NKR 33 Urininkontinens, PICO 10: Bør kvinder med urgency urininkontinens behandles med beta3-agonist frem for antimuskarinergika?

Review information

Authors

Sundhedsstyrelsen [1]

[1] [Empty affiliation]

Citation example: S. NKR 33 Urininkontinens, PICO 10: Bør kvinder med urgency urininkontinens behandles med beta3-agonist frem for antimuskarinergika? Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Contact person

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Dates

Assessed as Up-to-date:	
Date of Search:	
Next Stage Expected:	
Protocol First Published:	Not specified
Review First Published:	Not specified
Last Citation Issue:	Not specified

What's new

Date / Event	Description

History

Date / Event	Description

Characteristics of studies

Characteristics of included studies

Chapple 2013

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention ● *Age mean (sd)*: 59.2 (12.56) ● *Males n (%)*: 210 (25.9) ● *Type: Urge only n (%)*: 296 (36.5) ● *Type: Mixed incontinence n (%)*: 232 (28.6) ● *Type: without incontinence n (%)*: 284 (35.0) ● *Females n (%)*: 602 (74.1) Control ● *Age mean (sd)*: 59.2 (12.56) ● *Males n (%)*: 210 (25.9) ● *Type: Urge only n (%)*: 296 (36.5) ● *Type: Mixed incontinence n (%)*: 232 (28.6) ● *Type: without incontinence n (%)*: 284 (35.0) ● *Females n (%)*: 602 (74.1)

	Included criteria: Symptoms of OAB (urinary frequency and urgency with/without incontinence) for > 3moFrequency of micturition on average eight or more times per 24 h during the 3-d micturition diary periodThree or more episodes of urgency (grade 3 or 4) with/without incontinence during the 3-d micturition diary period **Excluded criteria:** Breastfeeding; pregnant; intending to become pregnant during the study; or of childbearing potential, sexuallyactive, and not practicing a highly reliable method of birth control. A pregnancy test (b-human chorionicgonadotropin in serum) at screening visit had to be negative in women of childbearing potentialClinically significant bladder outflow obstruction at risk of urinary retentionaSignificant stress incontinence or mixed stress/urge incontinence where stress was the predominant factoraAn indwelling catheter or practiced intermittent self-catheterizationDiabetic neuropathyEvidence of a symptomatic UTI, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvicradiation therapy, or previous or current malignant disease of the pelvic organsUncontrolled narrow-angle glaucoma, urinary or gastric retention, severe colitis ulcerosa, toxic megacolon,myasthenia gravis, or any other medical condition that contraindicated the use of anticholinergicsbCurrent nondrug treatment including electrostimulation therapy (a bladder training program or pelvic floorexercises that started>30 d prior to study entry was allowed to be continued)Use of medications intended to treat OABKnown/suspected hypersensitivity to tolterodine, other anticholinergics, mirabegron, otherb-AR agonists, or anyof the other inactive ingredientsAny clinically significant condition that made the patient unsuitable for the studybTreatment with any investigational drug within 30 d (90 d in the United Kingdom for all clinical studies except NCT00689104) prior to visit 1/screeningAverage total daily urine volume>3000 ml as recorded in the 3-d micturition diarySerum creatinine>150mmol/l, or AST or ALT more than two-fold the ULN range or GGT more than three-foldthe ULN, as assessed in screening samples and considered clinically significant in laboratory valuesbSevere hypertension (defined as a sitting average SBP180 mm Hg and/or average DBP110 mm Hg)HHAn abnormal ECG, which made the patient unsuitable for the studybComment: ALT = alanine aminotransferase; AR = adrenergic receptor; AST = aspartate aminotransferase; DBP = diastolic blood pressure; ECG = electrocardiogram;GGT =g-glutamyltransferase; OAB = overactive bladder; SBP = systolic blood pressure; ULN = upper limit of normal; UTI = urinary tract infection.aAs determined by the investigator.bIn the opinion of the investigator.Antihypertensive drugs were permitted, but dose increase was not permitted for loop diuretics
Interventions	**Intervention Characteristics** Intervention ● *Description*: oral mirabegron 50 mg once daily ● *Length of treatment (min 3 months)*: 12 months Control ● *Description*: tolterodine extended release (ER) 4 mg once daily

	● *Length of treatment (min 3 months)*: 12 months
Outcomes	*Inkontinensrelateret livskvalitet ved 3 mdr (incontence related QOL)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] *Antal bivirkninger, 3 mdr (Overall/any AE)* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] *Inkontinens episoder/døgn ved 3 mdr (Incontinence episodes/24hr)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] *Vandladninger/døgn ved 3 mdr (micturitions /24hr)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] *Frafald ved 3 mdr (drop out at 3 mths)* ● **Outcome type**: DichotomousOutcome ● **Measure names**: ["Final value"] *Alvorlige bivirkninger ved 3 mdr (Serious adverse events, 3 mths)* ● **Outcome type**: DichotomousOutcome ● **Measure names**: ["Final value"] *Patientoplevet effekt ved 3 mdr (Treatment benefit)* ● **Outcome type**: DichotomousOutcome ● **Measure names**: ["Baseline"] ● **Reporting**: Fully reported ● **Scale**: at least 50% decrease from baseline ● **Direction**: Higher is better *Antal urinvejsinfektioner 3 mdr (number of urinary tract infections)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"]

Mundtørhed, 3 mdr (Dry mouth)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Øjentørhed, 3 mdr. (eye disorder)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]
- **Reporting**: Not reported

Forstoppelse, 3 mdr. (Constipation el. obstipation)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Kvalme, 3 mdr (Nausea)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]
- **Reporting**: Not reported

Tachycardia EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Hypertension EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Atrial fibrillation EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Arrhytmia EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Diarrhea EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Cardiac disorders/ Cardiovascular TEAEs EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Eye disorders EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]
- **Reporting**: Fully reported

Livskvalitet EoT
- **Outcome type**: ContinuousOutcome
- **Measure names**: ["Change"]
- **Reporting**: Fully reported
- **Scale**: HRQL subscales of OABq
- **Range**: 0-100
- **Unit of measure**: Points
- **Direction**: Higher is better
- **Data value**: Change from baseline

Patientoplevet effekt EoT
- **Outcome type**: ContinuousOutcome
- **Measure names**: ["Change"]
- **Reporting**: Fully reported
- **Scale**: TS-VAS (Treatment Satisfaction VAS)
- **Range**: 0 - 10
- **Unit of measure**: Points
- **Direction**: Higher is better
- **Data value**: Change from baseline

Overactive bladder questionaire EoT
- **Outcome type**: ContinuousOutcome
- **Measure names**: ["Change"]
- **Reporting**: Fully reported
- **Scale**: OAB-q
- **Range**: Unclear

	● **Unit of measure**: Points ● **Direction**: Lower is better ● **Data value**: Change from baseline *Urinary tract infection EoT* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] *Antal tilfælde af inkontinens/ døgn EoT* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Change"] ● **Reporting**: Fully reported ● **Unit of measure**: Episodes ● **Direction**: Lower is better ● **Data value**: Change from baseline ● **Notes**: Subgroup of patients with incontinence *Vandladninger/døgn EoT* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Change"] ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Change from baseline
Identification	**Sponsorship source:** Christopher R.Chapple is a researcher and consultant for Astellas, Pfizer, Recordati, andOno, and a consultant for Lilly. David Mitcheson is a researcher andconsultant for Astellas Pharma and GlaxoSmithKline, and he is aresearcher for Eli Lilly, Schwartz Biosciences, ALZA, Ortho-McNeil,Plenaxia, Bayer, Pfizer, Solvay, Novartis, Sepracor, Indevus, DuraMed,Watson, Merck, Wyeth, Antares Pharma, Ferring Pharmaceuticals, VantiaTherapeutics, Johnson & Johnson, Bristol-Myers Squibb, Endo, Caris,Taris, Boehringer Ingelheim, and Sanofi-Aventis. The other authors have nothing to disclose.Funding/Support and role of the sponsor:Astellas Pharma helped designand conduct the study, and collect, manage, analyze, interpret, and review the data **Country:** Europe, US, Canada, South Africa and New Zealand **Setting:** Multinational, multicenter trial **Comments:** ClinicalTrials.gov identifier: NCT00688688https://clinicaltrials.gov/ct2/show/study/NCT00688688?sect=X01256

	Authors name: Chapple 2013 **Institution:** **Email:** **Address:**
Notes	*Allan Ryhammer* on 17/08/2015 16:34 **Select** Study regards safety and tolerability, not effect. Figures regarding effect are shown and include confidence intervals for several variables.Finde denne reference: Nitti V, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol. *Britta Tendal* on 28/08/2015 22:39 **Included** Der er mange data på clinical trial hjemmesiden https://clinicaltrials.gov/ct2/show/study/NCT00688688?sect=X01256 *Britta Tendal* on 28/08/2015 23:03 **Dichotomous Outcomes** SAE different numbers in publication and https://clinicaltrials.gov/ct2/show/study/NCT00688688?sect=X01256

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment	Unclear risk	Judgement Comment: Allocation not described
Sequence Generation	Low risk	Quote: "Eligible patients were randomized 1:1:1 using a computer-generated randomization scheme, prepared by Pierrel Research Europe (Essen, Germany), to receive oral mirabegron 50 mg or 100 mg, or tolterodine extended release (ER) 4 mg once daily for 12 mo."
Blinding of participants and personnel All outcomes	High risk	Quote: "Additionally, 81.3% of patients had been treated in prior phase 3 studies with mirabegron, tolterodine, or placebo, so they were not treatment naive." Quote: "The investigator, study site personnel, patients, and sponsor were blinded to treatment (including the medication received in prior trials)." Judgement Comment: From protocol: matching placebo tablets/capsules. Patients are likely to be aware

		of treatment due to earlier treatment with the same medication (like to recognize adverse events from treatments)
Blinding of participants and personnel Ikke påvirkbar	Unclear risk	
Blinding of outcome assessors All outcomes	Low risk	Quote: "blinded independent DSMB inspection of SAEs, discontinuation rates, overall AEs and TEAEs, clinical laboratory assessments, vital signs, and ECG readings concluded there were no relevant safety concerns during or at the end of the study across the treatment groups." Quote: "The investigator, study site personnel, patients, and sponsor were blinded to treatment (including the medication received in prior trials)."
Blinding of outcome assessors Ikke påvirkbar	Unclear risk	
Incomplete outcome data	High risk	Judgement Comment: mirabegron dropout=22.8%, tolterodine dropout%, high drop out rate.Imputation method not described.
Selective outcome reporting	Low risk	Judgement Comment: All study results posted on:https://clinicaltrials.gov/ct2/show/study/NCT00688688?sect=X01256
Other sources of bias	Low risk	Judgement Comment: No other apparent sources of bias

Chapple 2013a

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention ● *Age mean (sd)*: 56.9 (12.5) ● *Males n (%)*: 18 (10.8) ● *Type: Urge only n (%)*: 67 (40.1) ● *Type: Mixed incontinence n (%)*: 47 (28.1)

