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Urodynamic parameter improvements after mirabegron *vs.* antimuscarinics agents in non-neurogenic overactive bladder: a systematic review and meta-analysis of treatment effect

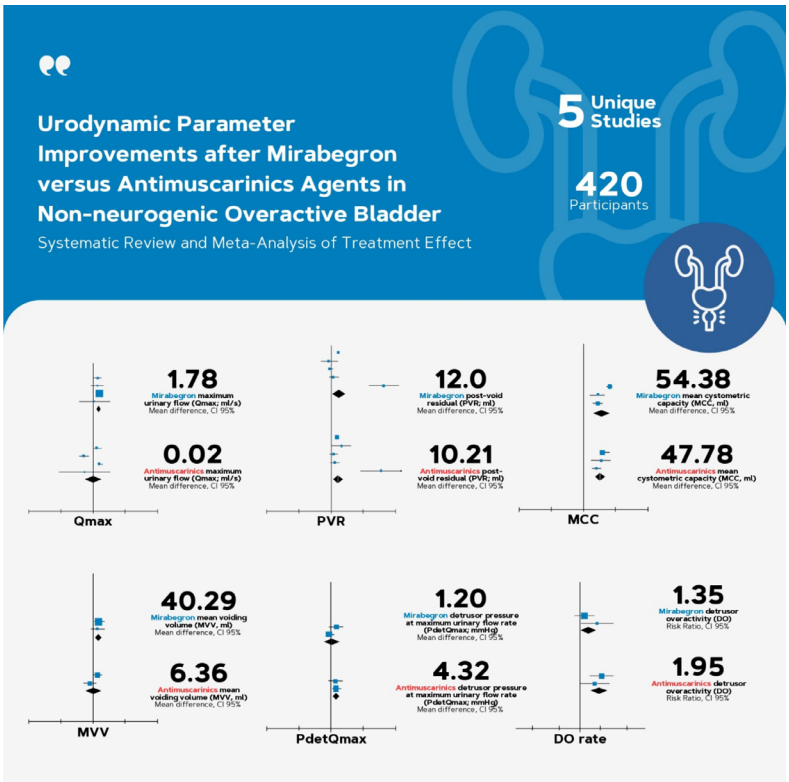
S.M. WARLI[1,2], N.N. FIRSTY[3], D. NATALIA[3], A.J. VELARO[3], Z.Z. TALA[4]

[1]Department of Urology, Universitas Sumatera Utara Hospital – Universitas Sumatera Utara, Medan, Indonesia
[2]Division of Urology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara-Haji Adam Malik General Hospital, Medan, Indonesia
[3]Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[4]Department of Nutrition, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Abstract. – OBJECTIVE: This review aimed to establish the comparison between mirabegron and antimuscarinic agents through the improvement of the urodynamic study (UDS) parameter among overactive bladder (OAB) populations.

MATERIALS AND METHODS: The PRISMA checklist and procedure were utilized to standardize our review of studies from scientific databases published between January 2013 and May 2022 in accordance with the applied eligibility criteria. This study mainly focused on UDS parameter improvement; hence, baseline and follow-up completion were mandatory to be included. The quality of each included study was assessed with the Cochrane risk-of-bias tool in RevMan 5.4.1.

RESULTS: We included a total of 5 clinical trials encompassing 430 clinically confirmed OAB individuals. Our meta-analysis demon-



Graphical Abstract. The findings of this study demonstrated that mirabegron possessed higher statistical influence on mean difference (MD) and risk ratio (RR) of the analyzed variables. The superiority of mirabegron is presented through Qmax, PVR, and MCC (Top, from left to right) plus MVV, PdetQmax, and DO rate (Bottom, from left to right).

Corresponding Author: Syah Mirsya Warli, MD; e-mail: warli@usu.ac.id

strated that the improvement of maximum urinary flow rate (Qmax) was more apparent in the mirabegron arm [mean difference (MD), 1.78 (1.31, 2.26); $p<0.05$] compared to antimuscarinics arm [MD, 0.02 (-2.53, 2.57); $p>0.05$) as analyzed in random-effect model (REM) analysis within 95% CI. Similar outcomes were also observed on the other UDS parameters related to the bladder's storage function, e.g., post-void residual (PVR) and detrusor overactivity (DO) cases, with most of the MDs favoring mirabegron.

CONCLUSIONS: Mirabegron is superior in improving most of the UDS parameter outcomes compared to the antimuscarinics agents though the current guideline should always refer to symptoms improvement. Emphasizing the role of UDS parameter measurements to objectively confirm a therapeutic effect should be considered in the upcoming studies.

