UNIVERSITY OF ALBERTA

ALBERTA CONTINENCE RESEARCH NETWORK

Amman, Jo

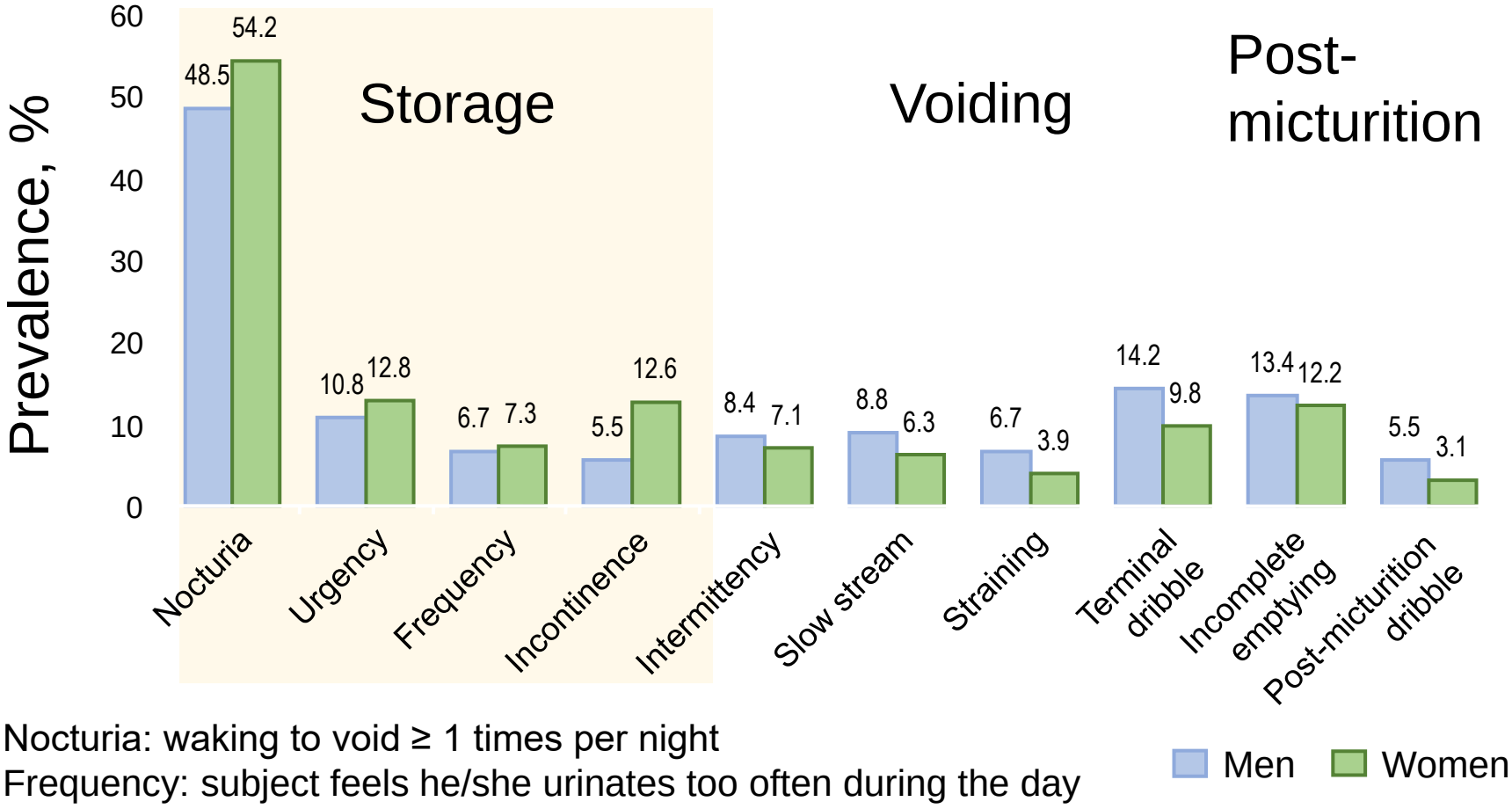
March 20th,

# Managing OAB in women from mi
# until late life - a physician
# perspectiv

# Disclosures

- **Astellas Pharma** – research grants, spaker honoraria and consulting
- **Essity Health & Hygiene AB** – research grants and consulting
- **Pfizer Corp** – research grants, consulting, speaker honoraria
- **Pierre Fabre** – speaker honoraria, consultancy

# Prevalence of LUTS in men and women



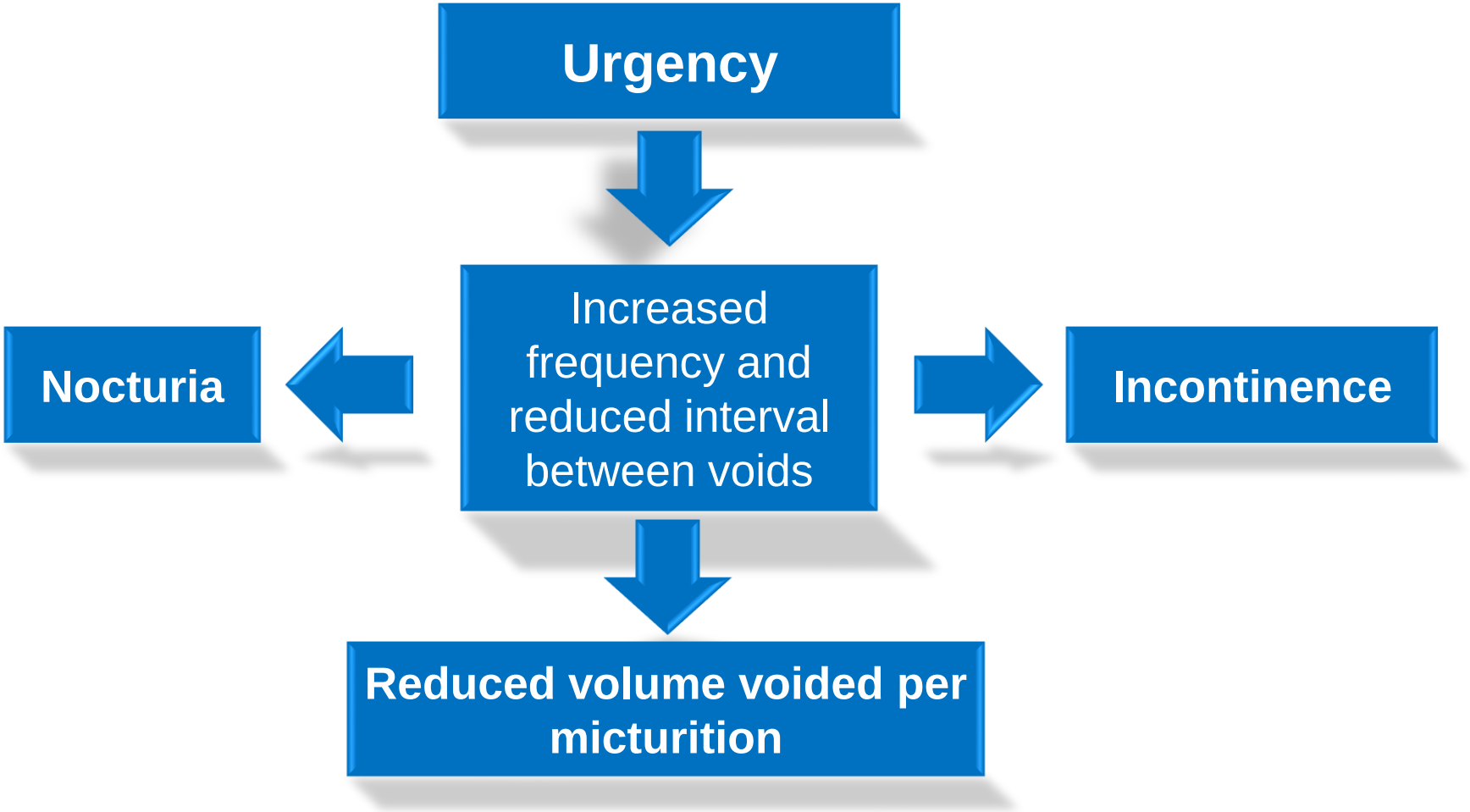

Nocturia: waking to void ≥ 1 times per night
Frequency: subject feels he/she urinates too often during the day

# What is OAB? A reminder of the most recent definition

**Overactive bladder (OAB, urgency) syndrome:** Urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with urinary incontinence (OAB-wet) or without (OAB-dry), in the absence of urinary tract infection or other detectable disease.

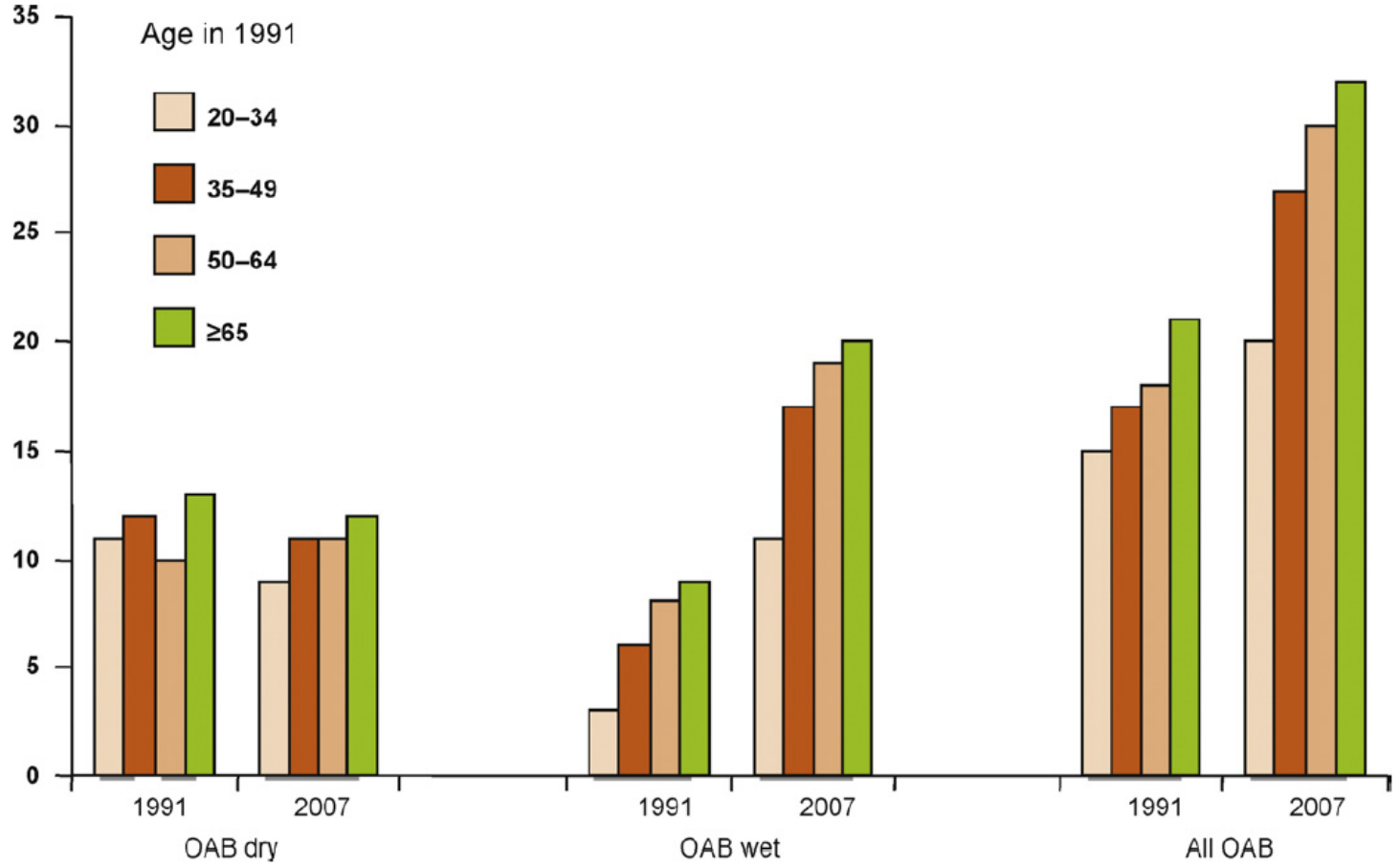
Neurourology and Urodynamics 2019;38: 433 - 477