	● *Type: without incontinence n (%)*: 53 (31.7) ● *Females n (%)*: 149 (89.2) Control ● *Age mean (sd)*: 56.9 (12.5) ● *Males n (%)*: 18 (10.8) ● *Type: Urge only n (%)*: 67 (40.1) ● *Type: Mixed incontinence n (%)*: 47 (28.1) ● *Type: without incontinence n (%)*: 53 (31.7) ● *Females n (%)*: 149 (89.2) **Included criteria:** Women≥ 18 years of age experiencing symptoms of OAB for≥ 3 months with frequency of micturition on average≥ 8 times per 24 h and at least three episodes of urgency (grade 3 or 4) [11], with or without incontinence, during a 3-day micturition diary period at baseline. **Excluded criteria:** linicallysignificant bladder outflow obstruction; significant post-voidresidual (PVR) volume (>200 ml); incontinence where stresswas the predominant factor; indwelling catheters or intermit-tent self-catheterization; diabetic neuropathy; symptomaticurinary tract infection, interstitial cystitis, bladder stones, pre-vious pelvic radiation therapy or previous or current malignantdisease of the pelvic organs; contraindications for anticholi-nergics; nondrug treatment, including electro-stimulation ther-apy (although bladder training or pelvic floor exerciseprograms that had started more than 1 month prior to the startof the study could be continued); use of other urinary incon-tinence medications; known or suspected hypersensitivity totolterodine, other anticholinergics, mirabegron, lactose, or anyof the excipients; clinically significant cardiovascular (includ-ing ECG abnormalities) or cerebrovascular disease; or anyother condition making the patient unsuitable for the study (asdeemed by the investigator).
Interventions	**Intervention Characteristics** Intervention ● *Description*: 50 mg mirabegron once daily ● *Length of treatment (min 3 months)*: 12 wk Control ● *Description*: tolterodine ER 4 mg once daily ● *Length of treatment (min 3 months)*: 12 wk

Outcomes	*Inkontinensrelateret livskvalitet EoT (incontence related QOL)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] ● **Reporting**: Partially reported ● **Direction**: Lower is better ● **Data value**: Change from baseline *Antal bivirkninger EoT (Overall/any AE)* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Inkontinens episoder/døgn EoT (Incontinence episodes/24hr)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] ● **Reporting**: Partially reported ● **Direction**: Lower is better ● **Data value**: Change from baseline *Vandladninger/døgn EoT (micturitions /24hr)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] ● **Reporting**: Partially reported ● **Direction**: Lower is better ● **Data value**: Change from baseline *Frafald ved EoT (drop out)* ● **Outcome type**: DichotomousOutcome ● **Measure names**: ["Final value"] ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint

Alvorlige bivirkninger EoT (Serious adverse events)

- **Outcome type**: DichotomousOutcome
- **Measure names**: ["Final value"]
- **Reporting**: Fully reported
- **Direction**: Lower is better
- **Data value**: Endpoint

Patientoplevet effekt EoT (Treatment benefit)

- **Outcome type**: DichotomousOutcome
- **Measure names**: ["Baseline"]
- **Reporting**: Fully reported
- **Direction**: Higher is better
- **Data value**: Endpoint

Antal urinvejsinfektioner EoT (number of urinary tract infections)

- **Outcome type**: ContinuousOutcome
- **Measure names**: ["Final value", "Change"]
- **Reporting**: Not reported
- **Direction**: Lower is better
- **Data value**: Endpoint

Mundtørhed EoT (Dry mouth)

- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]
- **Reporting**: Fully reported
- **Direction**: Lower is better
- **Data value**: Endpoint

Øjentørhed EoT (eye disorder)

- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]
- **Reporting**: Fully reported
- **Direction**: Lower is better
- **Data value**: Endpoint

Forstoppelse EoT (Constipation el. obstipation)

- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]
- **Reporting**: Fully reported
- **Direction**: Lower is better
- **Data value**: Endpoint

Kvalme EoT (Nausea)

- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]
- **Reporting**: Fully reported
- **Direction**: Lower is better
- **Data value**: Endpoint

Tachycardia EoT

- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]
- **Reporting**: Fully reported
- **Direction**: Lower is better
- **Data value**: Endpoint

Hypertension EoT

- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Atrial fibrillation EoT

- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Arrhythmia EoT

- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Diarrhea EoT

- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Cardiac disorders/ Cardiovascular TEAEs EoT

	● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] *Eye disorders EoT* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] *Urinary tract infection EoT* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"]
Identification	**Sponsorship source:** ChristopherChapple's institution has received fees for his role as a consultant toAllergan, American Medical Systems, Astellas, Lilly, Pfizer, andRecordati. It has also received grants or has grants pending fromAllergan, American Medical Systems, Astellas, Pfizer, and Recordatiand has been reimbursed for lectures conducted by ChristopherChapple, including service on speakers' bureaus, by Allergan, Astellas,Pfizer, and Recordati, and support for the trial with regard to documentcompilation and author liaison by Astellas.Vladimir Dvorak's institution has received support for travel inregards to this study from Astellas.Pjotr Radziszewski has received fees for his role as a consultant toAstellas, Lilly, GSK, ONO, Pfizer, Studio PR, and OCI; has receivedgrants or has grants pending (as does his institute) from NCBiR; and hasreceived payment for lectures, including service on speakers' bureaus,from Astellas, GSK, Lilly, G-Pharma, and Ipsen.Philip Van Kerrebroeck has received payment for lectures, includingservice with speakers' bureaus, from Astellas, and serves on the board ofAstellas; in addition, his institution has received grants or has grantspending from Astellas.Jean Jacques Wyndaele's institution has received consulting fees orhonoraria and support for travel from UZA and payment for lectures andconsultancy from Astellas.Osamu Yamaguchi is a member of the Board of Astellas, is a consultantto Astellas, Pfizer, Hisamitsu, and Ferring, has received grants or hasgrants pending from Astellas, Kyorin, Ono, and Kissei, has been reimbursedfor lectures by Astellas, Kyorin, Kissei, and Ono, and for thedevelopment of educational presentations by Astellas and Kyorin.Brigitte Bosman, Peter Boerrigter, Arwin Ridder, Ted Drogendijk,and Ingrid Van Der Putten-Slob are employees of the study sponsor. **Country:** Multinational study incl: UK, Czech Republic, Poland, The Netherlands, Belgium, Japan. **Setting:** a multinational, multicenter trial sponsored by Astellas **Comments:** **Authors name:** Chapple CR **Institution:** **Email:** **Address:**

Notes	*Allan Ryhammer* on 17/08/2015 16:14 **Select** mixed study population (90% females, no subgroup analysis)large study, power calculation (however not regarding direct comparison between beta 3 and tolterodine), relevant variables included. No direct comparison between beta 3 and tolterodine, however no difference between each of the groups against tolterodine. *Ane Vind* on 21/08/2015 19:44 **Select** Jeg er enig med Allans kommentarer, men er i tvivl om det kan bruges når der ikke er en direkte sammenligning mellem de to? Inkluderer - så må metodedamen evt. på banen *Jens Aaboe* on 25/08/2015 21:11 **Study Design** Intervention: peroral beta3-agonist behandling i min. 3 månederControl: peroral antimuskurinergika i ækvieffektiv dosis i min. 3 måneder *Jens Aaboe* on 26/08/2015 18:01 **Dichotomous Outcomes** Treatment benefit (patientoplevet effekt) er angivet som antal procent der er respondere i hver gruppe. citat: A responder for treatment benefit was defined by an improvement of at least one category at a visit relative to baseline (i.e., the response changing from“no”to“yes, a little”;from“no”to“yes, very much”;orfrom“yes, a little”to“yes, very much”). *Jens Aaboe* on 26/08/2015 19:25 **Adverse Outcomes** Kardiovaskulære bivirkninger er defineret i PICO10 som takykardi og palpitationer, derfor er der medtaget data for Tachycardia hvis dette er angivet. Hvis både tachycardia og Cardiac Arrythmia er angivet er tachycardia data valgt. Hvis ikke tachycardia eller Cardiac Arrythmia er der medtaget data for cardiac disorder. *Jens Aaboe* on 26/08/2015 19:33 **Continuous Outcomes** sd ikke angivet i data.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment	Unclear risk	Judgement Comment: Method of concealment not described,
Sequence Generation	Unclear risk	Quote: "Patients were enrolled into a single-blind, 2-week placebo run-in period followed by a 12-week double-blind treatment period in which patients were randomized to receive one of the following: an OCAS formulation of mirabegron QD at a dose of 25, 50, 100 or 200 mg, placebo or tolterodine ER 4 mg QD." Judgement Comment: randomization not described
Blinding of participants and personnel All outcomes	Low risk	
Blinding of participants and personnel Ikke påvirkbar	Low risk	Judgement Comment: Double-blinded study.
Blinding of outcome assessors All outcomes	Low risk	
Blinding of outcome assessors Ikke påvirkbar	Low risk	Judgement Comment: Double-blinded study.
Incomplete outcome data	Low risk	Judgement Comment: 16/169 (MIRABEGRON) and 3/85
Selective outcome reporting	Low risk	Judgement Comment: according to protocol, none missing
Other sources of bias	Low risk	Judgement Comment: First author and several co-authors are funded personally by Astella (Mirabegron) and Pfizer (Tolterodine), and several coauthors are employees of the study sponsor.