Key Words:
Antimuscarinics, Mirabegron, Overactive bladder, Urodynamics.

Introduction

Overactive bladder (OAB) is often considered a spectrum of bothersome chronic lower urinary tract symptoms (LUTS), substantially affecting the quality of life (QoL) through ineffective bladder control plus its remarkable social isolation issue[1,2]. As a syndrome, the International Continence Society (ICS) defined the disorder solely through symptoms finding e.g., urinary urgency rather than an observable clinical work-up or measurable data[3]. The OAB's prevalence is steadily increasing with age and statistically varies from 10.2% to 31.3%.[4] Nevertheless, the most efficacious approach of OAB remains within disagreement among experts, even though it is agreed that prioritizing complete bladder control is mandatory[1,5].

A suspicion in bladder's pathology should be raised among individuals with storage-dominant LUTS findings rather than conclude it as the commonly used term of 'detrusor overactivity' (DO) i.e., a urodynamic-based diagnosis. Managing OAB is revolving around reducing the impact of symptoms on an individual's QoL, thus the current global investigations is to establish an efficacious approach to ameliorate the symptoms[6]. As recommended by American Urological Association (AUA), behavioral treatment plus educating the patient placed as the first-line approach, followed by antimuscarinics agents if the symptoms persisted and intolerable[7-9]. In recent years, antimuscarinics has been considered as the cornerstone of OAB's pharmacologic treatment after decades of trials and confirmatory meta-analysis, however. A better understanding of OAB's pathophysiology demonstrated that the high expression of beta-3 (β3) receptors in detrusor muscle and urothelium might present as an explorable therapeutic options[10,11]. The emergence of β3 adrenoreceptor agonist generated a crucial research question in balancing the "treatment effect" and "side-effect". Therefore, it should be established whether the novel agent will perform better in managing OAB or antimuscarinic agents continue to prevail as second-line treatment in practice.

Since LUTS basically influence a physician's decision to treat OAB, we believe supportive evidence through more objective scope and evaluation should provide an additional clinical consideration. By evaluating the improvement of urodynamic study (UDS) parameter after a period of time, we believe bladder function's recovery to store urine might be assessed objectively rather than solely relying on the history taking-based report. Although we acknowledge that symptoms improvement is certainly a definitive goal in managing OAB, delineating the bladder's physiological function through urinary flow rate analysis, residual urine in the bladder, average anatomical pressure, etc., is clinically relevant in determining a cornerstone approach in case of failure after first-line treatment. Therefore, this review aimed to serve as an important benchmark investigation by presenting the role of mirabegron in improving UDS parameter among non-neurogenic OAB individuals; and establishing its role in modern urologic guideline without negating any importance of symptoms control or side-effect rates.

Materials and Methods

Study Protocol

The standard PRISMA guideline was implemented as the base foundation of this study and its protocol was introduced to the international database prospective registration of systematic review on PROSPERO with registered ID of CRD42022338876[12].

Eligibility Criteria

The applied PICO (Population, Intervention, Comparison, and Outcomes) strategies of this review are; participants-adult and/or pediatric patients with confirmed OAB syndrome as clinically confirmed by several diagnostic tools, e.g. OAB Symptom Score (OABSS), International Prostate Symptoms Score and Quality of Life (IPSS-QOL), or populations with suggestive symptoms of OAB (persistent urgency, frequency, with or without urgency urinary incontinence); intervention and Comparison-Mirabegron, a β3-adrenergic agonist and antimuscarinic agents as a single-regiment or combined with prior mainstay treatment (in age-matched controls); outcomes-urodynamic analysis as reported in baseline (pre-treatment) and final follow-up (post-treatment or final-reporting of the study), presented in numerical data within mean and SD. We also limit the studies to the controlled trial investigation, preferentially the large-scale trial with explicit protocol in English-based literature. The exclusion criteria are the incompatible design of trials (dose-ranging study, intervention *vs.* intervention plus comparison arm, intervention *vs.* placebo, etc.) and incomplete data reporting. Due to the exact and strict established eligibility criteria, this study may encounter a predictable limitation i.e., the smaller number of available studies. Nevertheless, we believe the identified studies will be sufficient to support our PICO model in conducting this systematic review and meta-analysis.