# Urgency is the pivotal symptom of OAB



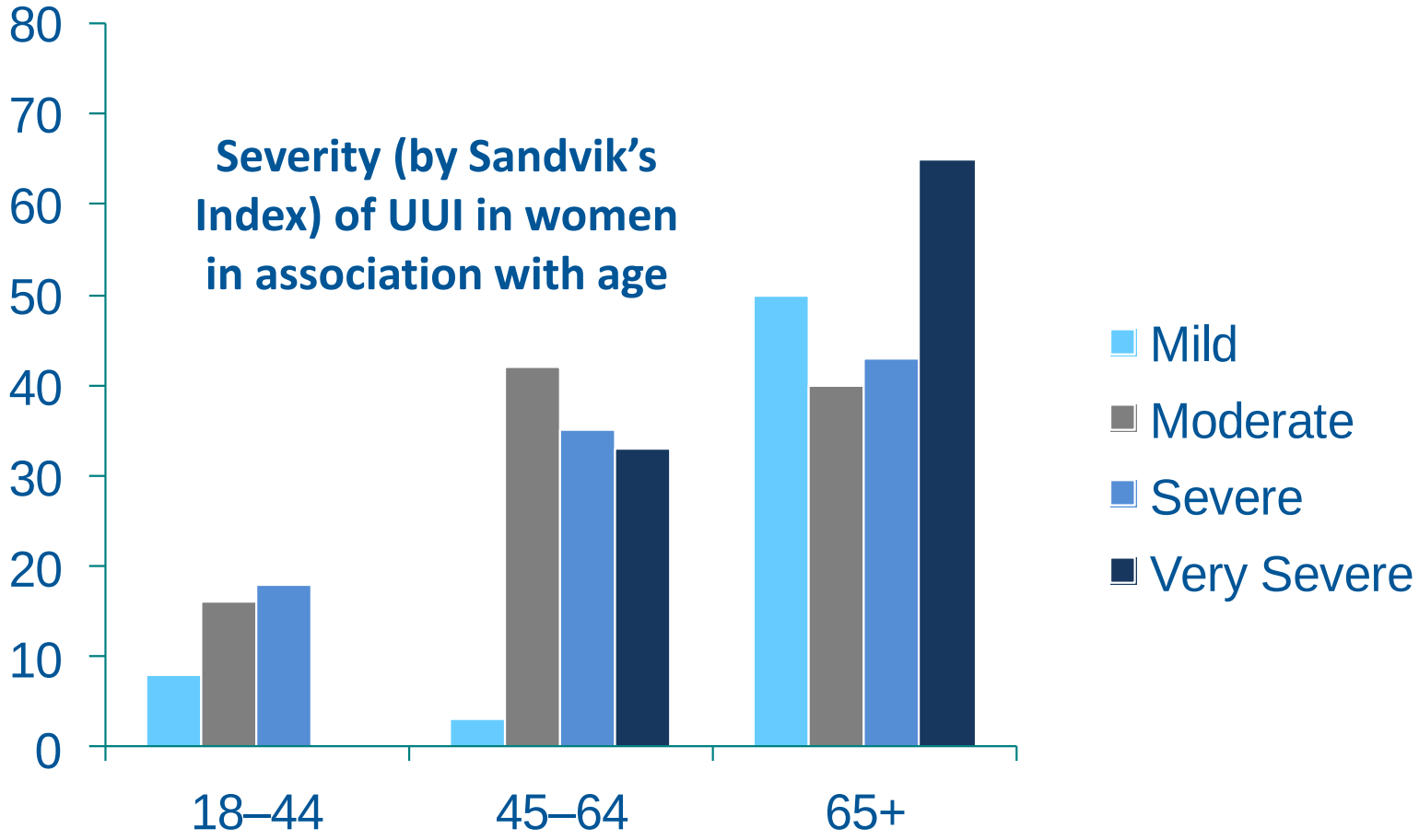

Chapple BJUI 2007

# OAB in ageing women



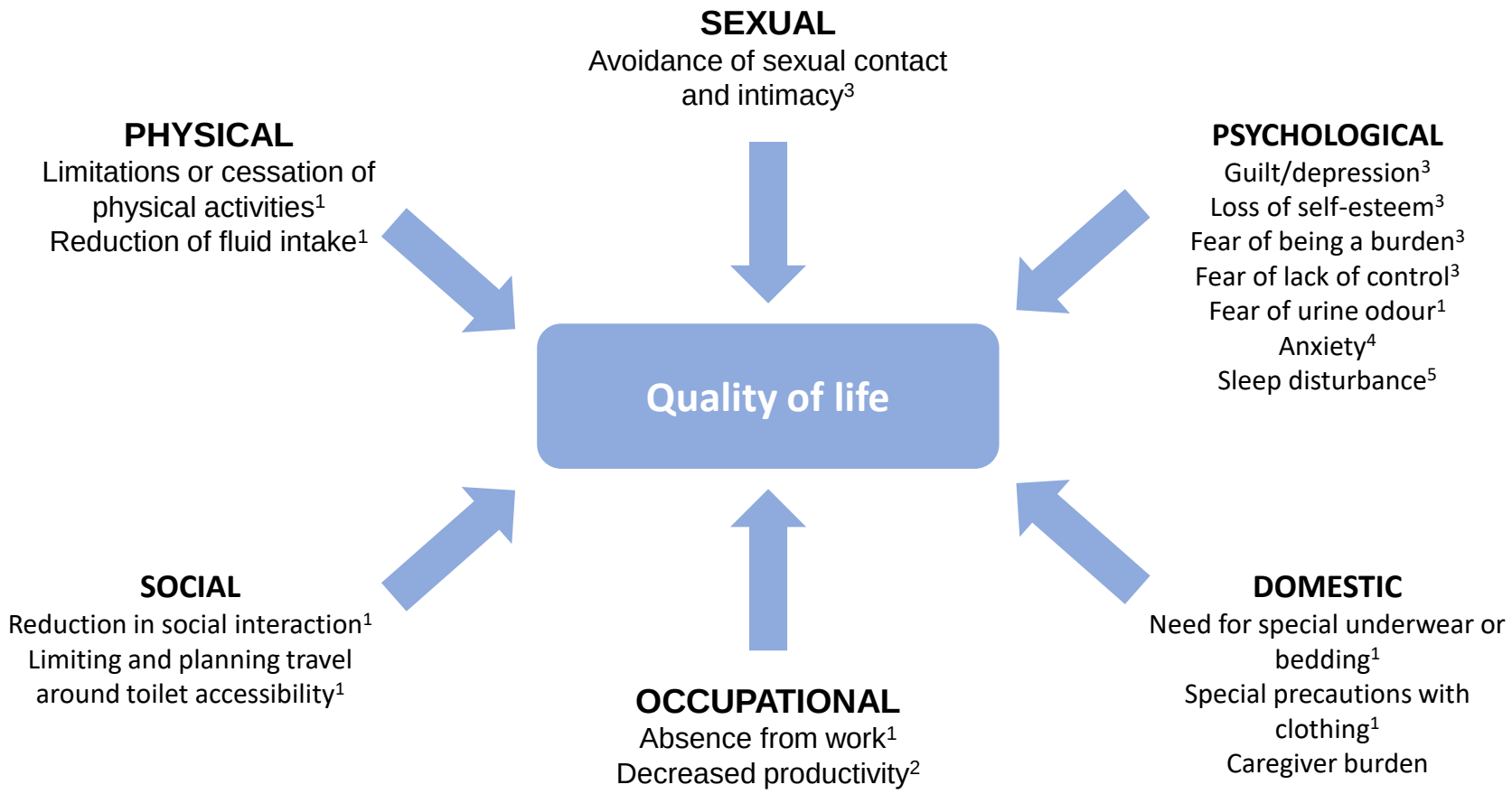

European Urology 2009; 55: 783–791

# Older people experience “more severe” disease



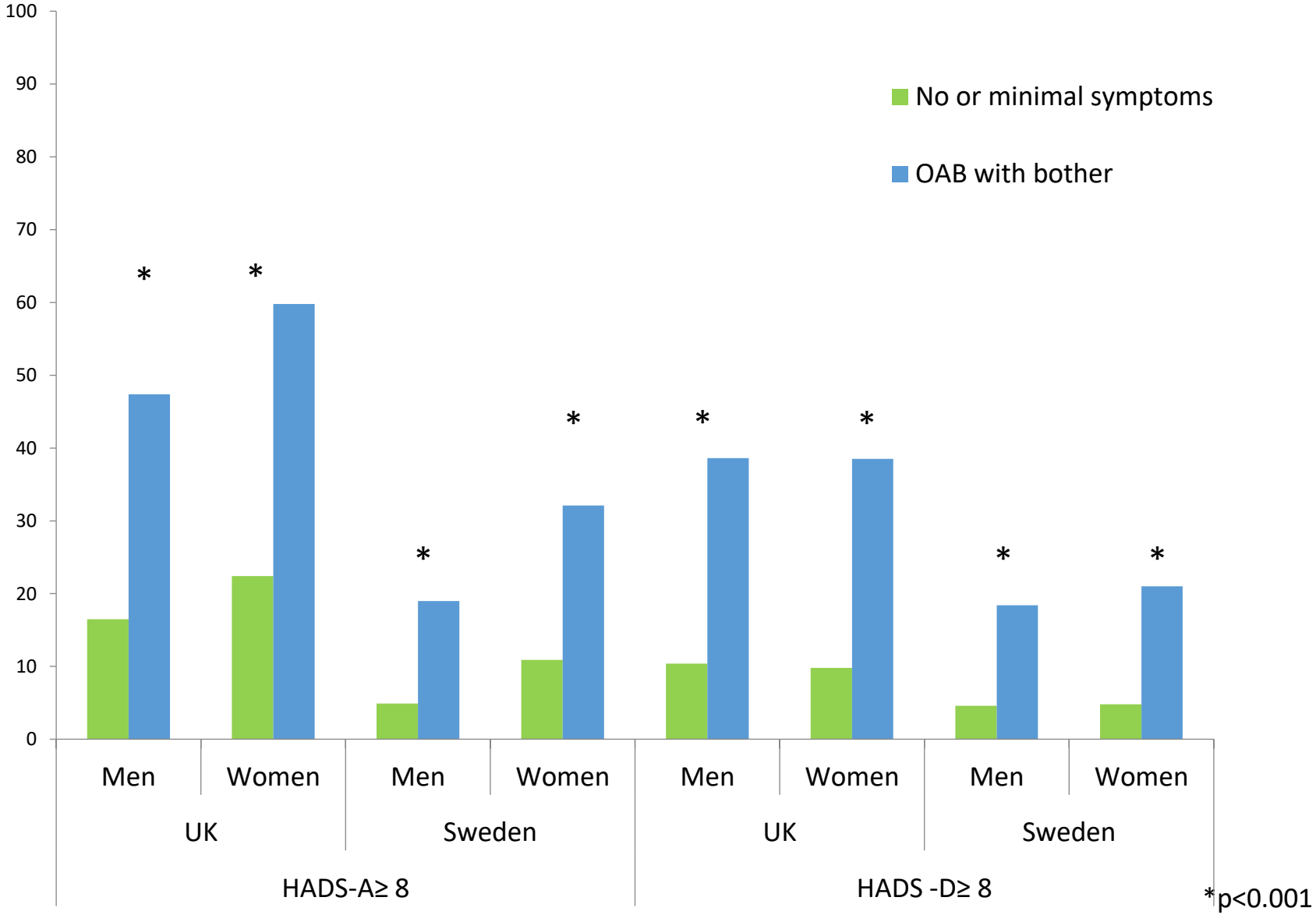

Wagg A et al. *BJU Int.* 2007;99;502-509.

# OAB can affect many areas of life




1. Abrams P et al. *Am J Manag Care* 2000; 6: S580–90; 2. Sexton CC et al. *Am J Manag Care* 2009; 15: S98–107;
3. Tubaro A. *Urology* 2004; 64(suppl 6A): 2–6; 4. Sexton CC et al. *J Am Geriatr Soc* 2011;59(8): 1456–70;
5. Stewart WF et al. *World J Urol*. 2003; 20: 327–36.

# Psychosocial impact of OAB (Hospital Anxiety and Depression Scale)




Coyne et al. BJU Int 2011; 108: 1459 - 71

# Case Study: The robust patient

Melissa is 43 years old.  She is a teacher who's life at work has been made increasingly difficult.

She can't teach a class without urgency and urgency incontinence – she has to wear pads to last a lesson

She has controlled hypertension and takes candesartan 8mg daily.