Khullar 2013

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention ● *Age mean (sd)*: 59.1 (12.36) ● *Males n (%)*: 136 (27.6) ● *Type: Urge only n (%)*: 192 (40.6) ● *Type: Mixed incontinence n (%)*: 108 (22.8) ● *Type: without incontinence n (%)*: 173 (36.6) ● *Females n (%)*: 356 (72.4) Control ● *Age mean (sd)*: 59.1 (12.36) ● *Males n (%)*: 136 (27.6) ● *Type: Urge only n (%)*: 192 (40.6) ● *Type: Mixed incontinence n (%)*: 108 (22.8) ● *Type: without incontinence n (%)*: 173 (36.6) ● *Females n (%)*: 356 (72.4) **Included criteria:** Subject is willing and able to complete the micturition diary and questionnaires correctlySubject has symptoms of overactive bladder (urinary frequency and urgency with or without urge incontinence) for ≥ 3 monthsSubject experiences frequency of micturition on average ≥ 8 times per 24-hour period during the 3-day micturition diary periodSubject must experience at least 3 episodes of urgency (grade 3 or 4) with or without incontinence, during the 3-day micturition diary period **Excluded criteria:** Subject is breastfeeding, pregnant, intends to become pregnant during the study, or of childbearing potential, sexually active and not practicing a highly reliable method of birth controlSubject has significant stress incontinence or mixed stress/urge incontinence where stress is the predominant factorSubject has an indwelling catheter or practices intermittent self-catheterizationSubject has diabetic neuropathySubject has evidence of a symptomatic urinary tract infection, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organsSubject receives non-drug treatment including

	electro-stimulation therapySubject has severe hypertensionSubject has a known or suspected hypersensitivity to tolterodine, other anticholinergics, YM178, other beta-adrenoreceptor (ß-AR) agonists, or lactose or any of the other inactive ingredientsSubject has been treated with any investigational drug or device within 30 days (90 days in the UK)Subject had an average total daily urine volume > 3000 mL as recorded in the 3-day micturition diary periodSubject has serum creatinine >150 umol/L, aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2x upper limit of normal range (ULN), or gamma glutamyl transferase (γ-GT) > 3x ULNSubject has a clinically significant abnormal electrocardiogram (ECG)
Interventions	**Intervention Characteristics** Intervention ● *Description*: mirabegron 50 mg orally once daily ● *Length of treatment (min 3 months)*: 12 weeks Control ● *Description*: tolterodine ER 4 mg orally once daily ● *Length of treatment (min 3 months)*: 12 weeks
Outcomes	*Inkontinensrelateret livskvalitet ved 3 mdr (incontence related QOL)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] *Antal bivirkninger, 3 mdr (Overall/any AE)* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] *Inkontinens episoder/døgn ved 3 mdr (Incontinence episodes/24hr)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] *Vandladninger/døgn ved 3 mdr (micturitions /24hr)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] *Frafald ved 3 mdr (drop out at 3 mths)* ● **Outcome type**: DichotomousOutcome ● **Measure names**: ["Final value"]

Alvorlige bivirkninger ved 3 mdr (Serious adverse events, 3 mths)
- **Outcome type**: DichotomousOutcome
- **Measure names**: ["Final value"]

Patientoplevet effekt ved 3 mdr (Treatment benefit)
- **Outcome type**: DichotomousOutcome
- **Measure names**: ["Baseline"]
- **Reporting**: Fully reported
- **Scale**: at least 50% decrease from baseline
- **Direction**: Higher is better

Antal urinvejsinfektioner 3 mdr (number of urinary tract infections)
- **Outcome type**: ContinuousOutcome
- **Measure names**: ["Final value", "Change"]

Mundtørhed, 3 mdr (Dry mouth)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Øjentørhed, 3 mdr. (eye disorder)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Forstoppelse, 3 mdr. (Constipation el. obstipation)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Kvalme, 3 mdr (Nausea)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Kardiovaskulære bivirkninger, 3 mdr (Tachycardia, 3 mths)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Hypertension EoT
- **Outcome type**: AdverseEvent

- **Measure names**: ["End of treatment"]

Atrial fibrillation EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Arrhythmia EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Diarrhea EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Cardiac disorders/ Cardiovascular TEAEs EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Eye disorders EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Livskvalitet EoT
- **Outcome type**: ContinuousOutcome
- **Measure names**: ["Change"]
- **Reporting**: Fully reported
- **Scale**: HRQoL subscale OABq
- **Range**: 0 - 100
- **Unit of measure**: Points
- **Direction**: Higher is better
- **Data value**: Change from baseline

Inkontinens/døgn
- **Outcome type**: ContinuousOutcome
- **Measure names**: ["Change"]
- **Reporting**: Fully reported
- **Unit of measure**: Episoder

	● **Direction**: Lower is better *Vandladninger/døgn* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Change"] ● **Reporting**: Fully reported ● **Unit of measure**: Ladninger ● **Direction**: Lower is better ● **Data value**: Change from baseline *TS-VAS* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Change"] ● **Reporting**: Fully reported ● **Scale**: Treatment satisfaction VAS ● **Range**: 0 - 10 ● **Unit of measure**: points ● **Direction**: Higher is better ● **Data value**: Change from baseline
Identification	**Sponsorship source:** Astellas Pharma GlobalDevelopment sponsored this study and was involved in the design,implementation, data analysis and interpretation, and report drafting andrevision.Allauthorswereresponsibleforthedecisiontosubmitthisreportfor publication and had complete access to the study data upon request **Country:** **Setting:** Multinational, multicenter trial **Comments:** This study isregisteredatClinicalTrials.gov,identifier NCT00689104 **Authors name:** Khullar 2013 **Institution:** **Email:** **Address:**

Notes	*Allan Ryhammer* on 17/08/2015 16:50 **Select** Mixed popolation (75% females), but no subgroup analysis. Also including patients with mixed incontinence.No direct comparison between beta 3 and tolterodineFindOhlstein EH, von Keitz A, Michel MC. A multicenter, double- blind, randomized, placebo-controlled trial of the b3-adrenoceptor agonist solabegron for overactive bladder. Eur Urol 2012;62: 834–40. *Allan Ryhammer* on 17/08/2015 16:50 **Select** Mixed popolation (75% females), but no subgroup analysis. Also including patients with mixed incontinence.No direct comparison between beta 3 and tolterodineFindOhlstein EH, von Keitz A, Michel MC. A multicenter, double- blind, randomized, placebo-controlled trial of the b3-adrenoceptor agonist solabegron for overactive bladder. Eur Urol 2012;62: 834–40. *Allan Ryhammer* on 17/08/2015 16:50 **Select** Mixed popolation (75% females), but no subgroup analysis. Also including patients with mixed incontinence.No direct comparison between beta 3 and tolterodineFindOhlstein EH, von Keitz A, Michel MC. A multicenter, double- blind, randomized, placebo-controlled trial of the b3-adrenoceptor agonist solabegron for overactive bladder. Eur Urol 2012;62: 834–40. *Allan Ryhammer* on 17/08/2015 16:50 **Select** Mixed popolation (75% females), but no subgroup analysis. Also including patients with mixed incontinence.No direct comparison between beta 3 and tolterodineFindOhlstein EH, von Keitz A, Michel MC. A multicenter, double- blind, randomized, placebo-controlled trial of the b3-adrenoceptor agonist solabegron for overactive bladder. Eur Urol 2012;62: 834–40. *Allan Ryhammer* on 17/08/2015 16:50 **Select** Mixed popolation (75% females), but no subgroup analysis. Also including patients with mixed incontinence.No direct comparison between beta 3 and tolterodineFindOhlstein EH, von Keitz A, Michel MC. A multicenter, double- blind, randomized, placebo-controlled trial of the b3-adrenoceptor agonist solabegron for overactive bladder. Eur Urol 2012;62:

	834–40.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment	Low risk	Quote: "Randomisation was accomplished using a computer-generated rando- misation scheme prepared by Pierrel Research Europe GmbH (Essen, Germany) with stratification by country; allocation to treatment groups at each site was accomplished via an interactive response system."
Sequence Generation	Low risk	
Blinding of participants and personnel All outcomes	Low risk	
Blinding of participants and personnel Ikke påvirkbar	Unclear risk	
Blinding of outcome assessors All outcomes	Low risk	
Blinding of outcome assessors Ikke påvirkbar	Unclear risk	
Incomplete outcome data	Low risk	
Selective outcome reporting	Low risk	Judgement Comment: All results reported on https://clinicaltrials.gov/ct2/show/study/NCT00689104?sect=X4356
Other sources of bias	Low risk	Judgement Comment: None detected

Kuo 2015

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention ● *Age mean (sd)*: 59 (15.1) ● *Males n (%)*: 38.2% ● *Type: Urge only n (%)*: 40 (52.6) ● *Type: Mixed incontinence n (%)*: 19 (25) ● *Type: without incontinence n (%)*: 17 (22.4) ● *Females n (%)*: 47 (61.8) Control ● *Age mean (sd)*: 59 (15.1) ● *Males n (%)*: 38.2% ● *Type: Urge only n (%)*: 40 (52.6) ● *Type: Mixed incontinence n (%)*: 19 (25) ● *Type: without incontinence n (%)*: 17 (22.4) ● *Females n (%)*: 47 (61.8) **Included criteria:** 1.Symptoms of overactive bladder for at least 12 weeks before initiation of therun-in period;2. An average of8 micturitions/24 hours; and3. An average of1 episode of urgency or urgency incontinence/24 hours,during a 3-day micturition diary period **Excluded criteria:** 1. Stress urinary incontinence as a predominant symptom at screening;2. Urinary tract infection, urinary stone, interstitial cystitis, or a history of recurrent urinary tract infection;3. Confirmed postvoid residual volume of100 mL or a clinically significantlower urinary tract obstructive disease;4. An average total daily urine volume3000 mL (as recorded in a 3-dayvoiding diary period);5. Uncontrolled hypertension (sitting systolic blood pressure180 mmHg ordiastolic blood pressure110 mmHg);6. Pulse rate 110 beats per minute (bpm) or<50 bpm; and7. Patient has indwelling catheter or practices intermittent self-catheterization

Interventions	**Intervention Characteristics** Intervention ● *Description*: oral mirabegron 50 mg once daily ● *Length of treatment (min 3 months)*: 12 weeks Control ● *Description*: oral tolterodine ER 4 mg once daily ● *Length of treatment (min 3 months)*: 12 weeks
Outcomes	*Inkontinensrelateret livskvalitet EoT (incontence related QOL)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] ● **Reporting**: Fully reported ● **Scale**: King's Health Questionaire. Incontinence Impact domain ● **Range**: Unclear ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Change from baseline *Antal bivirkninger EoT (Overall/any AE)* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] *Inkontinens episoder/døgn EoT (Incontinence episodes/24hr)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] *Vandladninger/døgn EoT (micturitions /24hr)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Final value", "Change"] *Frafald ved EoT (drop out)* ● **Outcome type**: DichotomousOutcome ● **Measure names**: ["Final value"] *Alvorlige bivirkninger EoT (Serious adverse events)*

- **Outcome type**: DichotomousOutcome
- **Measure names**: ["Final value"]

Patientoplevet effekt EoT (Treatment benefit)
- **Outcome type**: DichotomousOutcome
- **Measure names**: ["Baseline"]
- **Reporting**: Not reported

Antal urinvejsinfektioner EoT (number of urinary tract infections)
- **Outcome type**: ContinuousOutcome
- **Measure names**: ["Final value", "Change"]
- **Reporting**: Not reported

Mundtørhed EoT (Dry mouth)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Øjentørhed EoT (eye disorder)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Forstoppelse EoT (Constipation el. obstipation)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Kvalme EoT (Nausea)
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Tachycardia EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

Hypertension EoT
- **Outcome type**: AdverseEvent
- **Measure names**: ["End of treatment"]

	Atrial fibrillation EoT ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] *Arrhythmia EoT* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] *Diarrhea EoT* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] *Cardiac disorders/ Cardiovascular TEAEs EoT* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] *Eye disorders EoT* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"] *Urinary tract infection EoT* ● **Outcome type**: AdverseEvent ● **Measure names**: ["End of treatment"]
Identification	**Sponsorship source:** This study was an analysis of the Taiwanese data in the Asian Mirabegron Trial. Although Astellas sponsored the Asian Mirabegron Trial,Astellas did not have any input on any aspect of the study. We declare that we have no conflicts of interest with Astellas in relation to thiswork. **Country:** Taiwan **Setting:** **Comments:** The study is part of an Asian trial also involving sites in China, Korea and India. They state they have enrolled 1126 people. Obs more publications on this study coming up? **Authors name:** Kuo 2015 **Institution:** **Email:** **Address:**