Systematic Screening

We utilize several scientific databases e.g., PubMed, Cochrane Library, and ScienceDirect to perform studies screening according to the Boolean term search protocol. Two authors (N.N.F. and A.J.V.) identified the literatures using strategic keywords, e.g. ("mirabegron") AND ("antimuscarinic" or "anticholinergic" or "solifenacin" or "darifenacin" or "oxybutynin" or "tolterodine" or "fesoterodine") AND ("overactive bladder" or "OAB") as restricted to the mentioned keywords on either titles or abstracts. Adaptation of search strategy in other search engines from the Pubmed-based searching method was also conducted. We also manually screen the references list from the recent and relevant systematic reviews related to our objectives to secure every possible literature and included as "studies from other sources".

Risk of Bias Assessment and Data Extraction

Quality or risk of bias assessment was performed by an author (N.N.F.) by using the revised Cochrane risk-of-bias (RoB) tool for RCT as available on RevMan 5.4.1 software (Review Manager Web, The Cochrane collaboration, Copenhagen, Denmark), which consisted of 6 parameters, e.g., selection (random generation of sequence and allocation concealment), performance, detection, attrition, reporting, and the other potential bias.

The author's first name as obtained with respective study design, participants' inclusion criteria, intervention or comparison arm details, analyzed outcomes within its treatment duration of follow-up are some of the base characteristics' variables of our study. The main investigated data of our meta-analysis were basically revolving around the available or provided urodynamic studies e.g., maximum urinary flow rate (Qmax) in mL/s, along with several volume-based analysis i.e., post-void residual volume (PVR), maximum cystometric capacity (MCC), mean voiding volume (MVD) in mL and maximum pressure of detrusor during maximum urinary flow (Pdet. Qmax) in mmHg. The extracted data were mean value of the aforementioned outcomes in both baseline and final follow-up report. Additionally, we also studied the rate of detrusor overactivity (DO) cases by estimating its pooled cases per population in the Forest plot.

Statistical Analysis

We utilized different approaches to interpret our mathematical and structured analysis of this study by focusing on comparing the parameters' changes from baseline to a complete follow-up report. It focused more on data improvement rather than a specific checkpoints comparison, for the outcomes were presented in mean different (MD) changes of both arms. Thus, this review does not conclude the result by comparing checkpoint outcomes e.g., mirabegron *vs.* antimuscarinics on baseline or 3 months post-treatment, although the results of the latter model will be included in the supplementary section. The used analysis model is not precisely a standard strategy, but we believe it is plausible to measure the disease improvement as represented by the treatment's efficacy over time.

All the meta-analyses were performed using the Review Manager (RevMan) 5.4.1. statistical software by Cochrane (London, United Kingdom). The continuous data model was implemented to analyze both mean and SD values

for most of the outcomes except for the DO rate, which used the dichotomous model for event-total rate analysis and presented in risk ratio (RR) value. Overall heterogeneity of the outcomes was concluded by the I^2 value where <30.0% represented 'low heterogeneity', and the value of between 30.0-50.0% and >50.0% showed 'moderate' and 'substantial heterogeneity', respectively. To avoid further influence of studies' heterogeneity, several outcomes will be analyzed in random-effect model (REM) if the I^2 value was >50.0%.

The *p*-value of <0.05 was considered to be statistically significant for both outcomes and all sub-analysis conducted. We also estimated the statistical difference of the MD or RR from both pooled subgroups to confirm the statistical significance between sub-groups (in our review model: mirabegron *vs.* antimuscarinic agents).

Results

We identified 528 studies initially, corresponding with abstract and/or title findings strategies. A total of 246 literatures were excluded by thorough analysis on title/abstract section, followed by 10 un-retrievable records, and 38 studies were furtherly excluded after full-text review as presented in Figure 1 [Risk-of-bias (Rob) results in Figure 2]. We included 5 RCT which incorporated 420 patients to be