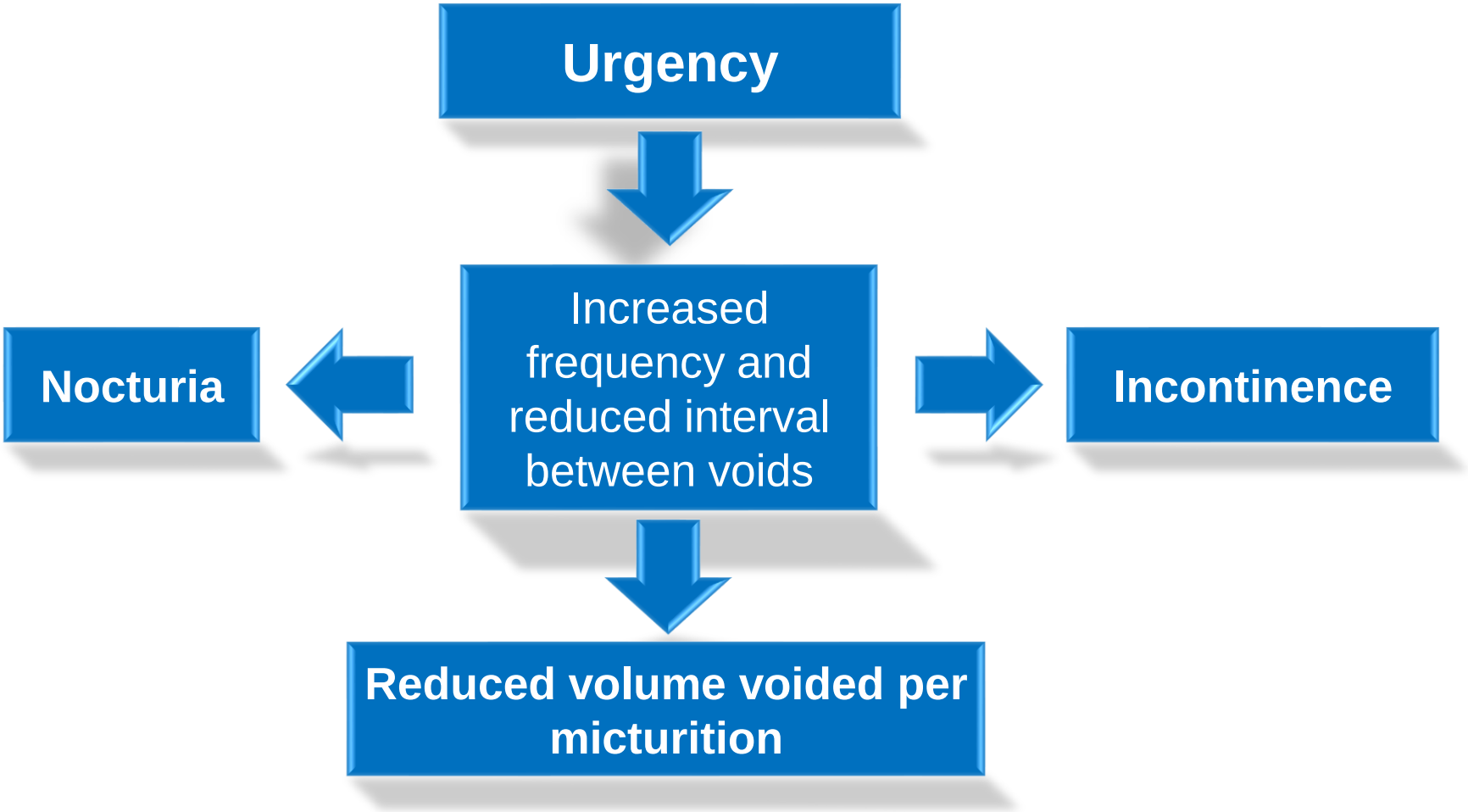
She neither smokes nor drinks alcohol

She is perimenopausal.

Clinical examination is normal.

She is most bothered by urinary urgency

# Urgency is the pivotal symptom of OAB




Chapple BJUI 2007

# Numbers needed to treat and harm

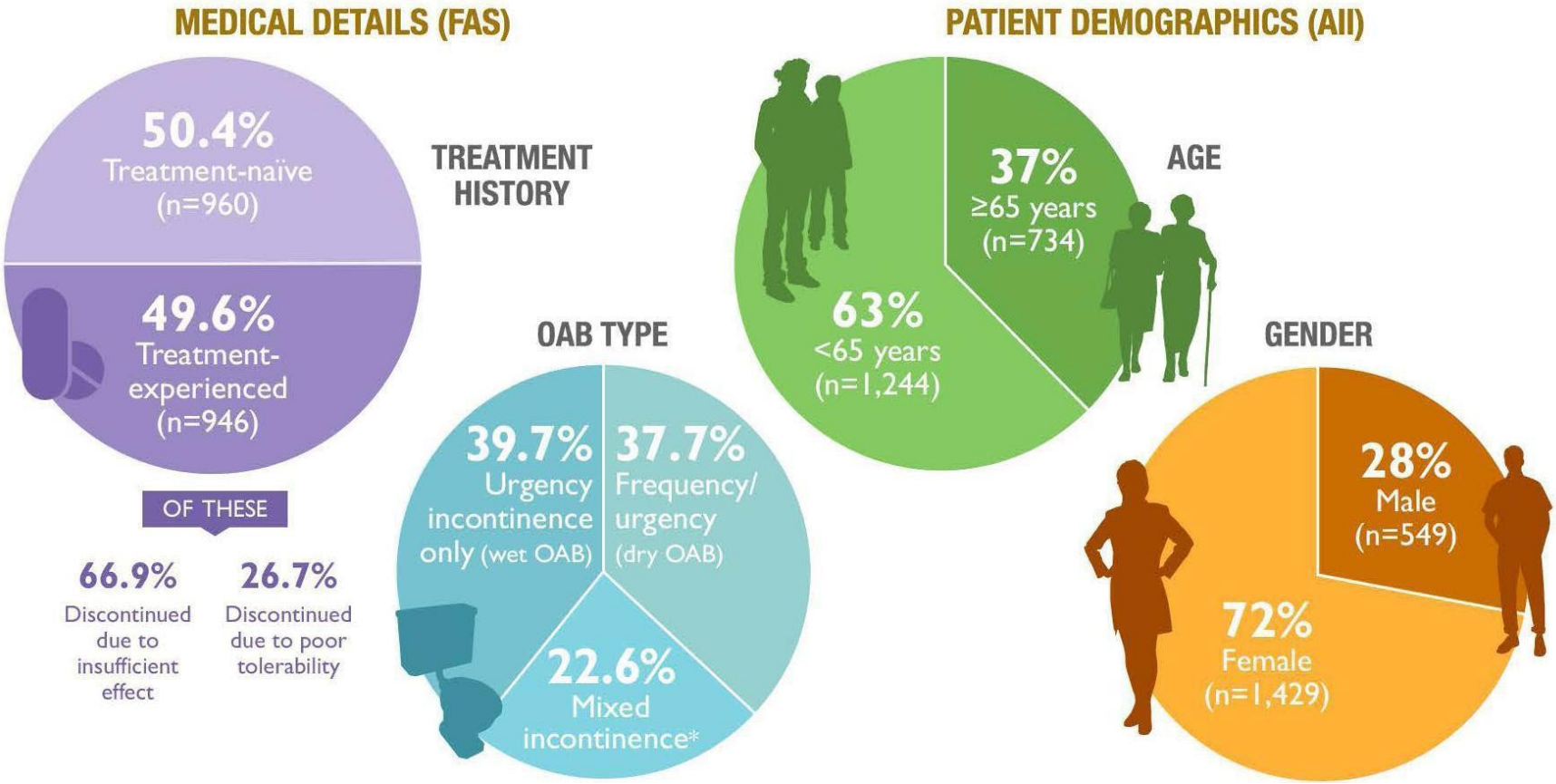
| | NNT n (95% CI) | NNH n (95% CI) |
|---|---|---|
| Fesoterodine | 8 (5 – 17) | 33 (18-102) |
| Oxybutynin | 9 (6 – 16) | 16 (8 – 86) |
| Solifenacin | 9 (6 – 17) | 78 (39 –823) |
| Tolterodine | 12 (8 – 25) | |
| Trospium | 9 (7 – 12) | 56 (30 – 228) |

Evidence was insufficient from which to conclude prediction of treatment effects by age, race, baseline severity of UI, and comorbidities.

NNT = number needed to treat
NNH = number needed to harm
CI = confidence interval

Shamliyan T, Wyman J, Kane RL. **Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness [Internet].**
Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Apr. Report No.: 11(12)-EHC074-EF.
AHRQ Comparative Effectiveness Reviews.

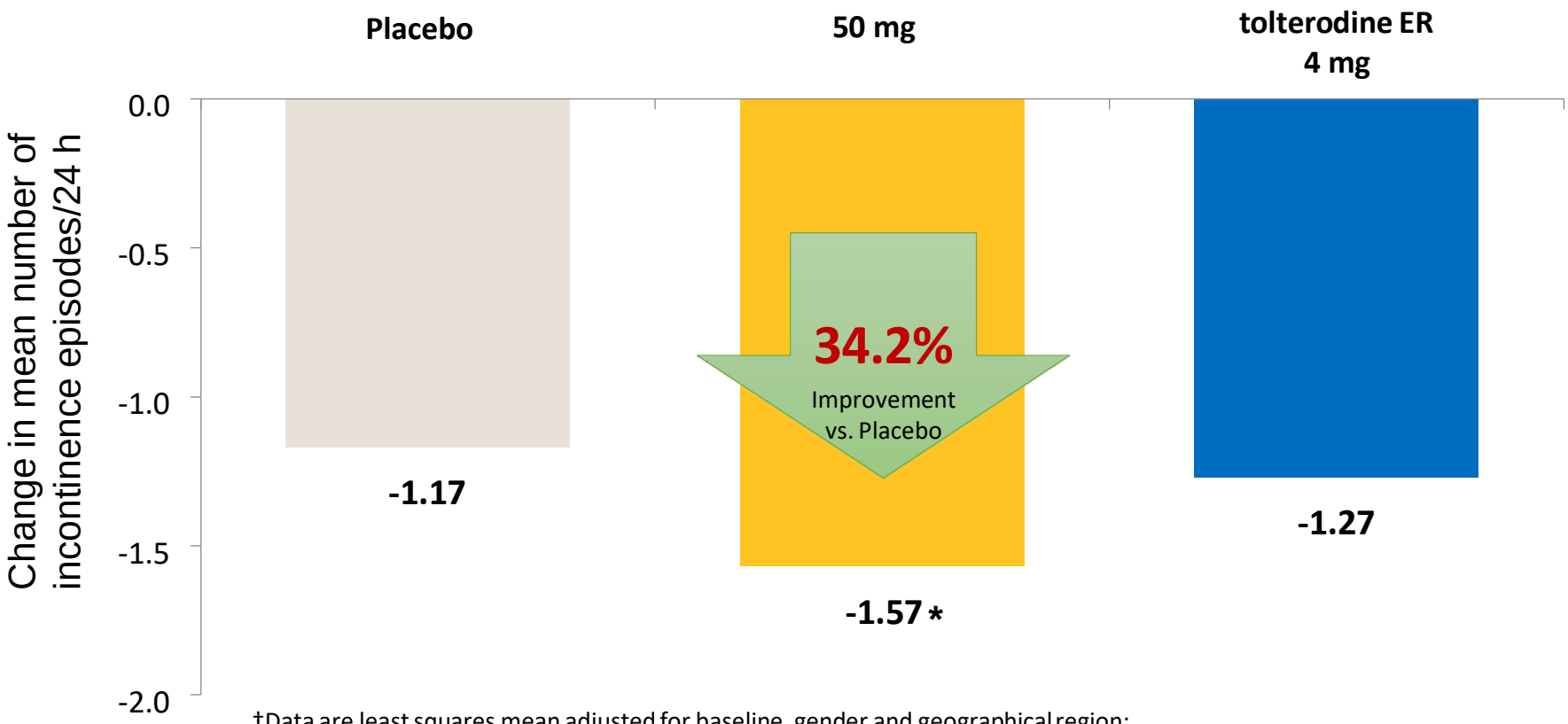
# Are mirabegron data relevant to Melissa?