Notes	*Allan Ryhammer* on 17/08/2015 15:58 **Select** small study, addresses questions included in PICO 10, but no direct statistical comparison between Beta 3 and anticholinergic treatment (Detrusitol)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment	Low risk	Quote: "During the placebo run-in period, patients were blinded to the identity of the study drug, and during the double- blind treatment, both patients and investigators were blinded to the identity of the randomized drug assignment." Judgement Comment: Details on how blinding of drug assignment are missing, but blinding seems reasonable
Sequence Generation	Low risk	Quote: "After having fulfilled all selection criteria at the end of the placebo run-in period (Visit 2), patients were randomized to one of the three treatment groups in a 1:1:1 ratio to receive placebo, mirabegron (50 mg), or tolterodine ER (4 mg) orally once daily for 12 weeks, using a computer-generated randomization list."
Blinding of participants and personnel All outcomes	Low risk	Judgement Comment: Both patients and investigators were blinded
Blinding of participants and personnel Ikke påvirkbar	Unclear risk	
Blinding of outcome assessors All outcomes	Low risk	Quote: "During the placebo run-in period, patients were blinded to the identity of the study drug, and during the double- blind treatment, both patients and investigators were blinded to the identity of the randomized drug assignment."
Blinding of outcome assessors Ikke påvirkbar	Unclear risk	

Incomplete outcome data	Low risk	Judgement Comment: Missing outcome data balanced in numbers across groups with similar reasons for missing data.
Selective outcome reporting	Unclear risk	Judgement Comment: he study protocol is available and all the study´s prespecified outcomes have been reported. Part of multicenter, but so far only this site has published results
Other sources of bias	Low risk	Judgement Comment: No other apparent sources of bias

Yamaguchi 2014

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention beta3-agonist ● *Age* : 58.3 (13.88) ● *Men %*: 58 (15.7) ● *weight kg*: 55.12 (9.840) ● *Mean (SD) duration of illness, months*: 70.0 (66.91) ● *Type of incontinence, n (%)*: ● *Absence*: 31 (8.4) ● *Urgency*: 230 (62.3) ● *Mixed*: 108 (29.3) control - antimuskarinergika ● *Age* : 58.3 (13.88) ● *Men %*: 58 (15.7) ● *weight kg*: 55.12 (9.840) ● *Mean (SD) duration of illness, months*: 70.0 (66.91) ● *Type of incontinence, n (%)*: ● *Absence*: 31 (8.4) ● *Urgency*: 230 (62.3) ● *Mixed*: 108 (29.3)

	Included criteria: Men or women aged ≥ 20 years, with OAB symptoms for ≥ 24 weeks **Excluded criteria:** Key OAB-related exclusion criteria included adiagnosis of genuine stress incontinence, an average total dailyurine volume >3000 mL during the 3-day pre-treatmentmicturition diary period, and a post-void residual urinevolume of at least 100 mL when measured before treatment.
Interventions	**Intervention Characteristics** Intervention beta3-agonist ● *Description*: one mirabegron 50 mgtablet and one tolterodine placebo capsule (active mirabegron50 mg group) ● *Length of treatment*: 12 weeks ● *Length of follow-up*: 2-weekfollow-up period (visit 6 [week 14]). control - antimuskarinergika ● *Description*: ; one mirabegron placebo tablet and onetolterodine 4 mg capsule (active tolterodine group) ● *Length of treatment*: 12 weeks ● *Length of follow-up*: 2-weekfollow-up period (visit 6 [week 14]).
Outcomes	*Inkontinensrelateret livkvalitet (QOL) endt behandling (End of treatment)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Time", "change values"] ● **Data value**: Endpoint *Antal tilfælde af inkontinens (episodes of incontinence) endt behandling (End of treatment)* ● **Outcome type**: ContinuousOutcome ● **Measure names**: ["Time", "change values"] ● **Reporting**: Partially reported ● **Unit of measure**: number per 24 hours ● **Direction**: Higher is better ● **Data value**: Change from baseline *Frafald (dropout) (endt behandling/end of treatment)* ● **Outcome type**: DichotomousOutcome ● **Measure names**: ["Time", "Change values"] *Alvorlige skadevirkninger (Serious adverse events) (endt behandling/end of treatment)* ● **Outcome type**: DichotomousOutcome ● **Measure names**: ["Time", "Change values"]

- **Reporting**: Not reported

Antimuskarinerge bivirkninger - forstoppelse (constipation) (endt behandling/end of treatment)
- **Outcome type**: DichotomousOutcome
- **Measure names**: ["Time", "Change values"]
- **Reporting**: Fully reported
- **Data value**: Endpoint

Mundtørhed (Dry mouth) (endt behandling/end of treatment)
- **Outcome type**: DichotomousOutcome
- **Measure names**: ["Time", "Change values"]
- **Reporting**: Fully reported
- **Data value**: Endpoint

Antal vandladninger per døgn (number of micturitions per day) endt behandling (End of treatment)
- **Outcome type**: ContinuousOutcome
- **Measure names**: ["Time", "change values"]
- **Reporting**: Not reported

Kardiovaskulære bivirkninger Palpitationer (cardiocascular adverse events palpitations) (endt behandling/end of treatment)
- **Outcome type**: DichotomousOutcome
- **Measure names**: ["Time", "Change values"]
- **Reporting**: Fully reported
- **Unit of measure**: no of pt's experiencing palpitations
- **Direction**: Lower is better
- **Data value**: Endpoint

Patientoplevet effekt (Patient reported effect) (endt behandling/end of treatment)
- **Outcome type**: DichotomousOutcome
- **Measure names**: ["Time", "Change values"]
- **Reporting**: Not reported

Antal urinvejsinfektioner (no of urinary tract infections) (endt behandling/end of treatment)
- **Outcome type**: ContinuousOutcome
- **Measure names**: ["Time", "change values"]

	● **Reporting**: Not reported *Kardiovaskulære bivirkninger hypertension (cardiocascular adverse events hypertension) (endt behandling/end of treatment)* ● **Outcome type**: DichotomousOutcome ● **Measure names**: ["Time", "Change values"] ● **Reporting**: Fully reported ● **Unit of measure**: no of patients experiencing hypertension ● **Direction**: Lower is better ● **Data value**: Endpoint *Kardiovaskulære bivirkninger Tachycardia (cardiocascular adverse events Tachycardia) (endt behandling/end of treatment)* ● **Outcome type**: DichotomousOutcome ● **Measure names**: ["Time", "Change values"] ● **Reporting**: Fully reported ● **Unit of measure**: no of patients experiencing ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** The study andeditorial support were funded by Astellas Pharma Inc. **Country:** Japan **Setting:** **Comments:** **Authors name:** Osamu Yamaguchi **Institution:** *Department ofHuman Arts Sciences, University and Graduate School of Human Arts Sciences, Saitama **Email:** yamaosa@ee.ce.nihon-u.ac.jp **Address:** Division ofBioengineering and LUTD Research, Nihon University, Schoolof Engineering, Koriyama, Japan
Notes	*Elisabeth Ginnerup-Nielsen* on 28/08/2015 19:42 **Continuous Outcomes** Der mangler generelt sd'er. Der er sd'er opgivet for baseline værdier. P værdier (< eller >) er opgivetLivskvalitet aflæst fra graf

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment	Unclear risk	
Sequence Generation	Unclear risk	
Blinding of participants and personnel All outcomes	Unclear risk	
Blinding of participants and personnel Ikke påvirkbar	Unclear risk	
Blinding of outcome assessors All outcomes	Unclear risk	
Blinding of outcome assessors Ikke påvirkbar	Unclear risk	
Incomplete outcome data	Unclear risk	
Selective outcome reporting	Unclear risk	
Other sources of bias	Unclear risk	

Footnotes

References to studies

Included studies

Chapple 2013

Chapple, C. R.; Kaplan, S. A.; Mitcheson, D.; Klecka, J.; Cummings, J.; Drogendijk, T.; Dorrepaal, C.; Martin, N.. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a beta(3)-adrenoceptor agonist, in overactive bladder. Eur Urol 2013;63(2):296-305. [DOI: http://dx.doi.org/10.1016/j.eururo.2012.10.048]

Chapple 2013a

Chapple, C. R.; Dvorak, V.; Radziszewski, P.; Van Kerrebroeck, P.; Wyndaele, J. J.; Bosman, B.; Boerrigter, P.; Drogendijk, T.; Ridder, A.; Van Der Putten-Slob, I.; Yamaguchi, O.; Dragon Investigator, Group. A phase II dose-ranging study of mirabegron in patients with overactive bladder. International urogynecology journal 2013;24(9):1447-58. [DOI: http://dx.doi.org/10.1007/s00192-013-2042-x]

Khullar 2013

Khullar, V.; Amarenco, G.; Angulo, J. C.; Cambronero, J.; Hoye, K.; Milsom, I.; Radziszewski, P.; Rechberger, T.; Boerrigter, P.; Drogendijk, T.; Wooning, M.; Chapple, C.. Efficacy and tolerability of mirabegron, a beta(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. European Urology 2013;63(2):283-95. [DOI: http://dx.doi.org/10.1016/j.eururo.2012.10.016]

Kuo 2015

Kuo,H. -C; Lin,H. -H; Yu,H. -J; Cheng,C. -L; Hung,M. -J; Lin,A. T. L.. Results of a randomized, double-blind, placebo-controlled study of mirabegron in a Taiwanese population with overactive bladder and comparison with other clinical trials.. Urological Science 2015;26(1):41-48. [DOI: http://dx.doi.org/10.1016/j.urols.2014.12.010]

Yamaguchi 2014

Yamaguchi O; Marui E; Kakizaki H; Homma Y; Igawa Y; Takeda M; Nishizawa O; Gotoh M; Yoshida M; Yokoyama O; Seki N; Ikeda Y; Ohkawa S. Phase III, randomised, double-blind, placebo-controlled study of the beta3-adrenoceptor agonist mirabegron, 50mg once daily, in Japanese patients with overactive bladder.. BJU international 2014;113(6):951-960. [DOI: http://dx.doi.org/10.1111/bju.12649]

Excluded studies

Batista 2015

Batista,J. E.; Kolbl,H.; Herschorn,S.; Rechberger,T.; Cambronero,J.; Halaska,M.; Coppell,A.; Kaper,M.; Huang,M.; Siddiqui,E.. The efficacy and safety of mirabegron compared with solifenacin in overactive bladder patients dissatisfied with previous antimuscarinic treatment due to lack of efficacy: Results of a noninferiority, randomized, phase IIIb trial.. Therapeutic Advances in Urology 2015;7(4):167-179. [DOI: http://dx.doi.org/10.1177/1756287215589250]

