncommon

SMART

- **S**ymptom **M**anagement **A**fter **R**educing **T**herapy
- European Urology 2003 (Barkin)
- Objective → examine short-term combi. tx with an α_1- blocker and dutasteride , followed by removal of the α_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
  - 2nd phase → 24 weeks single blind combi tx
  - 3rd 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

- **A**lfuzosin **L**ong-**T**erm **E**fficacy and **S**afety **S**tudy
- 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 → 1st 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

- **Alf**uzosin **On**c**e** 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 ptts 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_{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 ptts 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**