Khullar V, et al. Efficacy and Tolerability of Mirabegron, a b3-Adrenoceptor Agonist, in Patients with Overactive Bladder: Results from a Randomised European–Australian Phase 3 Trial; Eur Urol (2013) 283–295

# Incontinence episodes

Mirabegron significantly reduced the mean number of incontinence episodes/24h (FAS-I)†

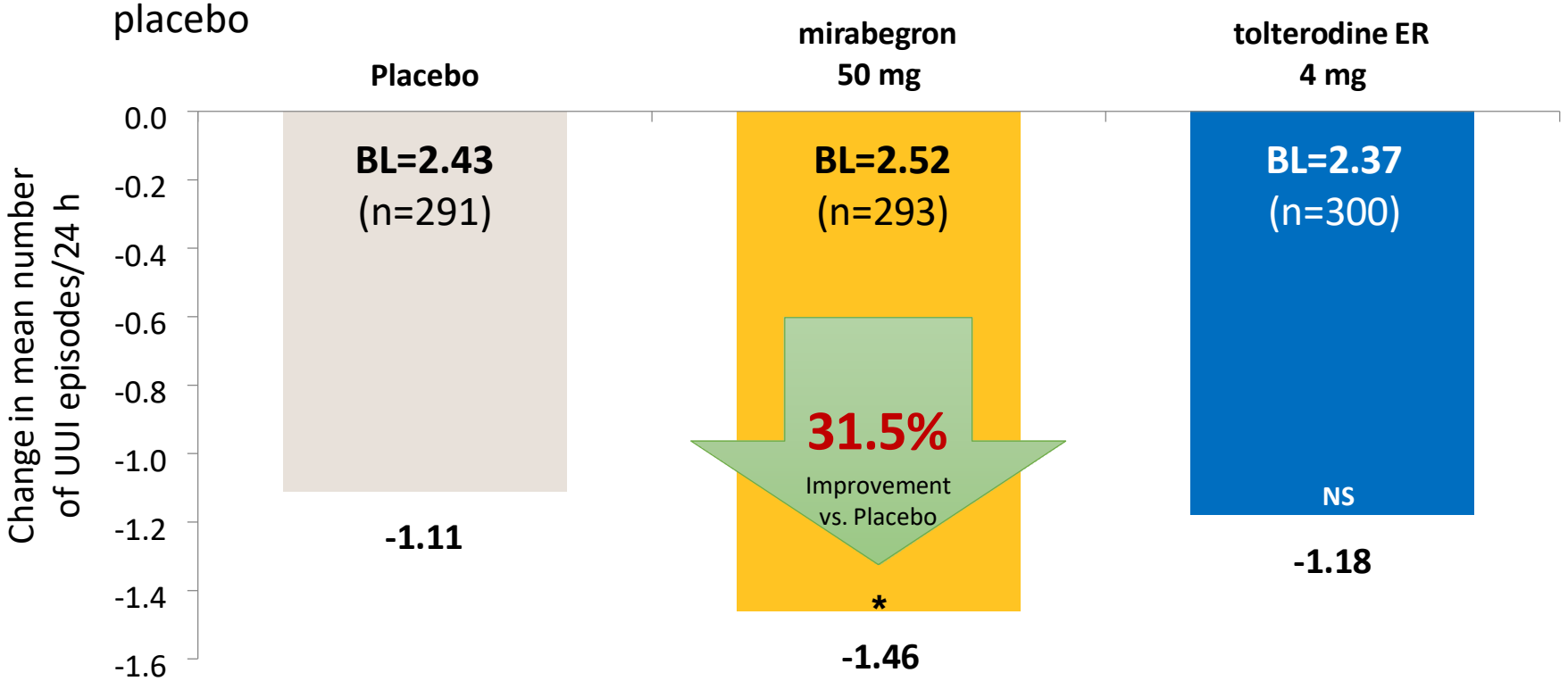



†Data are least squares mean adjusted for baseline, gender and geographical region;
*Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment; FAS-I=all FAS patients who had at least one incontinence episode at baseline;
BL=baseline value; ER=extended release; NS=not significant;

Eur Urol. 2013 Feb;63(2):283-95.

# Urgency Urinary Incontinence

Mirabegron significantly reduced mean number of urgency urinary incontinence (UUI) episodes/24h (FAS-I)† from baseline to Final Visit (End of Treatment) compared with placebo

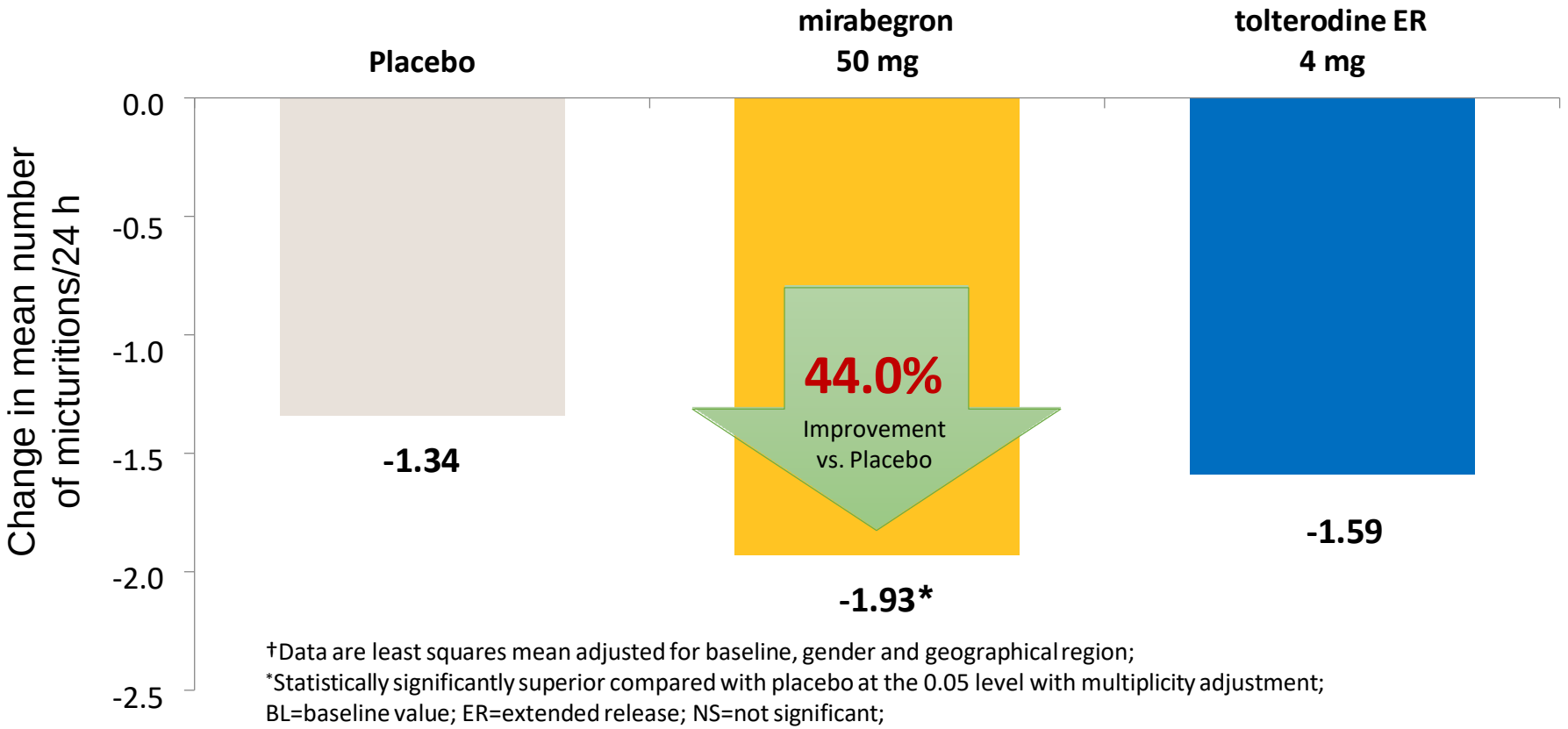



†Data are least squares mean adjusted for baseline, gender and geographical region; *Statistically significantly superior compared with placebo at the 0.05 level; FAS-I=all FAS patients who had at least one incontinence episode at baseline; FAS=full analysis set; NS=not significant; ER=extended release;

Eur Urol. 2013 Feb;63(2):283-95.

# Micturition Frequency

Mirabegron significantly reduced the mean number of micturitions/24h (FAS)† from baseline to Final Visit (End of Treatment) compared with placebo

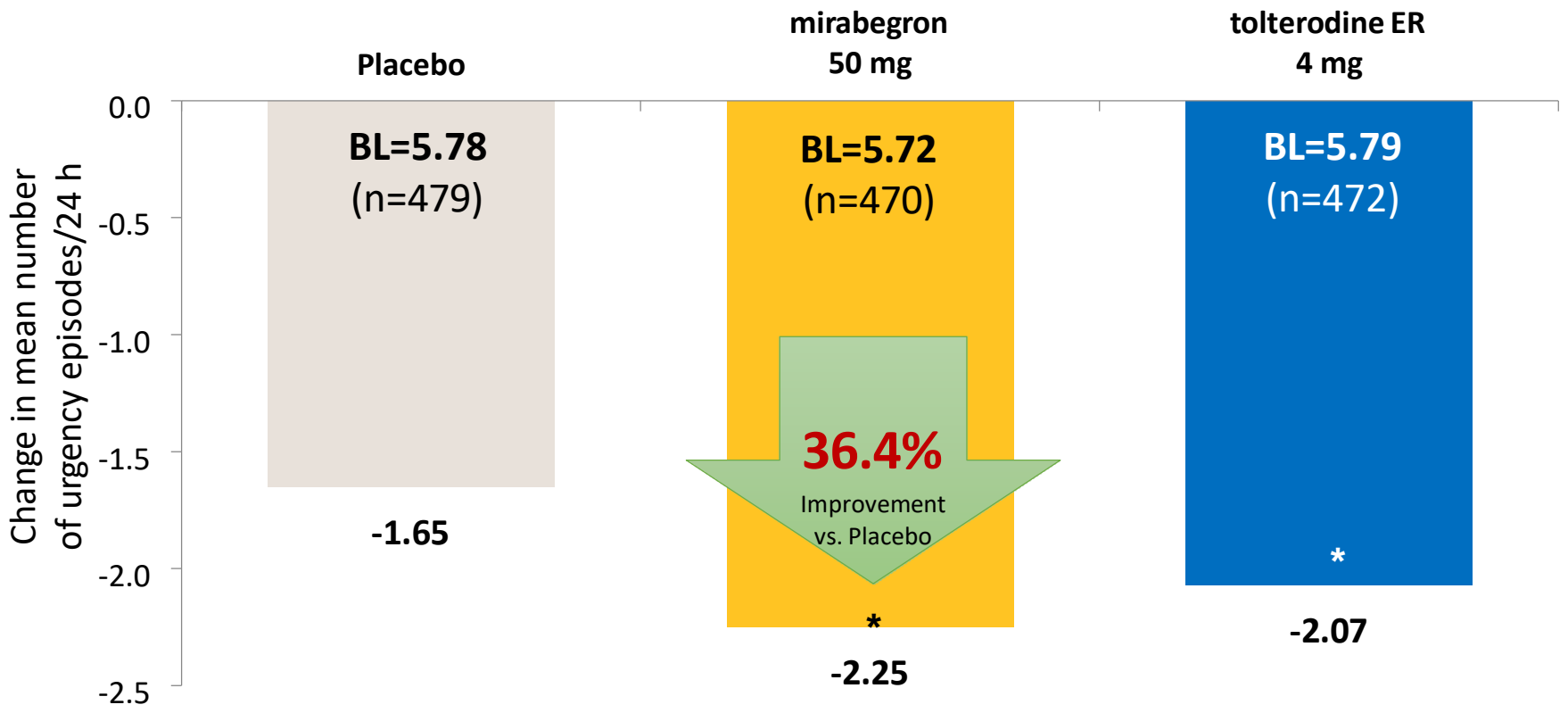



†Data are least squares mean adjusted for baseline, gender and geographical region;
*Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment;
BL=baseline value; ER=extended release; NS=not significant;

Eur Urol. 2013 Feb;63(2):283-95.

# Number of urgency episodes

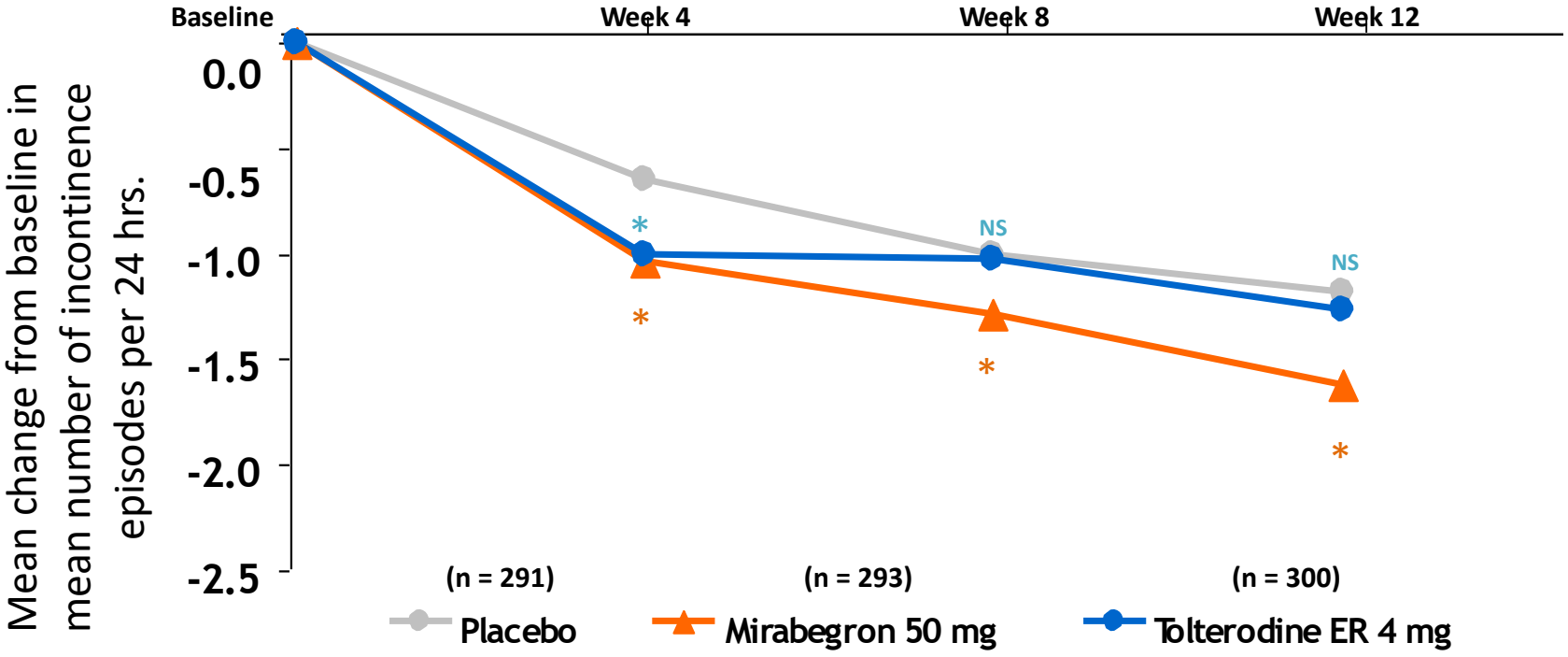
Mirabegron significantly reduced the mean number of urgency episodes (PPIUS grade 3 + 4) /24h (FAS)† from baseline at Final Visit compared with placebo




Eur Urol. 2013 Feb;63(2):283-95.