Khullar 2013a

Khullar, V.; Cambronero, J.; Angulo, J. C.; Wooning, M.; Blauwet, M. B.; Dorrepaal, C.; Martin, N. E.. Efficacy of mirabegron in patients with and without prior antimuscarinic therapy for overactive bladder: a post hoc analysis of a randomized European-Australian Phase 3 trial. BMC Urol 2013;13:45. [DOI: 10.1186/1471-2490-13-45]

Torimoto 2015

Torimoto,K.; Matsushita,C.; Yamada,A.; Goto,D.; Matsumoto,Y.; Hosokawa,Y.; Hirayama,A.; Fujimoto,K.. Clinical efficacy and safety of a beta3-adrenoceptor agonist (mirabegron) and an antimuscarinic agent (imidafenacin) in female patients with overactive bladder: A randomized crossover study.. Neurourology and urodynamics 2015;34(Journal Article):S396-S397. [DOI: http://dx.doi.org/10.1002/nau.22830]

Data and analyses

1 Intervention vs Control

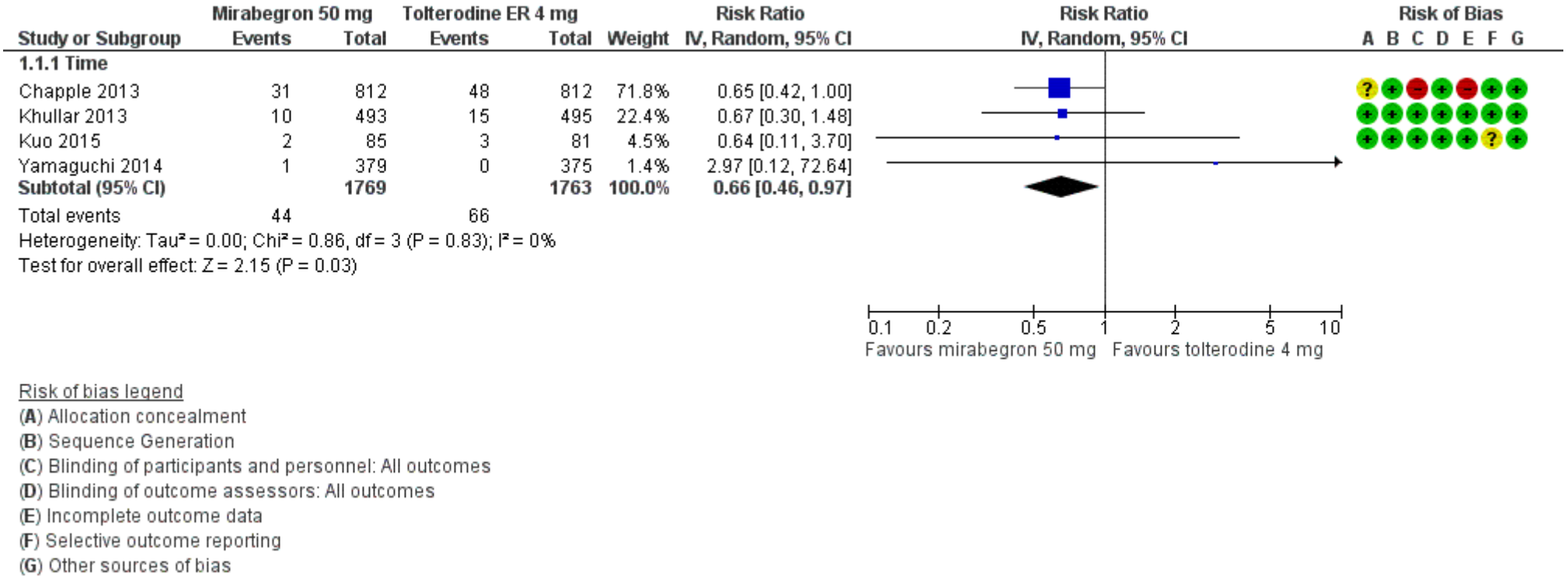
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Kardiovaskulære bivirkninger arytmi (arrhythmia) (endt behandling/end of treatment)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1.1 Time	4	3532	Risk Ratio (IV, Random, 95% CI)	0.66 [0.46, 0.97]
1.2 Kardiovaskulære bivirkninger hypertension (cardiocascular adverse events hypertension) (endt behandling/end of treatment)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.2.1 Time	4	3532	Risk Ratio (IV, Random, 95% CI)	0.88 [0.69, 1.14]
1.4 Mundtørhed (Dry mouth) (endt behandling/end of treatment)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.4.1 End of treatment (12 weeks)	5	3786	Risk Ratio (IV, Random, 95% CI)	0.33 [0.21, 0.51]
1.5 Kvalme EoT (nausea)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.5.1 End of treatment (12 weeks)	1	254	Risk Ratio (IV, Random, 95% CI)	1.01 [0.09, 10.94]
1.7 Forstoppelse (constipation) (end of treatment)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.7.1 End of treatment (12 weeks)	4	3620	Risk Ratio (IV, Random, 95% CI)	1.00 [0.66, 1.51]

1.8 Synsforstyrelser/øjentørhed (eye disorders) (end of treatment)	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.8.1 Time	3	2866	Risk Ratio (IV, Random, 95% CI)	2.26 [0.51, 10.06]
1.9 Livskvalitet - EoT	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.9.1 Change from baseline	5	3651	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.12, 0.09]
1.12 Antal tilfælde af inkontinens/ døgn EoT	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.12.1 Change from baseline	5	2565	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.37, 0.19]
1.13 Vandladninger/døgn EoT	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.13.1 Change from baseline	5	3660	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.52, 0.11]
1.17 Frafald ved EoT (drop out)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.17.1 End of treatment (12 weeks)	5	3799	Risk Ratio (IV, Random, 95% CI)	1.05 [0.87, 1.27]
1.18 SAE Alvorlige bivirkninger EoT (Serious adverse events)	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.18.1 End of treatment (12 weeks)	3	2778	Risk Ratio (IV, Random, 95% CI)	0.99 [0.69, 1.43]
1.19 Patientoplevet effekt EoT (Treatment benefit)	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.19.1 End of treatment (12 weeks)	3	1812	Risk Ratio (IV, Random, 95% CI)	1.03 [0.93, 1.15]
1.23 Adverse events	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.23.1 End of treatment (12 weeks)	5	3786	Risk Ratio (IV, Random, 95% CI)	0.90 [0.79, 1.02]
1.24 Diarre (diarrhea) (end of treatment)	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.24.1 End of treatment (12 weeks)	2	1790	Risk Ratio (IV, Random, 95% CI)	0.88 [0.45, 1.72]

1.25 Urinary tract infections EoT	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.25.1 End of treatment (12 weeks)	2	2612	Risk Ratio (IV, Random, 95% CI)	0.89 [0.62, 1.27]

Figures

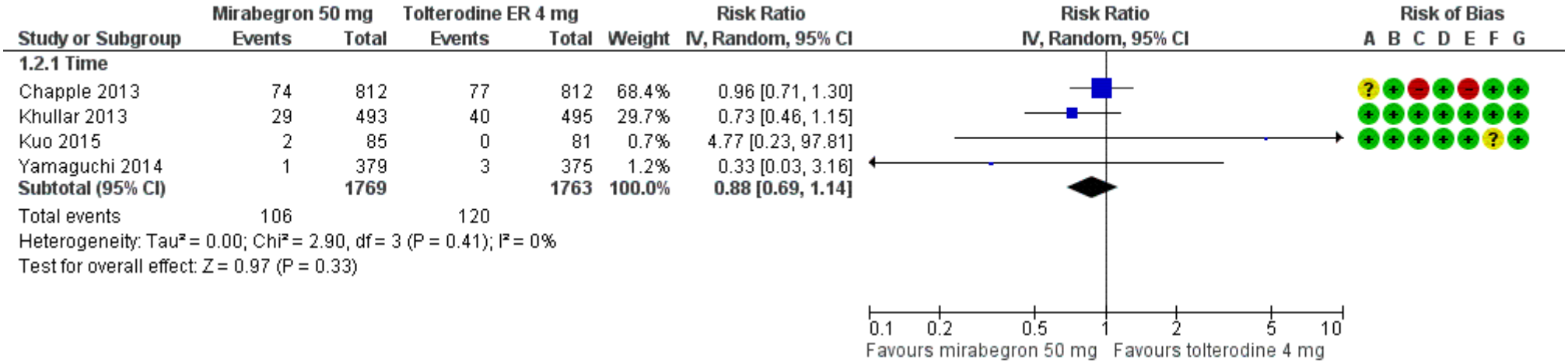
Figure 1 (Analysis 1.1)



Risk of bias legend
(**A**) Allocation concealment
(**B**) Sequence Generation
(**C**) Blinding of participants and personnel: All outcomes
(**D**) Blinding of outcome assessors: All outcomes
(**E**) Incomplete outcome data
(**F**) Selective outcome reporting
(**G**) Other sources of bias

Forest plot of comparison: 1 Intervention vs Control, outcome: 1.1 Kardiovaskulære bivirkninger arytmi (arrhythmia) (endt behandling/end of treatment).

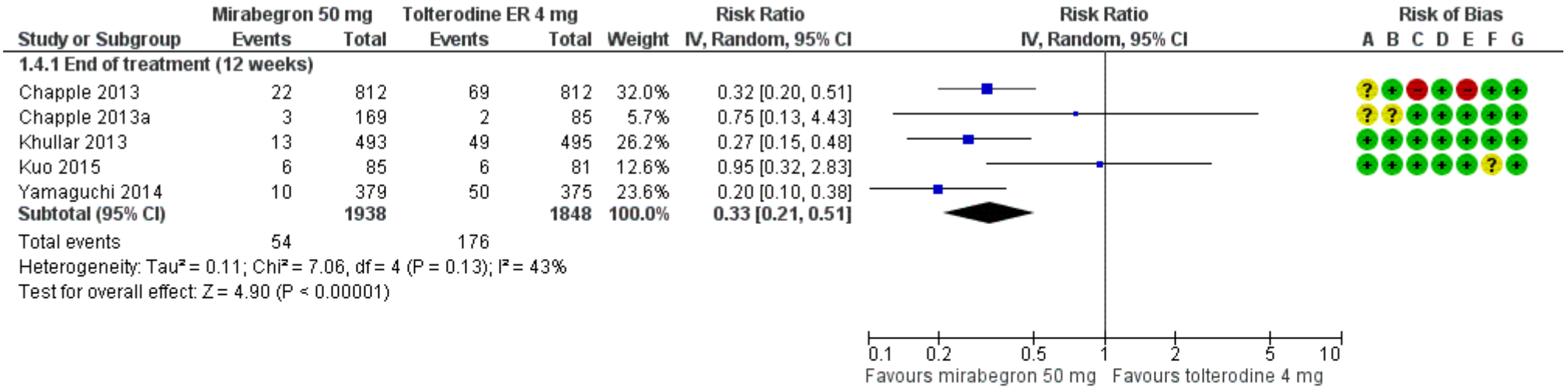
Figure 2 (Analysis 1.2)



Risk of bias legend
(A) Allocation concealment
(B) Sequence Generation
(C) Blinding of participants and personnel: All outcomes
(D) Blinding of outcome assessors: All outcomes
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

Forest plot of comparison: 1 Intervention vs Control, outcome: 1.2 Kardiovaskulære bivirkninger hypertension (cardiocascular adverse events hypertension) (endt behandling/end of treatment).