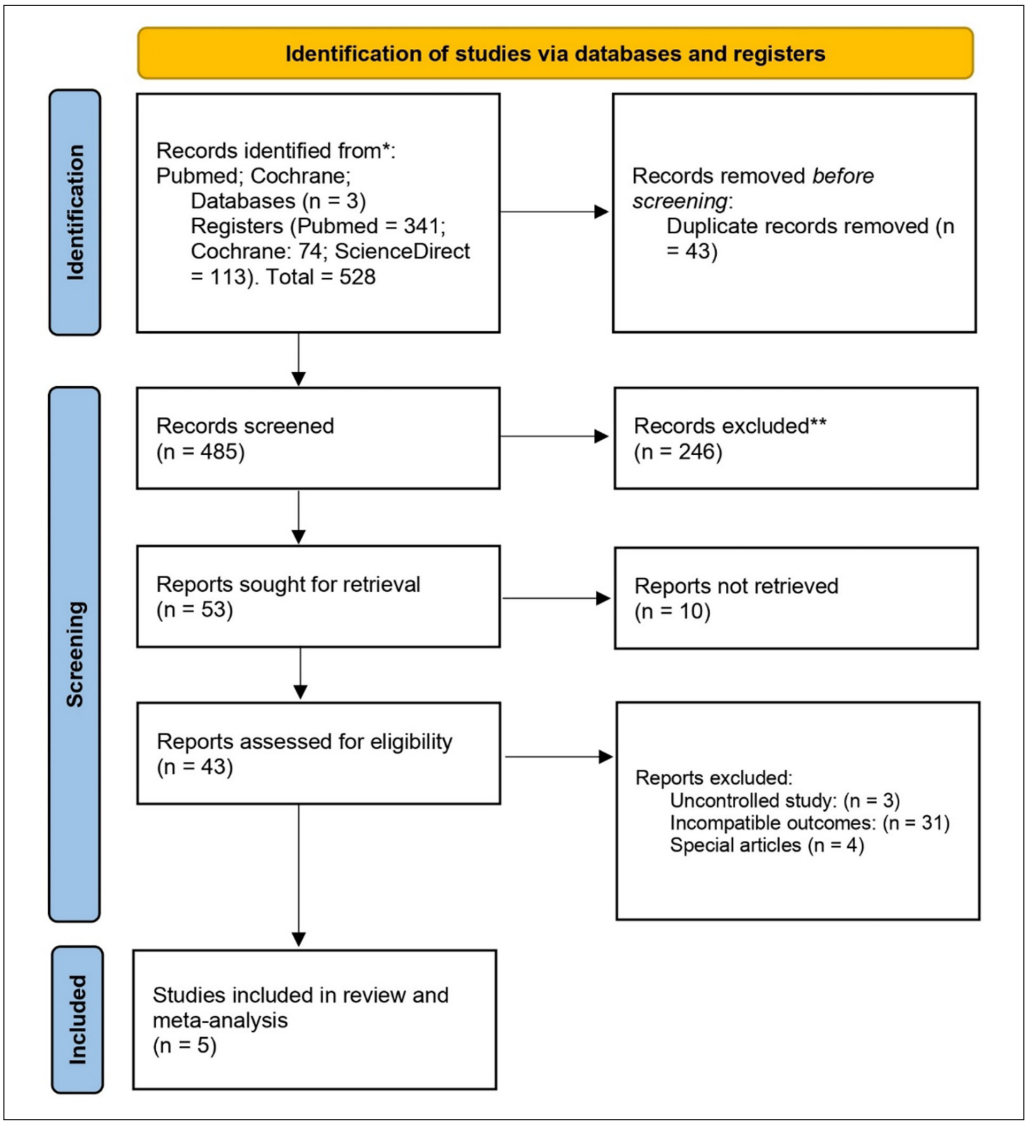


Figure 1. PRISMA flow used to identify the analyzed study in this review.