# The effect on incontinence episodes was sustained over 12 weeks

Mean change from baseline in incontinence episodes at each visit



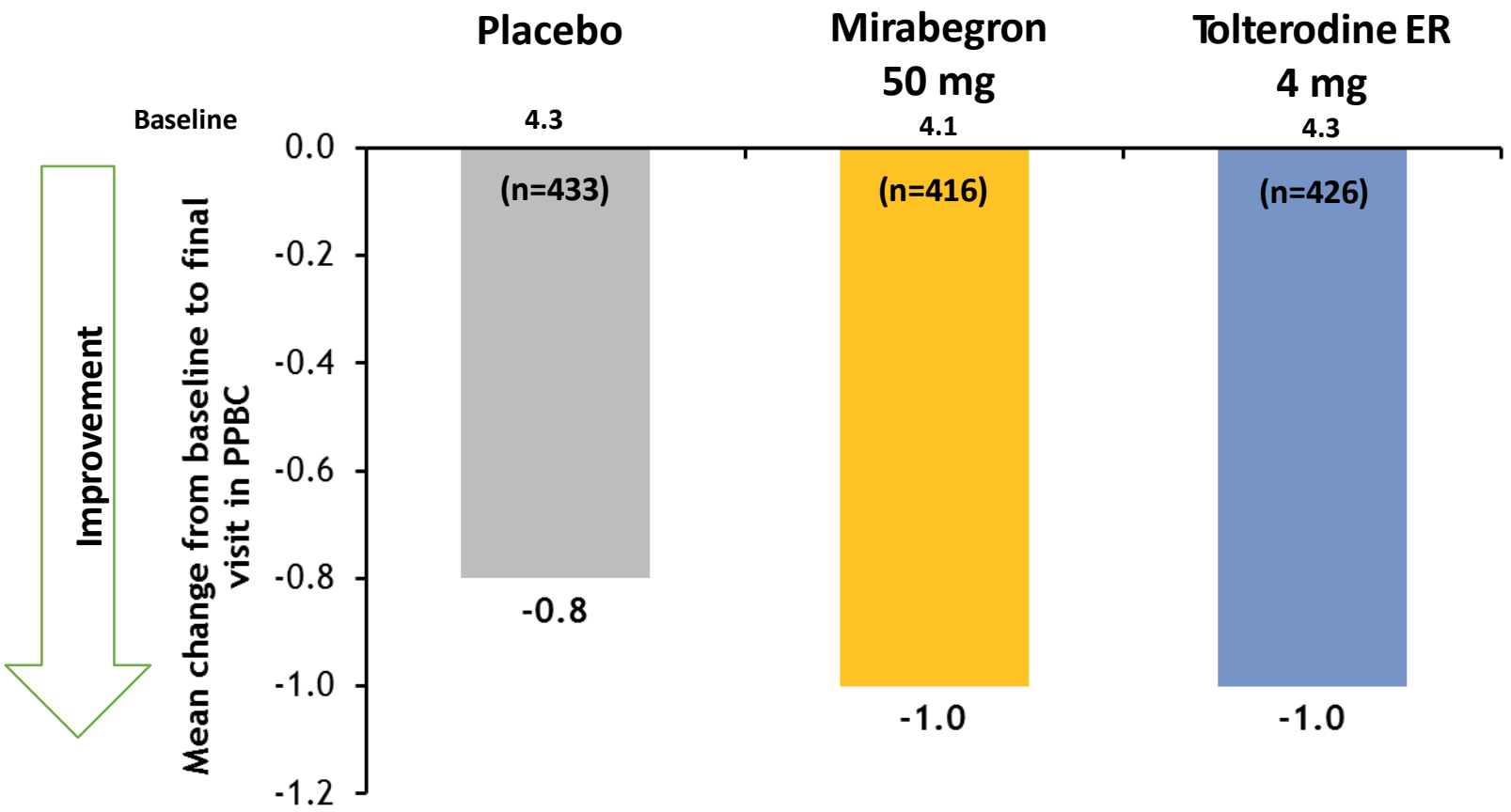

FAS Incontinence Set

NS, No statistically significant improvement versus placebo

*Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustments

Eur Urol. 2013 Feb;63(2):283-95.

# Mirabegron & PPBC




* Statistically significant improvement versus placebo at 0.05 level

Khullar V, et al. Efficacy and Tolerability of Mirabegron, a b3-Adrenoceptor Agonist, in Patients with Overactive Bladder: Results from a Randomised European–Australian Phase 3 Trial; Eur Urol (2013) 283–295

FAS, Full Analysis Set; PPBC, Patient Perception of Bladder Condition

# Treatment-emergent adverse events (SAF)

| | Placebo, N=442 | Mirabegron 25 mg, N=226 | Mirabegron 50 mg, N=219 | Mirabegron Total, N=445 |
|---|---|---|---|---|
| ≥1 TEAE[a] | 174 (39.4) | 100 (44.2) | 109 (49.8) | 209 (47.0) |
| Drug-related TEAEs | 57 (12.9) | 47 (20.8) | 37 (16.9) | 84 (18.9) |
| Serious TEAEs | 12 (2.7) | 7 (3.1) | 8 (3.7) | 15 (3.4) |
| Serious drug-related TEAEs | 2 (0.5) | 0 | 0 | 0 |
| TEAEs leading to discontinuation | 14 (3.2) | 8 (3.5) | 6 (2.7) | 14 (3.1) |
| Most frequent TEAEs[b] | | | | |
| Urinary tract infection[c] | 31 (7.0) | 16 (7.1) | 9 (4.1) | 25 (5.6) |
| Headache | 12 (2.7) | 15 (6.6) | 8 (3.7) | 23 (5.2) |
| Diarrhea | 6 (1.4) | 11 (4.9) | 2 (0.9) | 13 (2.9) |
| Fatigue | 14 (3.2) | 6 (2.7) | 4 (1.8) | 10 (2.2) |
| Upper respiratory tract infection | 10 (2.3) | 3 (1.3) | 7 (3.2) | 10 (2.2) |
| Nausea | 6 (1.4) | 7 (3.1) | 1 (0.5) | 8 (1.8) |
| Dizziness | 7 (1.6) | 1 (0.4) | 5 (2.3) | 6 (1.3) |
| Nasopharyngitis | 10 (2.3) | 3 (1.3) | 2 (0.9) | 5 (1.1) |

MedDRA version 20.1

a. Treatment-emergent adverse event (TEAE), an adverse event that started or worsened during the study period after first study medication dose.

b. Affecting ≥2% of any treatment group.

c. Escherichia urinary tract infection, streptococcal urinary tract infection, urinary tract infection, or urinary tract infection bacterial.

# What about the longer term?

# Similar demographic characteristics

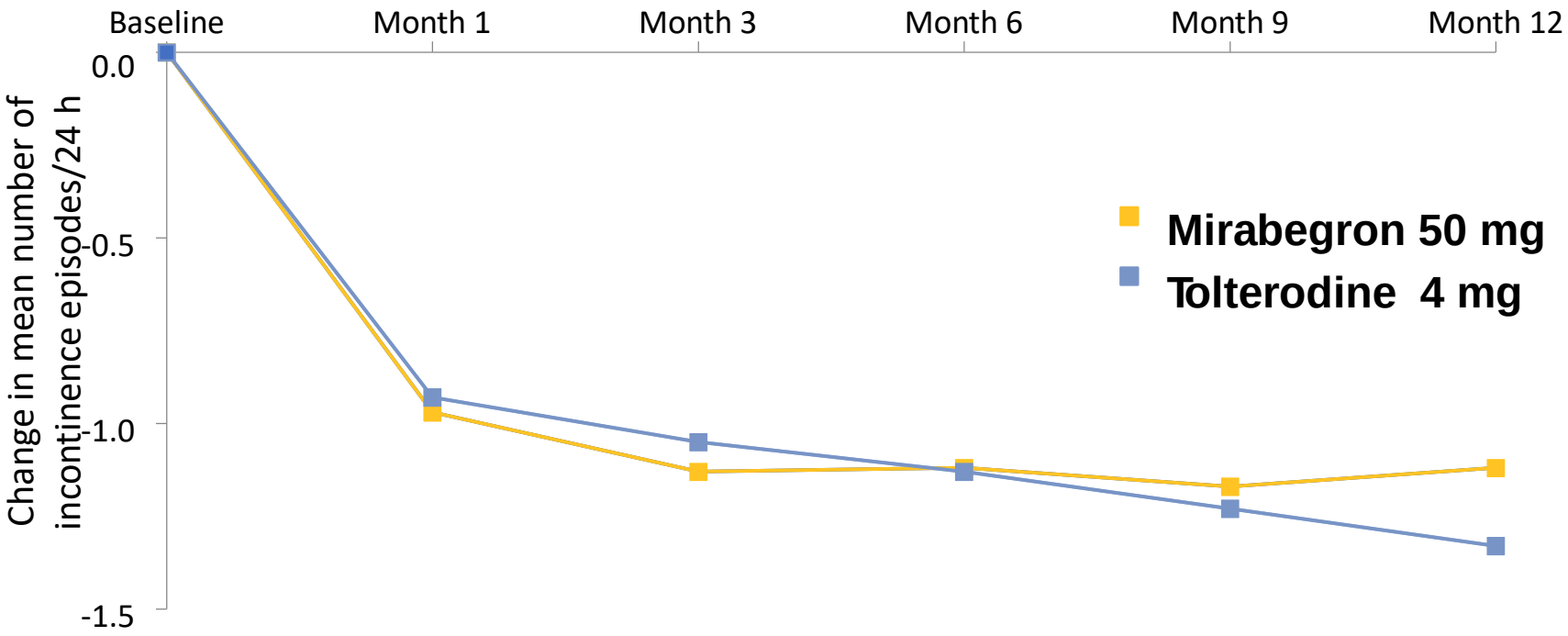
| Variable | Tolterodine ER 4 mg (n=812) | Mirabegron 50 mg (n=812) |
|---|---|---|
| **Male** | 212 (26.1%) | 210 (25.9%) |
| **Female** | 600 (73.9%) | 602 (74.1%) |
| **White** | 780 (96.1%) | 778 (95.8%) |
| **Age (mean)** | 59.6 | 59.2 |
| <65 years | 509 (62.7%) | 523 (64.4%) |
| <75 years | 729 (89.8%) | 737 (90.8%) |
| **Type of incontinence** | | |
| Urgency Incontinence | 317 (39.0%) | 296 (36.5%) |
| Mixed stress/urge incontinence | 210 (25.9%) | 232 (28.6%) |
| Frequency | 285 (35.1%) | 284 (35.0%) |
| **Used prior OAB drug, n (%)** | 447 (55.0%) | 446 (54.9%) |
| **OAB mean duration (months)** | 83.8 | 87.4 |

Safety Analysis Set (SAF) – all randomized patients who took ≥1 dose of double-blind study drug

Chapple CR, et al, Randomized Double-blind, Active-controlled Phase 3 Study to Assess 12-Month Safety and Efficacy of Mirabegron in OAB, Eur Urol 2013;63: 296-305.