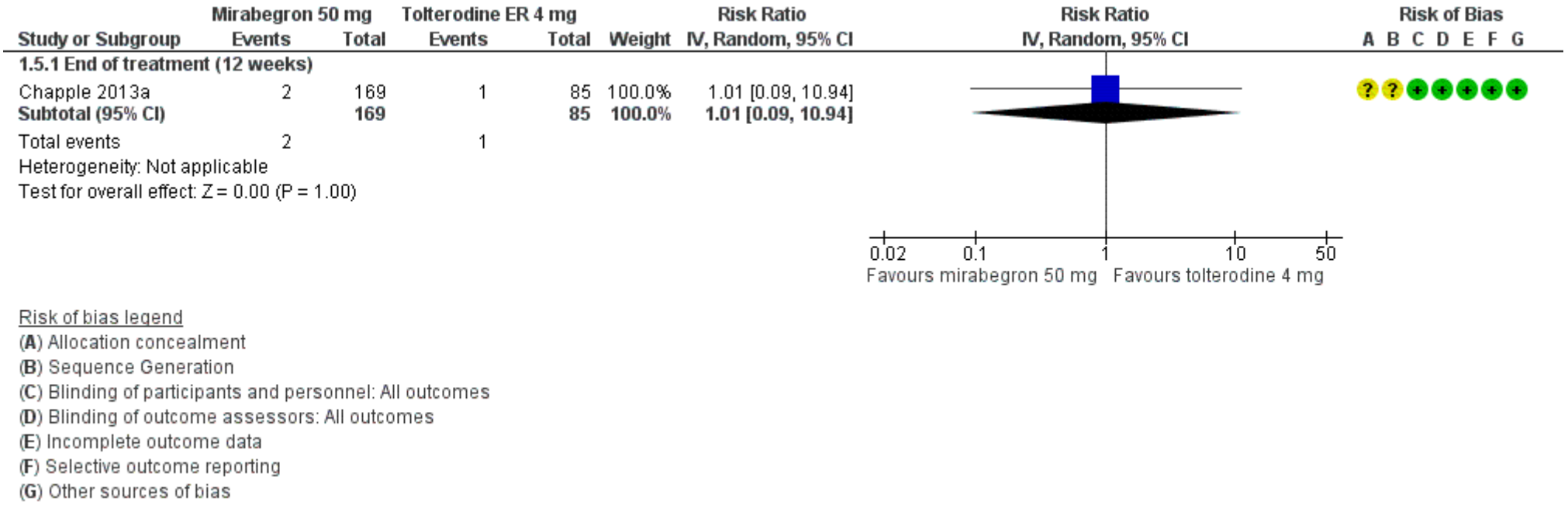
Figure 4 (Analysis 1.4)



Risk of bias legend
(A) Allocation concealment
(B) Sequence Generation
(C) Blinding of participants and personnel: All outcomes
(D) Blinding of outcome assessors: All outcomes
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

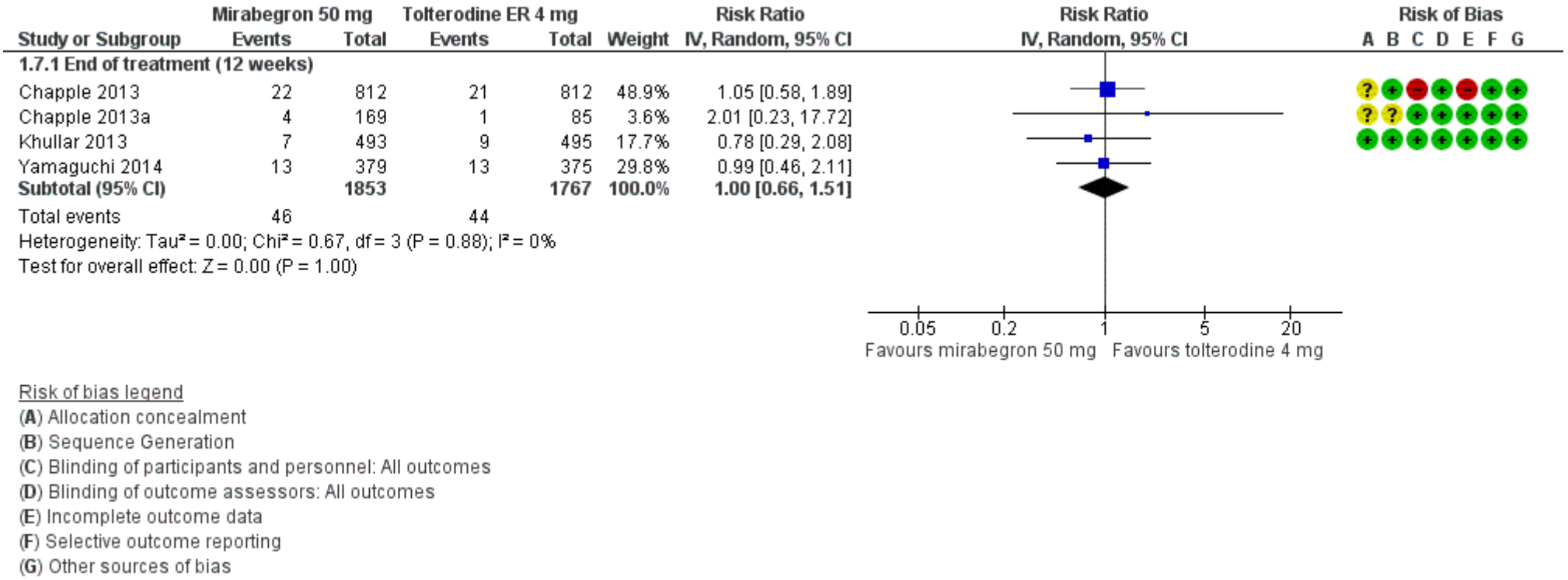
Forest plot of comparison: 1 Intervention vs Control, outcome: 1.4 Mundtørhed (Dry mouth) (endt behandling/end of treatment).

Figure 5 (Analysis 1.5)



Forest plot of comparison: 1 Intervention vs Control, outcome: 1.5 Kvalme EoT (nausea).

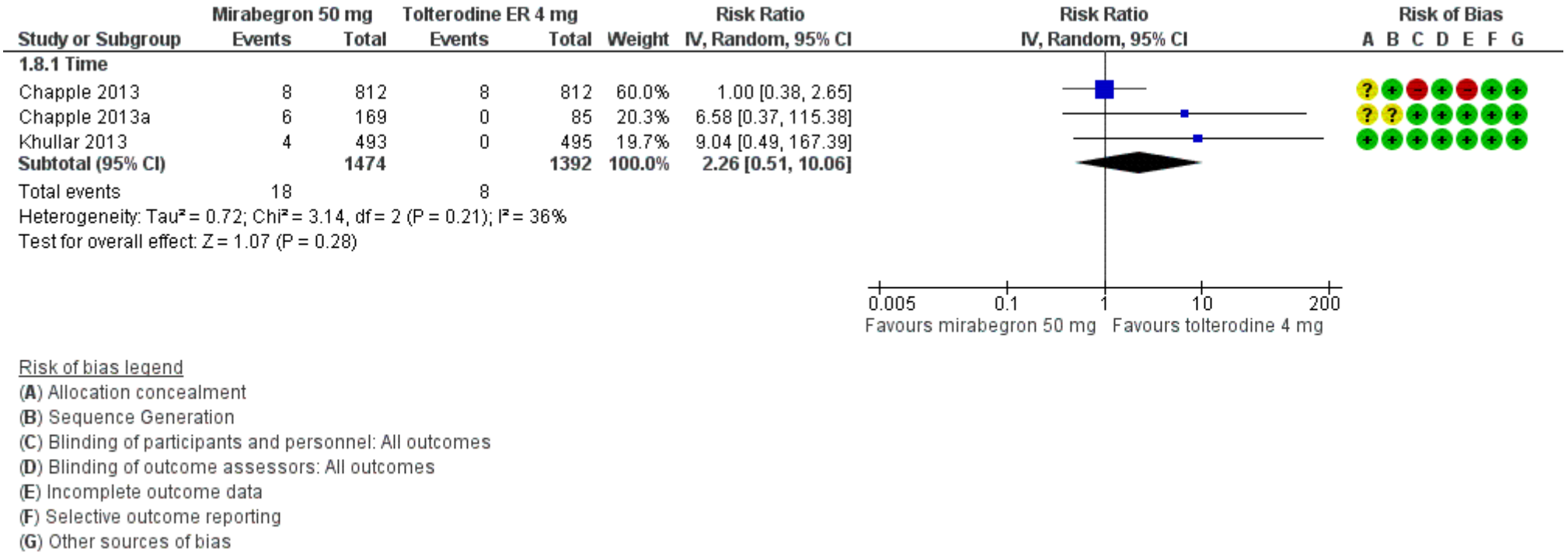
Figure 7 (Analysis 1.7)



Risk of bias legend
(**A**) Allocation concealment
(**B**) Sequence Generation
(**C**) Blinding of participants and personnel: All outcomes
(**D**) Blinding of outcome assessors: All outcomes
(**E**) Incomplete outcome data
(**F**) Selective outcome reporting
(**G**) Other sources of bias

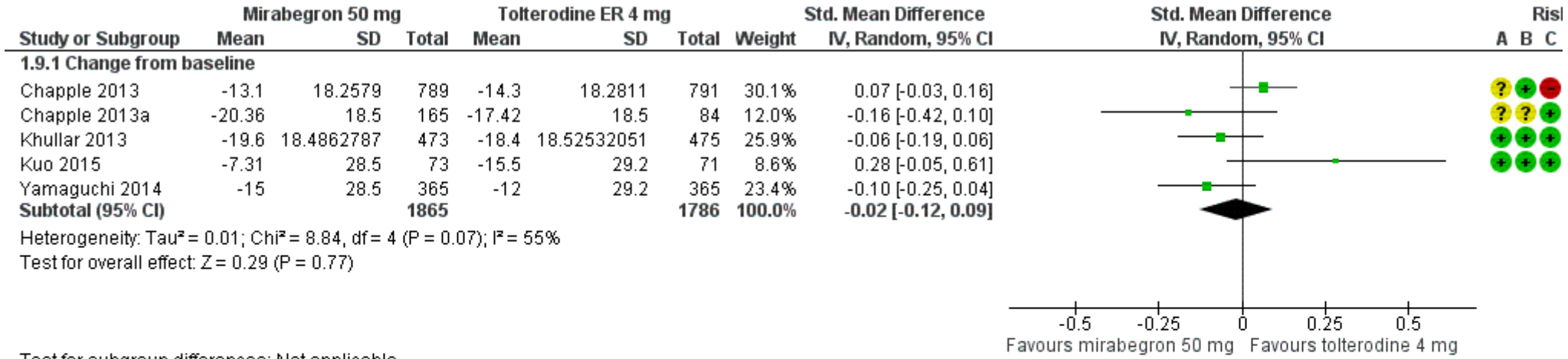
Forest plot of comparison: 1 Intervention vs Control, outcome: 1.7 Forstoppelse (constipation) (end of treatment).