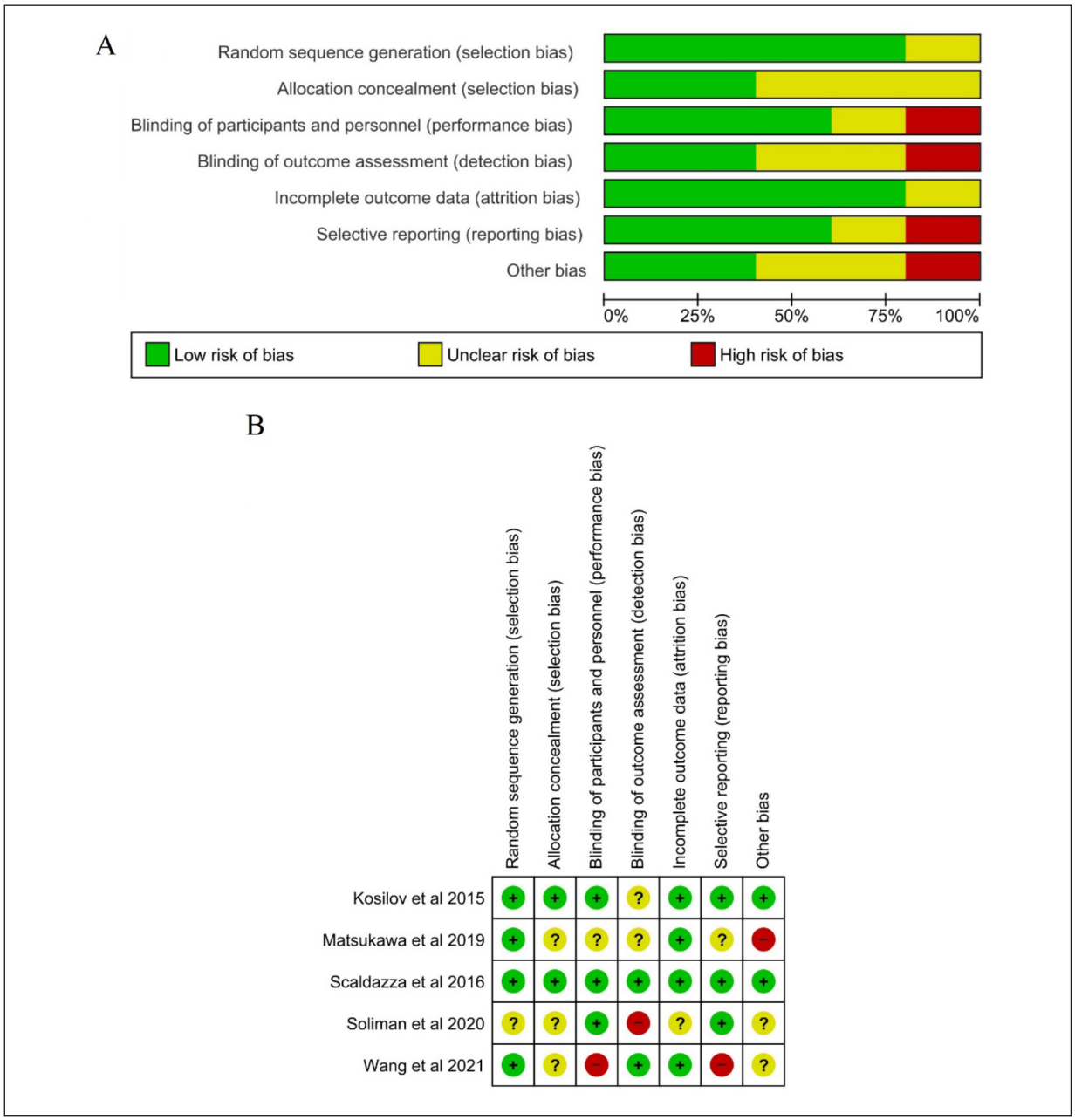


Figure 2. Risk of bias analysis (**A**) and results (**B**) of the included studies.

systematically analyzed further and quantified into Forest plot if possible. Three studies[20,21,26] applied mirabegron 50 mg QD alone and the other two[19,22] added an α-blocker agent (silodosin and tamsulosin) to be compared with the control arm (Table I). All studies utilized their own diagnostic criteria to identify the populations, e.g., the presence of symptoms (depending on the used scoring method), regardless of the prior treatment. Therefore, the final analysis of this study limited our review to compare urodynamic properties of mirabegron-added arm *vs.* non-mirabegron-added arm (or standard therapy) among OAB patients.

The mirabegron arm had a statistically significant improvement of uroflowmetry (Qmax) outcome with a MD of 1.78 (1.31, 2.26) ml/s with *p*-value of <0.05 from baseline to complete follow-up, in REM model analysis and 95% CI. Correspondingly, the control arm failed to exhibit a significant outcome, as it was only able to improve the Qmax for 0.02 (-2.53, 2.57) ml/s through the

Table I. Summary of trials and its patients' characteristics.