# Sustained reduction in incontinence episodes

Mirabegron reduced the mean number of incontinence episodes/24h (FAS-I) from baseline to End of Treatment

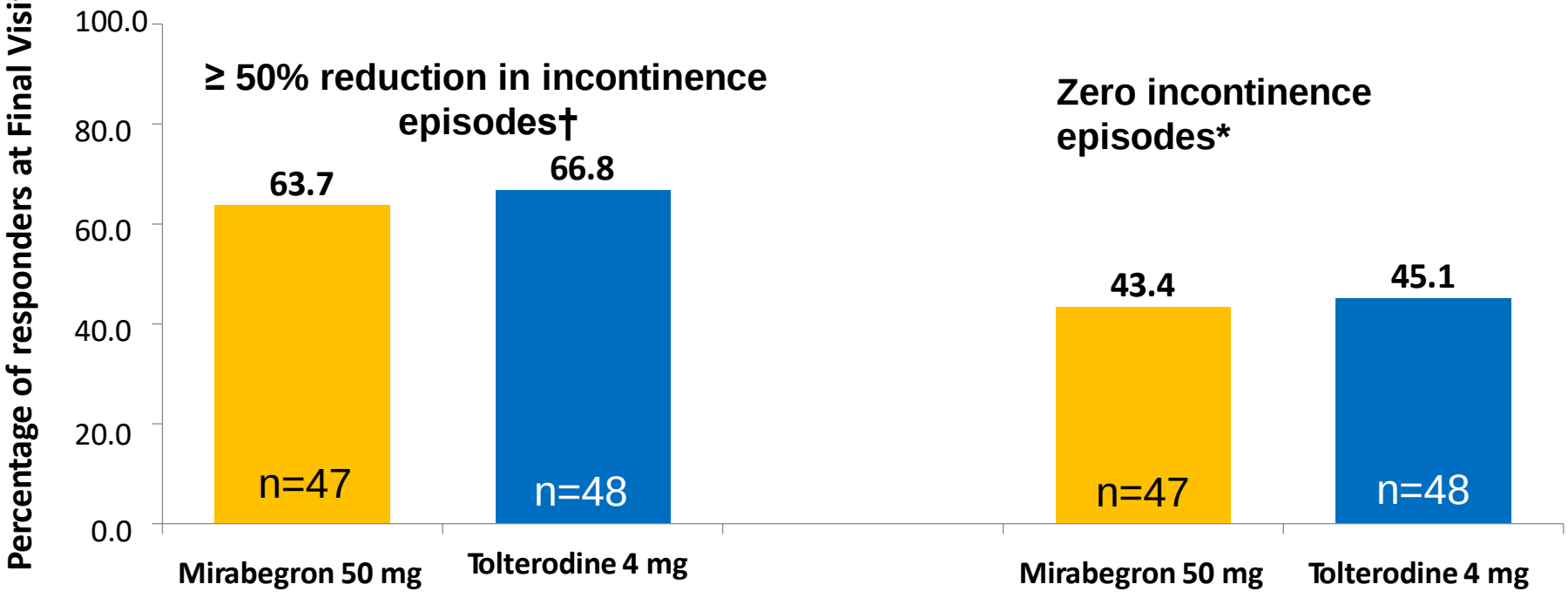



FAS-I=all FAS patients who had at least one incontinence episode at baseline;
No direct statistical comparisons of efficacy were made between treatment groups

Eur Urol 2013; 63: 296-305.

# Responder for zero incontinence episodes or ≥50% reduction in incontinence episodes

Mirabegron increased the number of responders experiencing zero incontinence episodes or a reduction in incontinence episodes (FAS-I) from baseline to Final Visit (End of Treatment)




*Responder defined as a subject who becomes continent during the treatment period;

† Responder defined as a subject with at least 50% decrease from baseline in mean number of incontinence episodes;

Eur Urol 2013; 63: 296-305.

# Overview of TEAEs

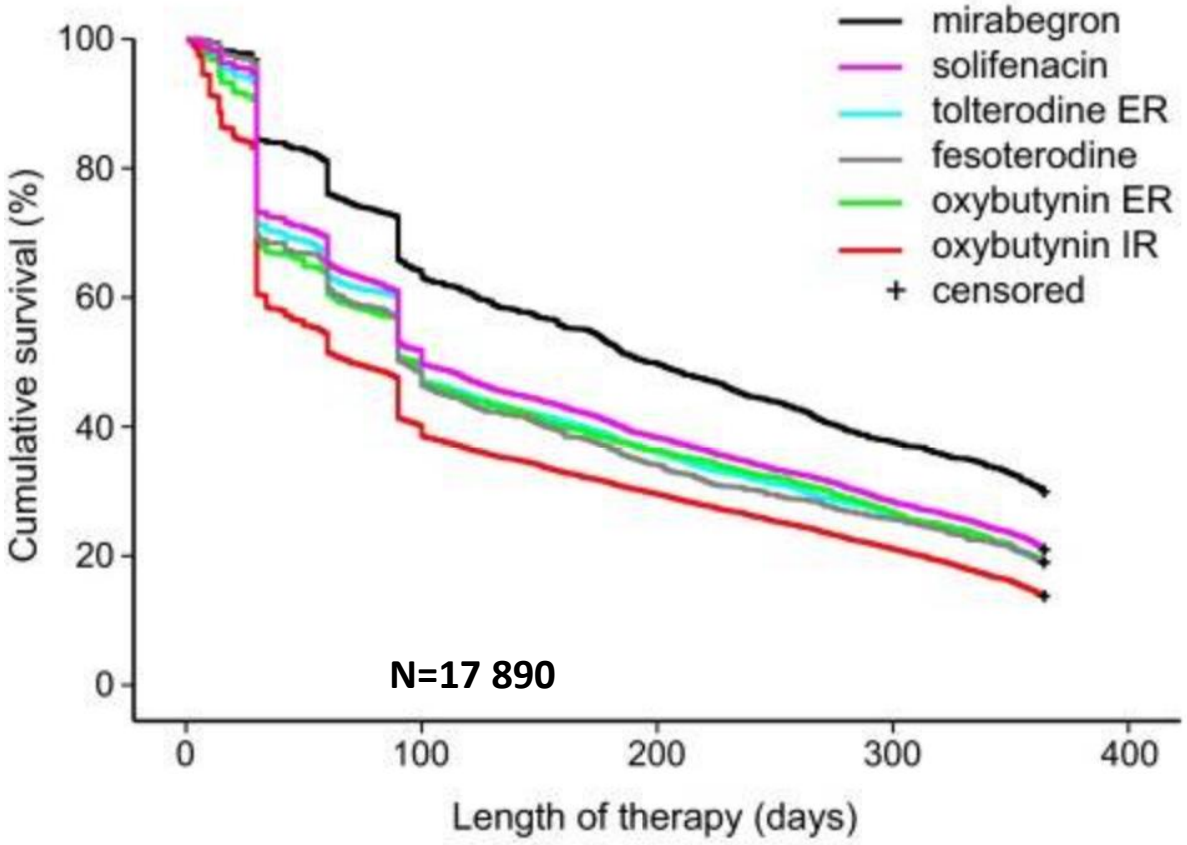
| Parameter | Tolterodine ER 4mg (n=812) n (%) | Mirabegron 50 mg (n=812) n (%) |
|---|---|---|
| **Adverse events (AEs)** | 508 (62.6%) | 485 (59.7%) |
| **Treatment-related AEs** | 224 (27.6%) | 213 (26.2%) |
| **AEs by severity†** | 251 (30.9%) | 222 (27.3%) |
| Mild | | |
| Moderate | 218 (26.8%) | 212 (26.1%) |
| Severe | 39 (4.8%) | 51 (6.3%) |
| **Deaths‡** | 2 (0.2%) | 2 (0.2%) |
| **Serious AEs** | 44 (5.4%) | 42 (5.2%) |
| **Treatment-related serious AEs** | 5 (0.6%) | 10 (1.2%) |
| **AEs leading to study drug discontinuation** | 46 (5.7%) | 48 (5.9%) |
| **Treatment-related AEs leading to study drug discontinuation** | 31 (3.8%) | 35 (4.3%) |

Safety Analysis Set (SAF) – all randomized patients who took ≥1 dose of double-blind study drug
† The number of patients shows maximum severity ('missing' is handled as most severe)
Patients with 1 or more adverse events within a level of the MedDRA term were counted only once in that level
‡ An additional (non-treatment-emergent) death occurred in 1 patient in the Betmiga™ 50 mg group
TEAE, treatment-emergent adverse event

Chapple CR, et al, Randomized Double-blind, Active-controlled Phase 3 Study to Assess 12-Month Safety and Efficacy of Mirabegron in OAB, Eur Urol 2013; 63: 296-305.

# Ensure persistence is optimized..

- Give realistic expectations, what and by when
- Deal with adverse events swiftly
- Counsel appropriately
- Be prepared to switch



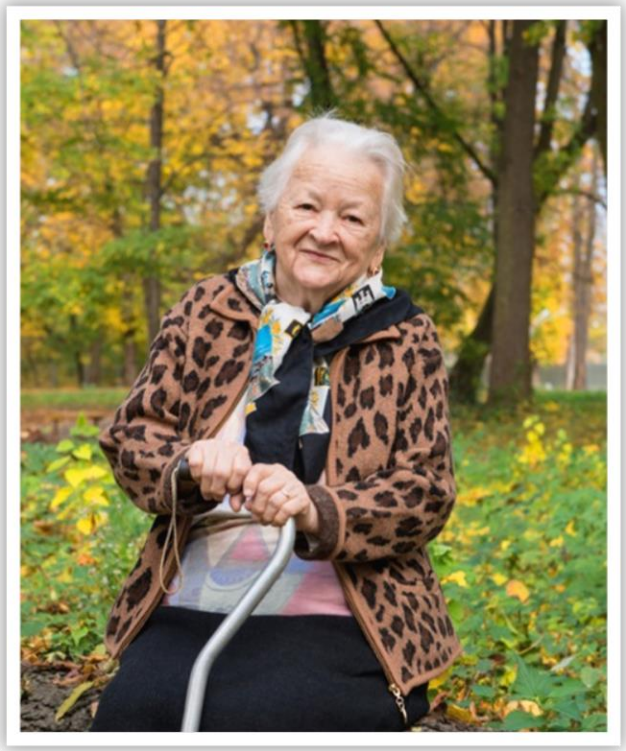

Expert Rev Pharmacoecon Outcomes Res. 2016 Aug;16(4):475-81
Can Urol Assoc J. 2015 Sep-Oct;9(9-10):343-50.

# In conclusion,

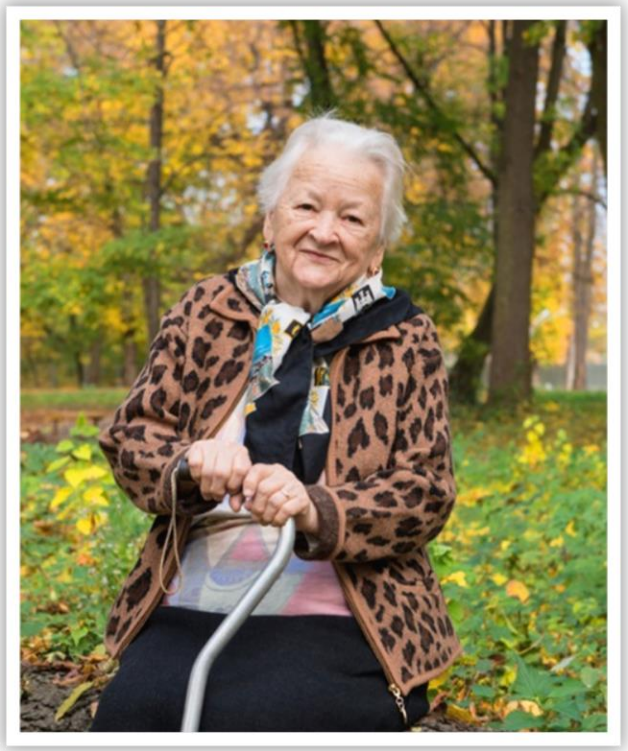
- Mirabegron is effective, tested in OAB dry and OAB wet
- Tolerability profile different from AM drugs
- Longer term efficacy proven
- Hypertension, nasopharyngitis and urinary tract infection were the most common TEAEs with mirabegron.
- Incidence of Major Adverse Cardiovascular Events was low and similar across treatment groups.

# Case Study 2: The Complex Patient

Elizabeth is 83 years old and has type 2 diabetes, hypertension, dyslipidemia, diabetic retinopathy, osteoarthritis, and a history of two episodes of delirium associated with acute illness



- OAB with UUI for >2 years
- **Medications**: metformin, sitagliptin, ramipril, amitriptyline, atorvastatin, low dose aspirin and acetaminophen
- OAB symptoms are troublesome for her, affect her quality of life
- She has become less mobile over the last few years



# Cognition

- Concerns contribute to the under-treatment of OAB in this patient group
- M1 and M2 muscarinic receptors are expressed in the prefrontal cortex and hippocampus, with roles for attention, executive function, and memory
- **Older individuals have added risks**:
  - increased permeability of the BBB
  - changes in hepatic and renal function
  - presence of comorbidities
  - concomitant drugs

*BJU Int.* **99,** 502–509 (2007)
*Int. J. Clin. Pract.* **64,** 1279–1286 (2010)..
*Neurourol. Urodyn.* **29,** 165–178 (2010).
*J. Am. Geriatr. Soc.* **56,** 1333–1341 (2008).