Figure 8 (Analysis 1.8)



Forest plot of comparison: 1 Intervention vs Control, outcome: 1.8 Synsforstyrelser/øjentørhed (eye disorders) (end of treatment).

Figure 9 (Analysis 1.9)



Test for subgroup differences: Not applicable

Risk of bias legend

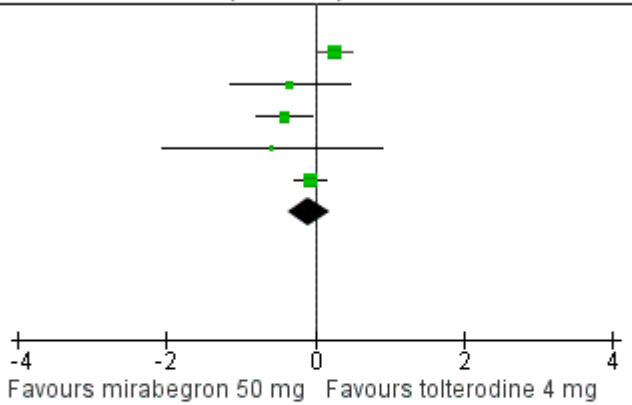
(**A**) Allocation concealment
(**B**) Sequence Generation
(**C**) Blinding of participants and personnel: All outcomes
(**D**) Blinding of outcome assessors: All outcomes
(**E**) Incomplete outcome data
(**F**) Selective outcome reporting
(**G**) Other sources of bias

Forest plot of comparison: 1 Intervention vs Control, outcome: 1.9 Livskvalitet - EoT.

Figure 10 (Analysis 1.12)

Study or Subgroup	Mirabegron 50 mg Mean	SD	Total	Tolterodine ER 4 mg Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of A B C D
1.12.1 Change from baseline									
Chapple 2013	-1.01	1.96974618	479	-1.26	1.98816498	488	30.8%	0.25 [0.00, 0.50]	? + − +
Chapple 2013a	-1.15	3.72	108	-0.81	2.02	108	9.5%	-0.34 [-1.14, 0.46]	? ? + +
Khullar 2013	-1.62	2.3451	293	-1.21	2.3729	300	23.4%	-0.41 [-0.79, -0.03]	+ + + +
Kuo 2015	-1.37	3.72	33	-0.79	2.02	26	3.3%	-0.58 [-2.07, 0.91]	+ + + +
Yamaguchi 2014	-1.01	1.34	365	-0.95	1.58	365	33.0%	-0.06 [-0.27, 0.15]	
Subtotal (95% CI)			**1278**			**1287**	**100.0%**	**-0.09 [-0.37, 0.19]**	

Heterogeneity: Tau² = 0.05; Chi² = 9.85, df = 4 (P = 0.04); I² = 59%
Test for overall effect: Z = 0.63 (P = 0.53)



Test for subgroup differences: Not applicable

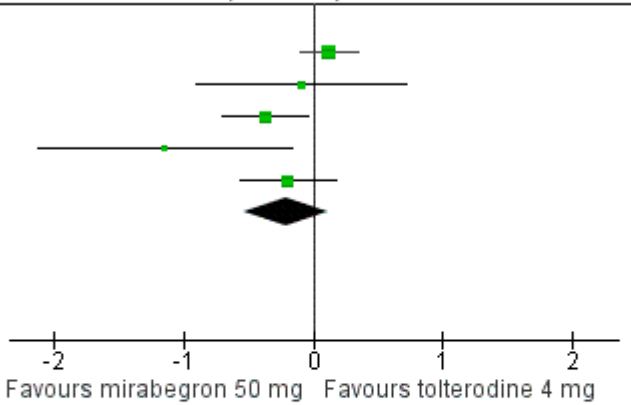
Risk of bias legend
(**A**) Allocation concealment
(**B**) Sequence Generation
(**C**) Blinding of participants and personnel: All outcomes
(**D**) Blinding of outcome assessors: All outcomes
(**E**) Incomplete outcome data
(**F**) Selective outcome reporting
(**G**) Other sources of bias

Forest plot of comparison: 1 Intervention vs Control, outcome: 1.12 Antal tilfælde af inkontinens/ døgn EoT.

Figure 11 (Analysis 1.13)

Study or Subgroup	Mirabegron 50 mg Mean	SD	Total	Tolterodine ER 4 mg Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.13.1 Change from baseline								
Chapple 2013	-1.27	2.2471315	789	-1.39	2.24997778	791	30.9%	0.12 [-0.10, 0.34]
Chapple 2013a	-2.08	2.91	167	-1.99	3.18	85	10.8%	-0.09 [-0.90, 0.72]
Khullar 2013	-1.94	2.5228	473	-1.57	2.6807	475	26.0%	-0.37 [-0.70, -0.04]
Kuo 2015	-2.12	2.91	76	-0.98	3.18	74	8.1%	-1.14 [-2.12, -0.16]
Yamaguchi 2014	-1.85	2.56	365	-1.66	2.56	365	24.2%	-0.19 [-0.56, 0.18]
Subtotal (95% CI)			**1870**			**1790**	**100.0%**	**-0.21 [-0.52, 0.11]**

Heterogeneity: Tau² = 0.07; Chi² = 10.91, df = 4 (P = 0.03); I² = 63%
Test for overall effect: Z = 1.29 (P = 0.20)



Test for subgroup differences: Not applicable

Risk of bias legend
(**A**) Allocation concealment
(**B**) Sequence Generation
(**C**) Blinding of participants and personnel: All outcomes
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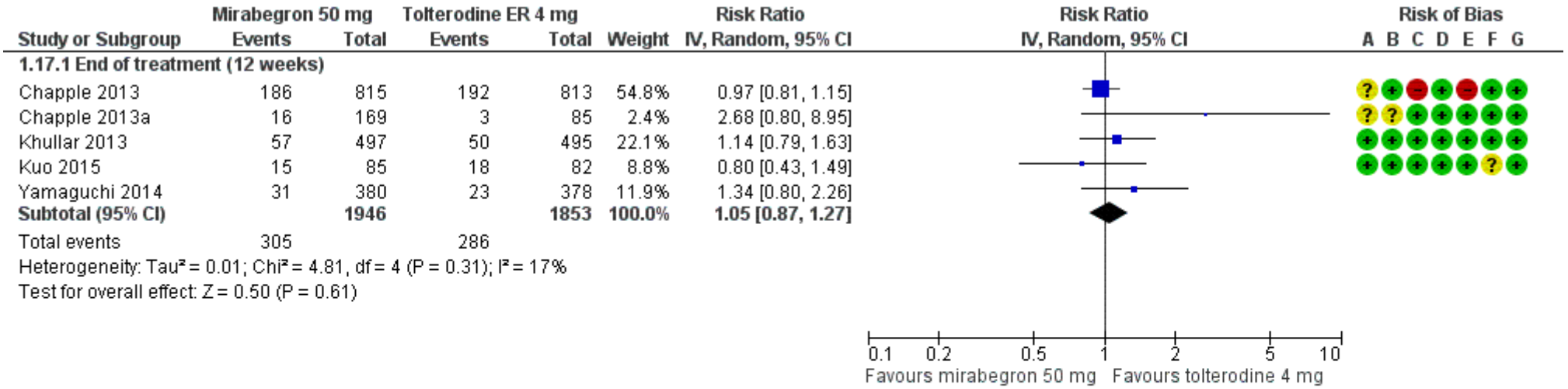
(**E**) Incomplete outcome data
(**F**) Selective outcome reporting
(**G**) Other sources of bias

Forest plot of comparison: 1 Intervention vs Control, outcome: 1.13 Vandladninger/døgn EoT.

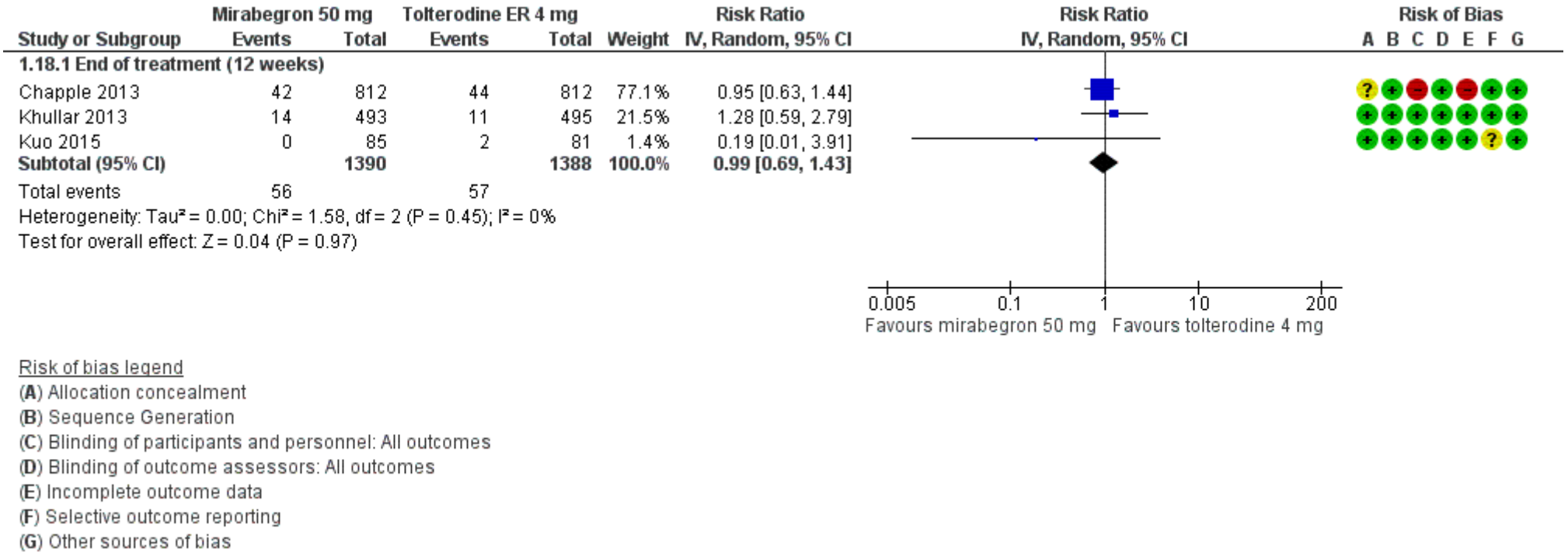
Figure 12 (Analysis 1.17)