Study, design	Sample size (M/C)	Mirabegron dose plus applied regiment and comparison (weeks of treatment)	Patients' inclusion criteria in intervention arm
Kosilov et al[26]; Phase II RCT	63/52	Mirabegron 50 mg QD and Solifenacin 10 mg QD (12 weeks)	Adult male/female (ratio: ±1:1.5; aged > 65 years old; mean 71.2 years old) with severe symptoms of OAB (EI ≥ 3/day) within unmentioned etiology (possibly non-neurogenic OAB). Prior oral antimuscarinic drugs of different generations for ≤ 1 year before trial.
Matsukawa et al[22]; Prospective RCT	52/50	(Mirabegron 50 mg QD and Fesoterodine 4 mg QD) + silodosin 8 mg QD (12 weeks)	Adult male (aged ≥ 50 years old) with non-neurogenic OAB despite unmentioned etiology plus BPH as confirmed by IPSS ≥ 8, IPSS-QOL ≥ 3 , total OABSS ≥ 3, ≥ 1 urinary urgency episodes/week, prostate volume ≥25 mL (transabdominal USG). Prior oral α1-blocker monotherapy (silodosin, 8 mg/day) for 12-24 weeks.
Vecchioli Scaldazza et al[20]; Phase II RCT	31/29	Mirabegron 50 mg QD and Solifenacin 5 mg QD (12 weeks)	Adult [aged 48-73 (mean: 56) years old] female with non-neurogenic OAB despite of unmentioned etiology as confirmed by OABSS-based diagnostic evaluation. Prior treatment or intervention was unmentioned.
Soliman et al[19];	46/46	(Mirabegron 50 mg QD and Solifenacin 5 mg QD) + Tamsulosin 0.4 mg QD (12 weeks)	Adult male (aged ≥ 50 years old) with non-neurogenic OAB despite unmentioned etiology plus BPO for at least 12 weeks as confirmed by OABSS ≥ 3 with ≥1 urinary urgency episodes/week. Prior oral α1-blocker monotherapy (tamsulosin, 0.4 mg/day) for 12 due to BPO-related LUTS (based on USG assessment of prostate size, and previous PVR or uroflowmetry).
Wang et al[21];	31/30	Mirabegron 50 mg QD and Solifenacin 5 mg QD (48 weeks)	Adult male/female [ratio: ±1:1.4; aged 24-89 (mean: 70.0±12.4) years old] with non-neurogenic OAB despite unmentioned etiology. Prior intravesical onobotulinumtoxin A (BoNT-A) for 1 month before trial.

BPH, Benign prostate hypertrophy; IPSS, International prostate symptoms score; LUTS, Lower urinary tract symptoms; OAB, Overactive bladder; OABSS, Overactive bladder symptoms score; QD, Quaque die or once a day; QOL, Quality of life; RCT, Randomized clinical trial; USG, ultrasonography.