# Cognitive Side Effects

- Antimuscarinics vary in their effects.
- Differences in properties are important to consider, especially
  - interactions with the M1 receptors in the central nervous system
  - binding profiles
  - lipophilicity
  - ability to cross the blood brain barrier

*Int. J. Clin. Pract.* **64,** 1279–1286 (2010)
*Neurourol. Urodyn.* **29,** 165–178 (2010).

# Antimuscarinics and cognitive function (factors increasing susceptibility)

- ↑ BBB permeability
  - Age
  - Comorbidity
    - Diabetes
    - dementias
    - Multiple sclerosis
    - Hypertension, ischaemia
    - Parkinson's disease
- Neurological deficits
- Cognitive impairment
- Reduced density of muscarinic receptors
- Anticholinergic burden

Chancellor MB et al. *Drugs Aging.* 2012; 29(4): 259-73.

You know that the antimuscarinics that do not cross the blood brain barrier are less likely to cause cognitive effects.

Additionally, brain penetration is low for antimuscarinics that are P-gp substrates.

Which of these OAB agents are substrates for the permeability glycoprotein system?

A. trospium, oxybutynin, and darifenacin

B. oxybutynin, solifenacin, and tolterodine

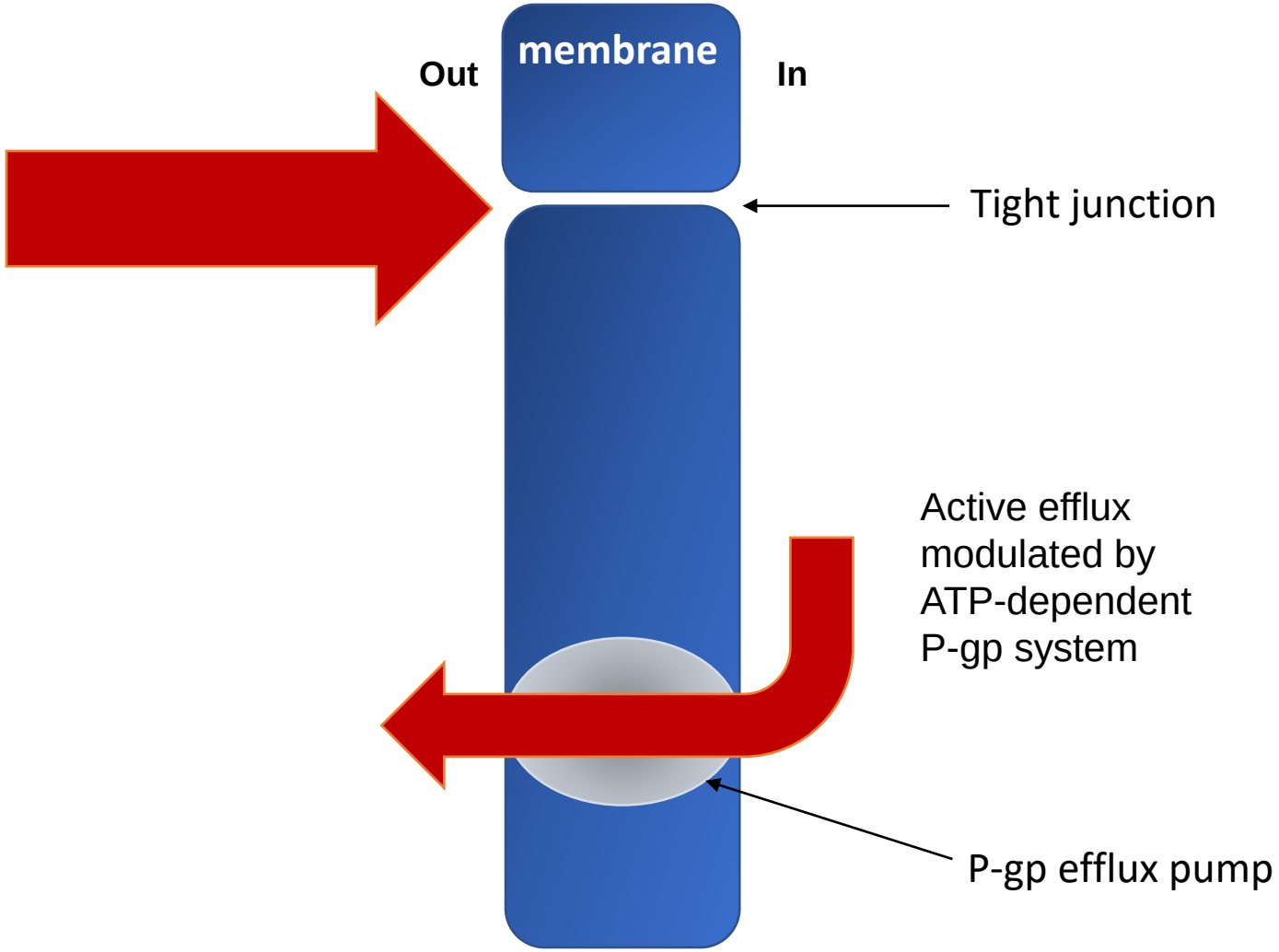
C. darifenacin, solifenacin, and tolterodine

D. 5-HMT (fesoterodine), darifenacin, and trospium

# BBB function in relation to antimuscarinics

Properties that
↓ passive diffusion:

- Large molecular size
- Polarity
- Low lipophilicity




Adapted from Chancellor MB et al. *Drugs Aging.* 2012; 29(4):259-73.

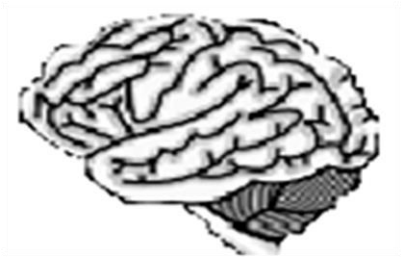
# Reported CNS AEs of antimuscarinics

| | Case Reports | Cognitive Testing | Significant CNS Penetration |
|---|---|---|---|
| Darifenacin | n/a | Yes | No |
| Fesoterodine | n/a | Yes | No |
| Oxybutynin | Yes (memory loss, neuropsychiatric AEs) | Yes | Yes |
| Solifenacin | n/a | Yes | Yes |
| Tolterodine | Yes (memory loss, hallucinations, confusion) | Yes | Yes |
| Trospium | n/a | Yes | No |

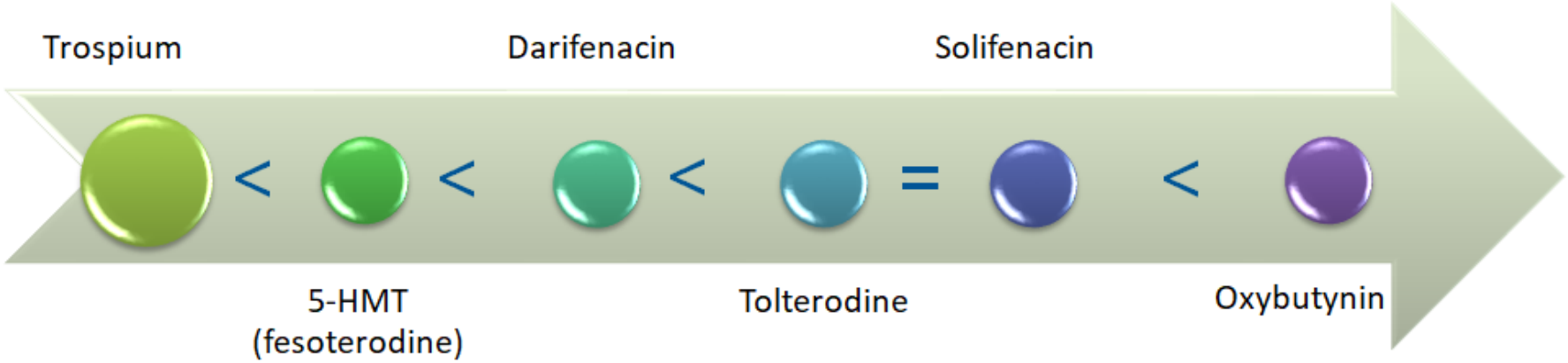
Adapted from Wagg A. *European Urological Review.* 2012; 7(1): 42-49.

# CNS penetration potential

Low Penetration



High Penetration




* Based on physicochemical properties, *in vitro* and *in vivo* CNS penetration, affinity for P-glycoprotein and clinical findings. Comparative clinical significance not fully established.

Callegari E et al. Br. J. Clin. Pharm. 2011;72: 235-246.

## Antimuscarinics and cognitive function

- Meta Analysis
  - 33 studies satisfied eligibility criteria:
    - Darifenacin (4)
    - Fesoterodine (3)
    - Oxybutynin (11)
    - Propiverine (2)
    - Solifenacin (3)
    - Tolterodine (12)
    - Trospium (3)

- **Summary**
  - Of all agents, oxybutynin is the most likely agent to affect cognition
  - Even low doses of oxybutynin could induce symptoms in vulnerable older adults

Paquette A et al. *J Am Geriatr Soc*. 2011;59: 1332-39.

# CNS monitoring with antimuscarinics

- MMSE lacks adequate sensitivity to change
- MoCA – not formally tested
- So; look for…
  - not thinking straight
  - behaving differently
  - more confused / clouded thinking
  - “Not quite him/herself”

# Prospectively gathered data on old (65+) and oldest old (75+)

## Darifenacin

**STUDY:**

n = 400, mean age 72 years randomized (2:1) to receive 12 weeks of double-blind treatment with darifenacin (7.5 mg once daily for 2 weeks, then optional titration to 15 mg daily) or placebo

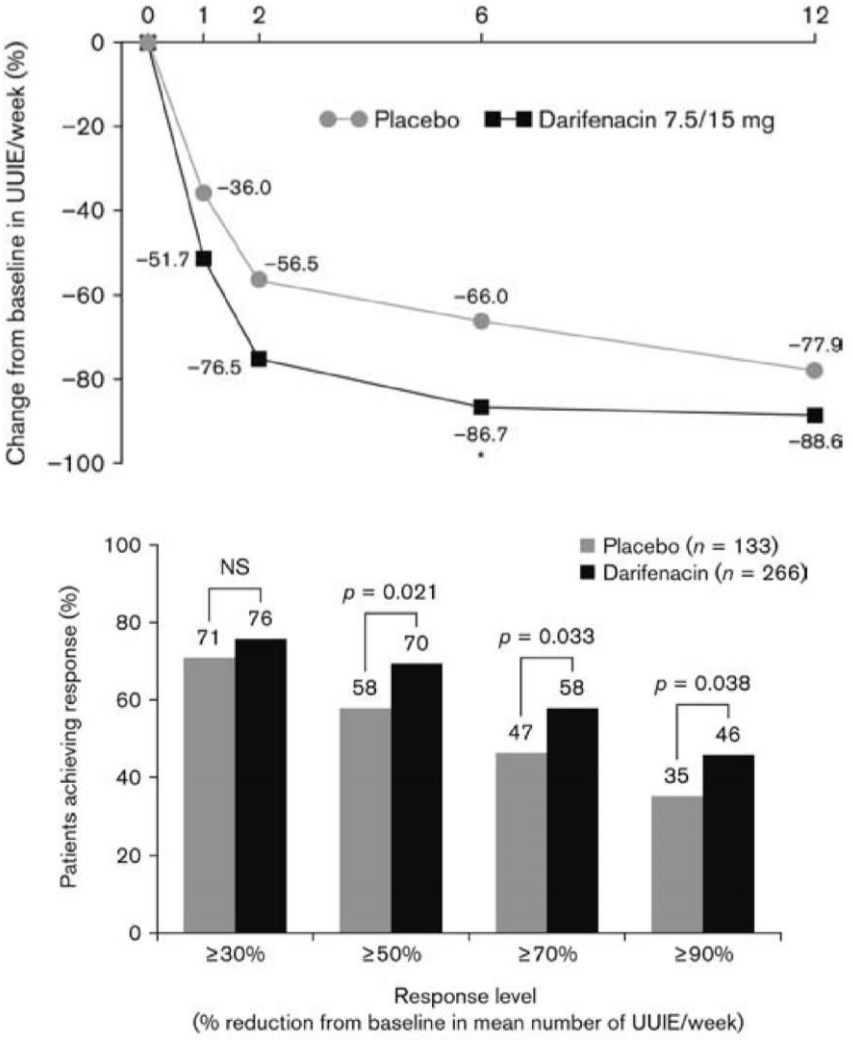
**AE:**

149 patients (56.0%) receiving darifenacin and 60 patients (45.1%) receiving placebo, of which 99 (37.2%) and 24 (18.0%) were considered to be related to the study drug, respectively

dry mouth – darifenacin 59 (22.2%), placebo 5 (3.8%) and constipation, darifenacin, 41 (15.4%) placebo, 11 (8.3%)

**PROM:**

Total OAB-q score treatment differences of 7.6 and 8.1 at Weeks 6 and 12, respectively in favour of darifenacin, $p < 0.001$ at both time points




Curr Med Res Opin. 2007 Oct;23(10):2347-58

# Prospectively gathered data on old (65+) and oldest old (75+)

## Fesoterodine

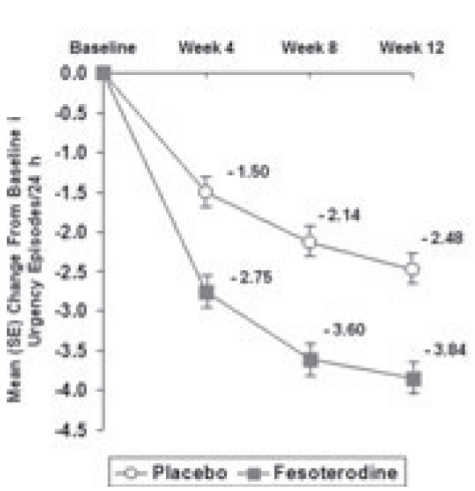
**STUDY:**

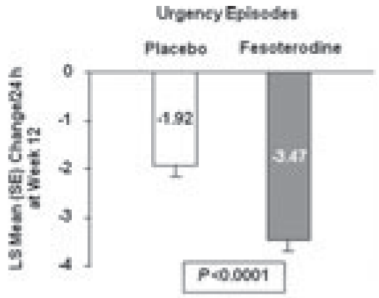
Fesoterodine or placebo for 12 weeks, with stratification according to age (>75 vs ≤75) and dosing time. Participants started on 4 mg and could increase to 8 mg at week 4 or 8 and de-escalate to 4 mg at week 8

**AE:**

Any AE – 36.1% placebo, 62.2% fesoterodine. Dry mouth fesoterodine 33.9%, placebo 5.3% (76% mild-moderate). No change in MMSE scores.