Risk of bias legend
(A) Allocation concealment
(B) Sequence Generation
(C) Blinding of participants and personnel: All outcomes
(D) Blinding of outcome assessors: All outcomes
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

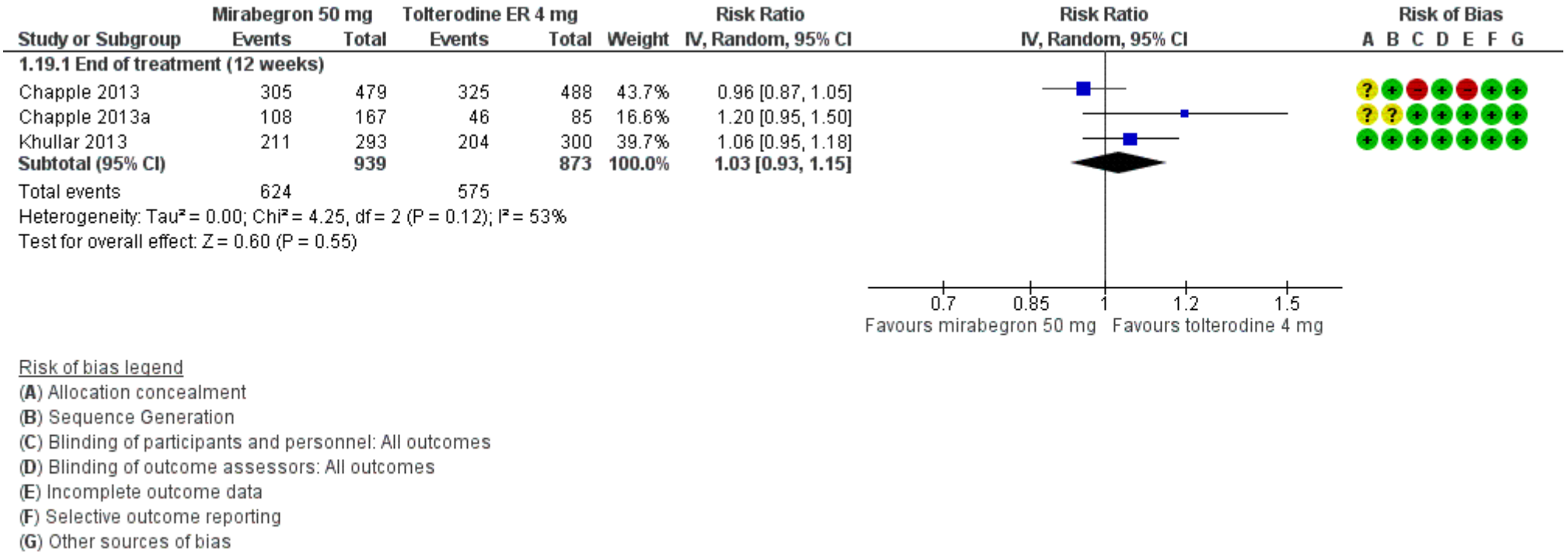
Forest plot of comparison: 1 Intervention vs Control, outcome: 1.17 Frafald ved EoT (drop out).

Figure 13 (Analysis 1.18)



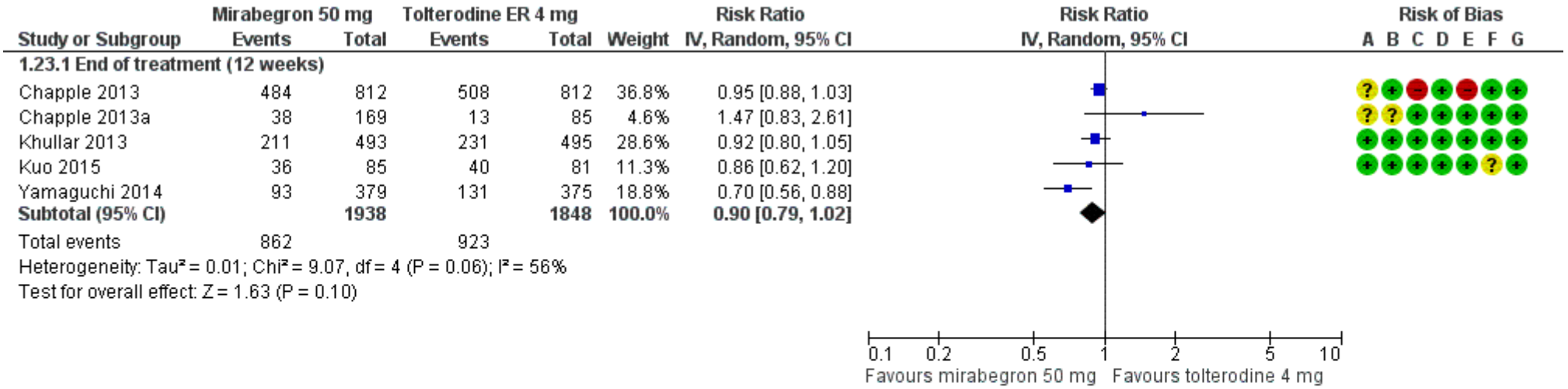
Forest plot of comparison: 1 Intervention vs Control, outcome: 1.18 SAE Alvorlige bivirkninger EoT (Serious adverse events).

Figure 14 (Analysis 1.19)



Forest plot of comparison: 1 Intervention vs Control, outcome: 1.19 Patientoplevet effekt EoT (Treatment benefit).

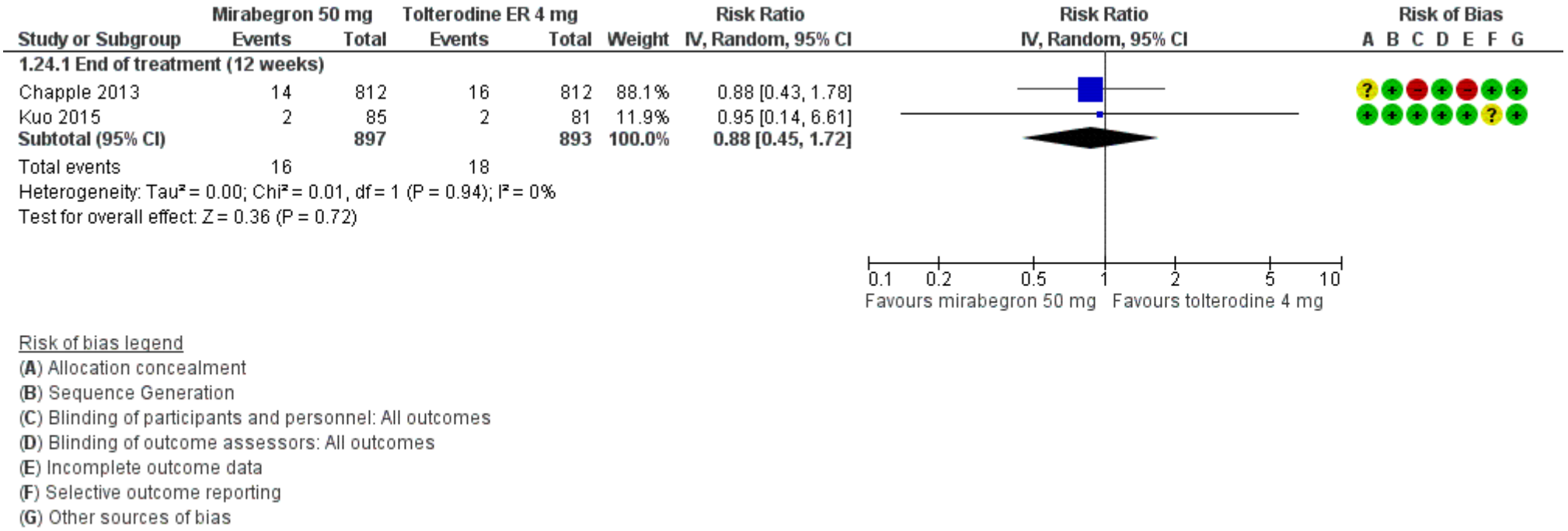
Figure 16 (Analysis 1.23)



Risk of bias legend
(A) Allocation concealment
(B) Sequence Generation
(C) Blinding of participants and personnel: All outcomes
(D) Blinding of outcome assessors: All outcomes
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

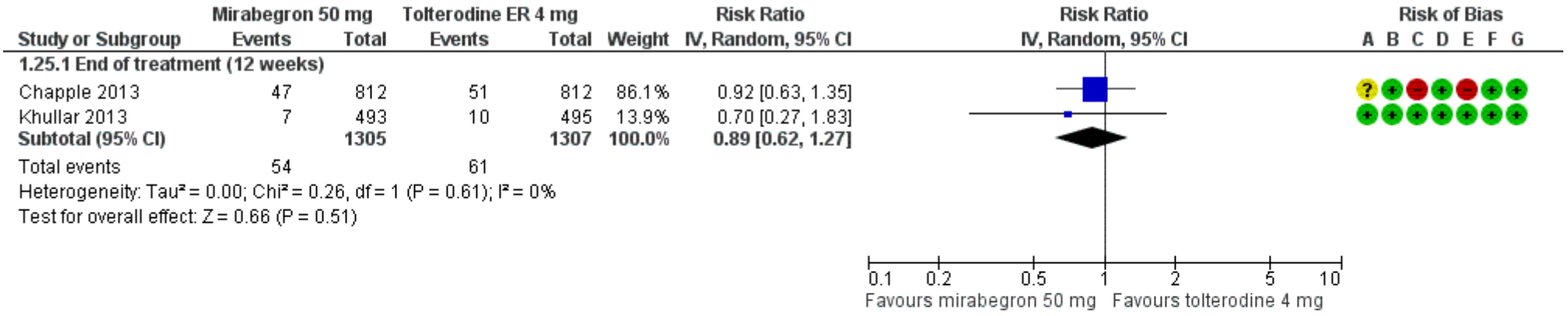
Forest plot of comparison: 1 Intervention vs Control, outcome: 1.23 Adverse events.

Figure 17 (Analysis 1.24)



Forest plot of comparison: 1 Intervention vs Control, outcome: 1.24 Diarre (diarrhea) (end of treatment).

Figure 18 (Analysis 1.25)



Risk of bias legend
(**A**) Allocation concealment
(**B**) Sequence Generation
(**C**) Blinding of participants and personnel: All outcomes
(**D**) Blinding of outcome assessors: All outcomes
(**E**) Incomplete outcome data
(**F**) Selective outcome reporting
(**G**) Other sources of bias

Forest plot of comparison: 1 Intervention vs Control, outcome: 1.25 Urinary tract infections EoT.