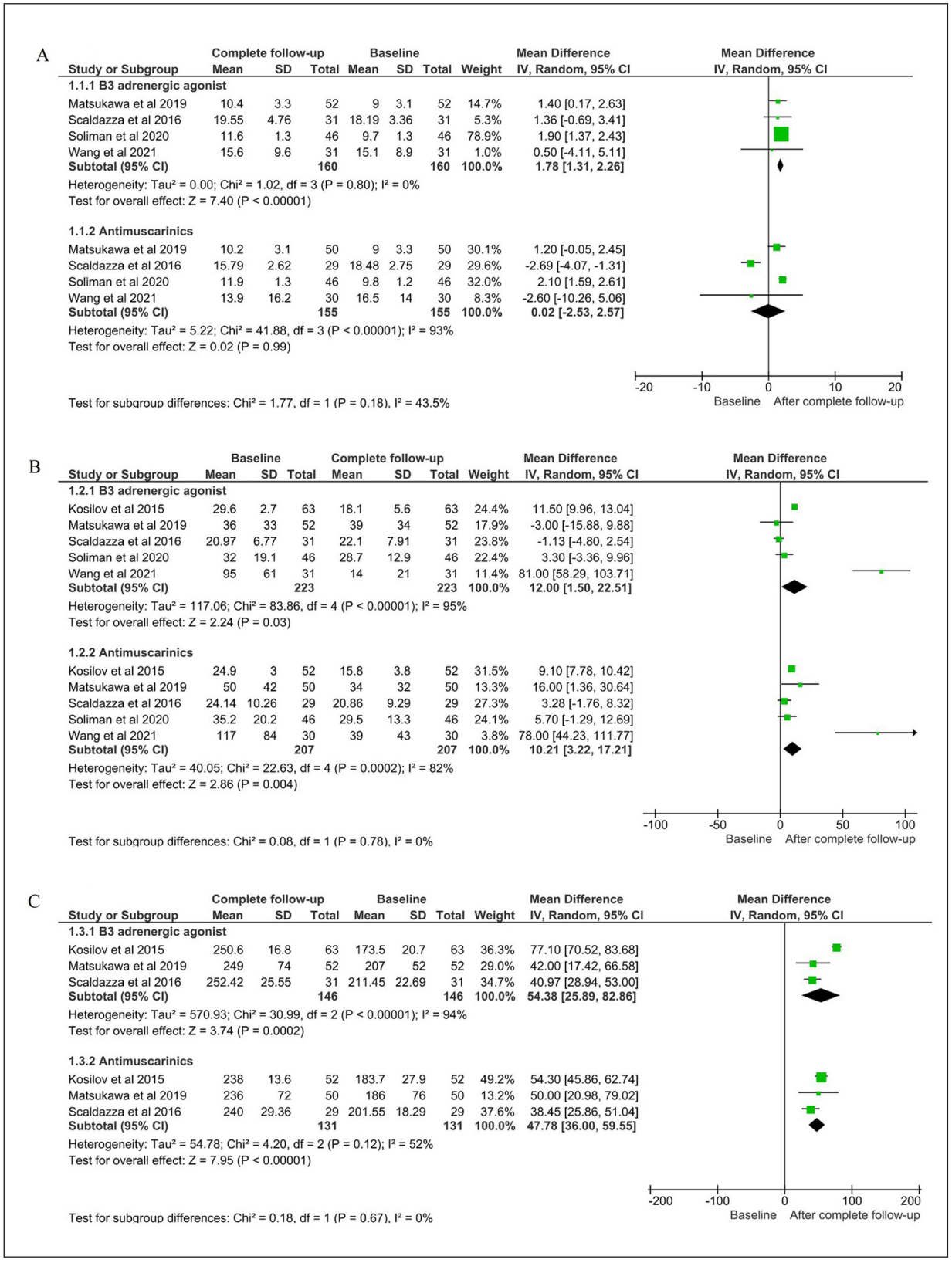


Figure 3. **A**, Meta-analysis of Maximum urinary flow or Qmax (m/s). **B**, Post-void residual or PVR (mL). **C**, Mean cystometric capacity or MCC (mL).