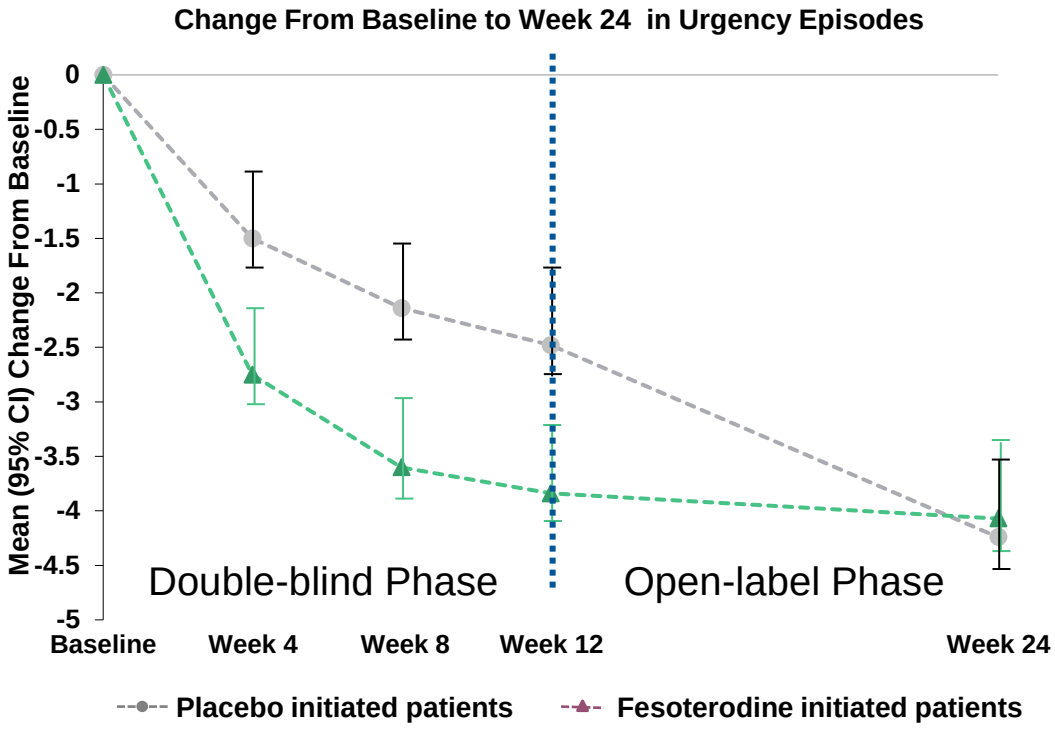
**PROM:**
The odds of response on the TBS, OAB-S, PPBC, and UPS were significantly greater in the fesoterodine group than placebo (P < .001 for TBS, OAB-S, and PPBC




J Am Geriatr Soc. 2013 Feb;61(2):185-93

# SOFIA: Fesoterodine
# Urgency Episodes *(Primary endpoint)*




- **By week 8, 64% of fesoterodine-treated participants opted for dose escalation.**
- **At week 12, all patients received fesoterodine**

Wagg et al. Neurourol Urodynam 2014;33:106–114.

# Prospectively gathered data on old (65+) and oldest old (75+)

## Fesoterodine in the vulnerable elderly

**STUDY:**

566 patients, mean age 75 (65-91) randomized 1:1 fesoterodine: placebo. All pts VES-13 >3. 50% of subjects in each group demonstrated significant levels of exhaustion and fatigue on the CES-D, 42% demonstrated impaired mobility on the TUG.

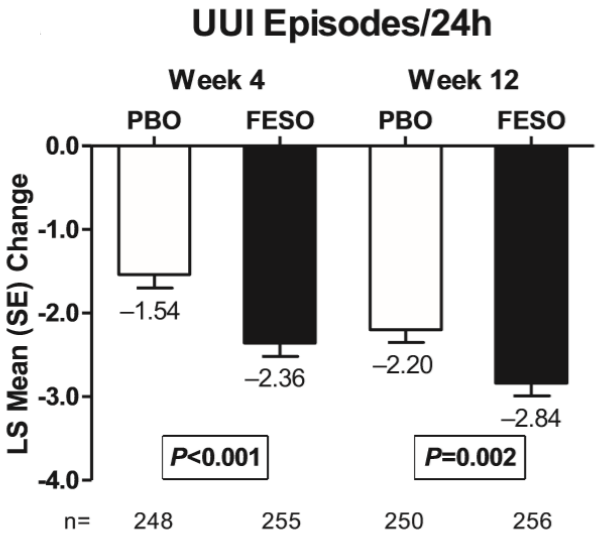
**AE:**

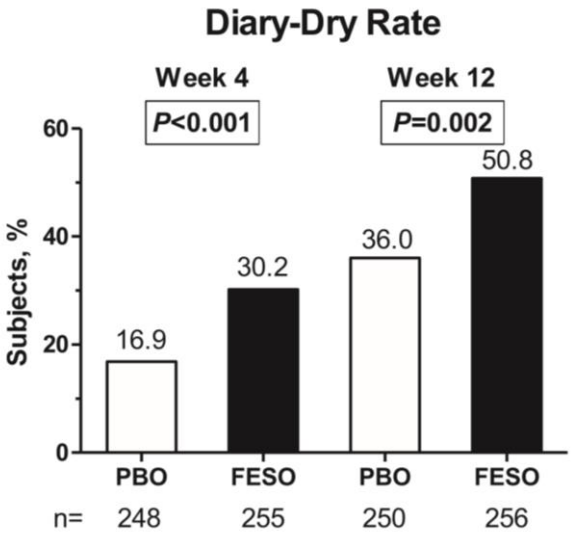
TEAE: placebo 42.7% fesoterodine 56.2%. Dry mouth, p:6.0% fesoterodine 23.5%, constipation, p: 4.3%, fesoterodine 11.1% urinary retention p: 0 fesoterodine 3.2% - 1/3 required catherization

No change in MMSE.

**PROM:**

12 week change in OAB symptom bother: placebo: -20.1(1.6), fesoterodine: -28.1 (1.6), p<0.005




J Urol 2014;191(2):395-404

# In the PILLAR study:

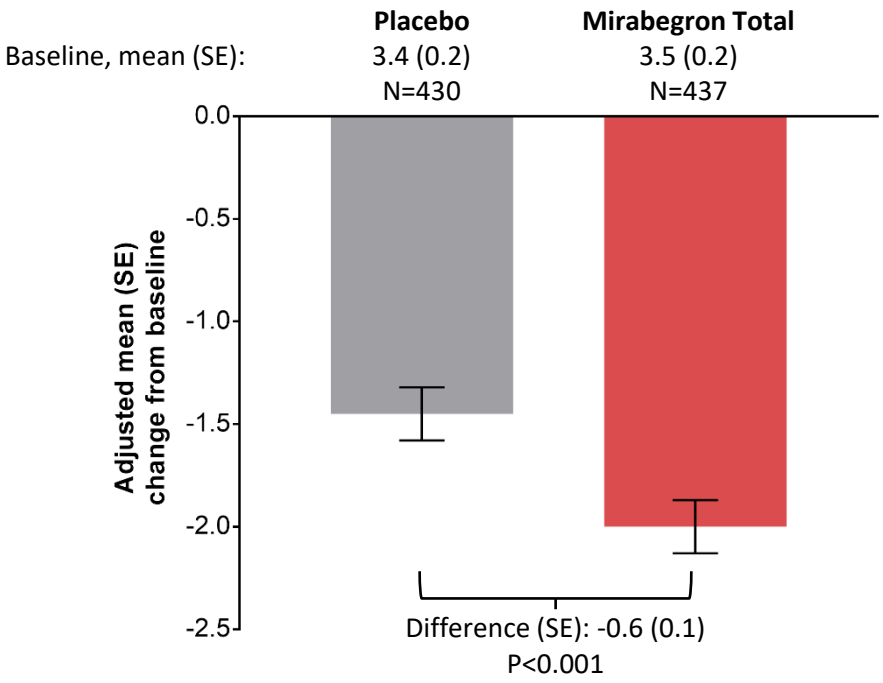
**No significant change in Montreal Cognitive Assessment score**

Mean (SD) score change from baseline to EOT:

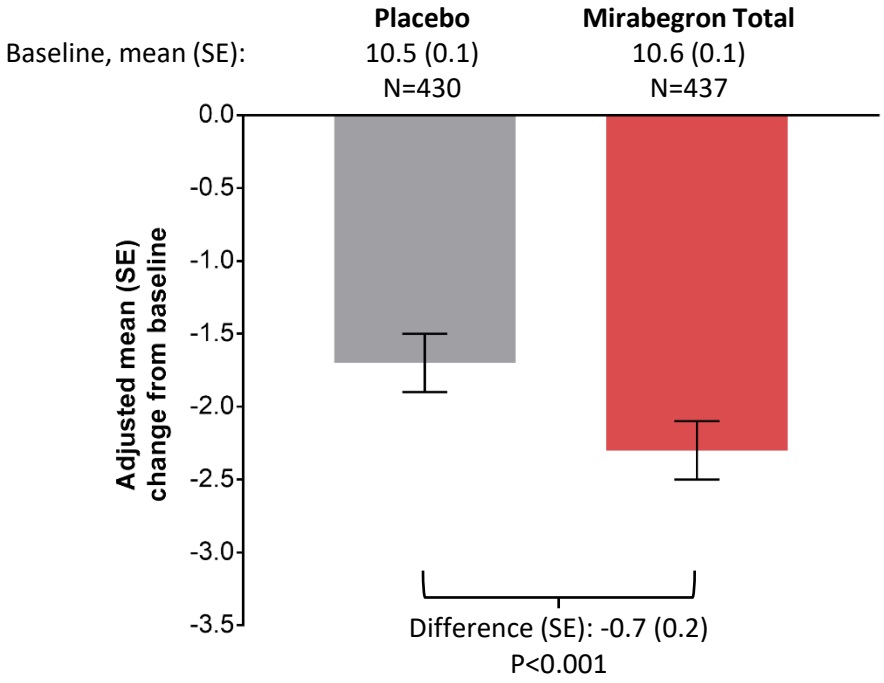
- Placebo: 0.2 (2.3)
- Mirabegron Total: 0.1 (2.4)

Wagg A, presented at ICS 2018

## Change in mean number of incontinence episodes/24 h from baseline to EOT




## Change in mean number of micturitions/24 h from baseline to EOT




## Number of patients with zero incontinence episodes at EOT:

Placebo: 30.4%  Mirabegron Total: 38.4%

OR (95% CI): 1.50 (1.09–2.06); P=0.012

Adjusted mean changes generated from ANCOVA models with treatment group, sex, age group (<75 or ≥75 years), and country as fixed factors and baseline value as a covariate.

ANCOVA, analysis of covariance; SE, standard error.

# Summary

- OAB is a troublesome condition for many, made worse by incontinence
- Diagnosis is easy with a good history
- No complicated investigations are needed
- Management, for the majority of adults, can be evidence informed
- There are effective pharmacological and conservative measures for the majority