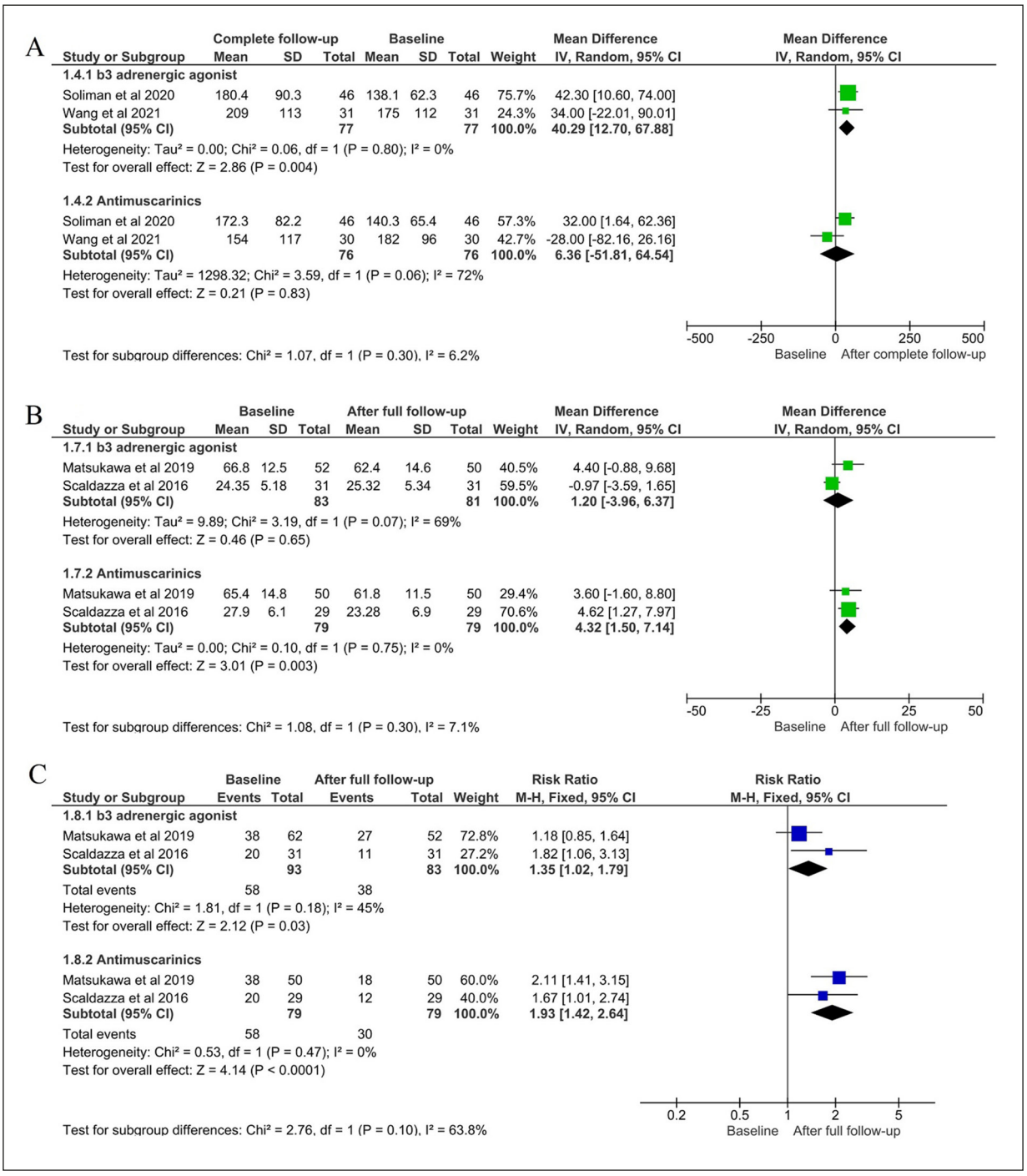


Figure 4. Meta-analysis of mean voiding volume or MVV (mL) (**A**), detrusor pressure at maximum urinary flow rate (cmH_2O) (**B**), and risk ratio of detrusor overactivity (DO) cases (**C**).

study period within the same analysis model (Figure 3A). However, we also found the difference between both subgroup improvement to be insignificant (p=.18), even though an individual arm of mirabegron-related flow amelioration was evident.

Our analysis of the PVR outcome revealed that both arms had effectively and significantly increased the PVR volume, with a value of 12.00 (-22.51, -1.50) mL and 10.21 (-17.21, -3.22) mL in mirabegron and antimuscarinics arm,

respectively (p<0.05) in both REM sub-analysis, though any statistical difference between those analyses was not observable (Figure 3B). Similar outcomes were also found in MCC analysis since both agents had a significant improvement after full study period, presented by an increase of MCC volume in mirabegron [MD, 54.38 (25.89, 82.86) ml; REM, 95% CI, p<0.05] and antimuscarinics [MD, 47.78 (36.00, 59.55) ml; REM, 95% CI, p<0.05] as presented in Figure 3C. A statistically meaningful (p<.05) increase in MVV was found among mirabegron arm by positive MD of 40.29 (12.70, 67.88) ml compared to 6.36 (-51.81, 64.54 ml in the antimuscarinics arm (Figure 4A); though both arm's difference was not significant (p= 0.3). In Pdet.Qmax, we observed a significant increase in antimuscarinics arm [MD, 4.32 (1.50, 7.14) cmH_2O] *vs.* mirabegron arm [MD, 1.20 (-3.96, 6.37) cmH_2O] which demonstrated insignificant outcomes (p>0.05) (Figure 4B). Moreover, we found both arms still disclosed a remarkable amount of DO cases in significantly proven analysis, even though the rate were quantitatively higher among antimuscarinics [RR; 1.93 (1.42, 2.64)] *vs.* mirabegron [RR; 1.35 (1.02, 1.79)] as exhibited in Figure 4C.

Discussion

The function of UDS parameter to evaluate a treatment's efficacy is commonly placed on such "grey" terms, to the point where its role is overlapped with the patient's questionnaire-based assessment as covered in OAB syndrome diagnosis. Although UDS is not an initial approach for individuals with LUTS, its mathematical delineation to represent the functional aspect of a urinary tract is becoming a considerable feature to be evaluated as it may act as a reliable and objective measurement[13,14]. Theoretically, profiling the UDS parameter by direct measurement of LUT function is correlated with radiological findings on ultrasonography (USG), which translates into a plausible association between UDS and subjective interpretation by details of patients reported symptoms[15]. However, "symptom" itself is eventually a subjective attitude reported by the patients without any exception on LUTs. Therefore, the role of UDS as an empirical evidence may remain as a mathematical reference rather than a guiding variable to confirm a treatment's efficacy[16].

This study basically focused on objective improvement as evaluated by UDS after a period, although the duration of the included studies varies. Whilst medication-based (e.g., mirabegron) is not the most preferred choice in approaching OAB, the necessity to explore a potentially compelling addition is relatively mandatory in modern urology; specifically, to document objective outcomes, hence confirming its efficacy. It represents an improvement from the pathomechanism perspective, for the dysfunctionality of the LUT will be depicted in patterns. The UDS parameter testing is also enabling approaches toward individualized approach in which the physician might have a better understanding of the disease, thus leaving a well-tailored decision-making in managing each case[14,17,18]. For that reason, the expectation to gather observable and anatomy-sensitive outcomes through UDS after either mirabegron as a β-3 agonist or antimuscarinics agents administration is a well-grounded premise.

Our study revealed mirabegron might significantly increase the mean Qmax by 1.78 ml/s, compared to the insignificant increase in the antimuscarinics arm with only 0.02 ml/s (p>.05) difference after a period of time[19-22]. An increase in Qmax is considered a positive influence among OAB populations since the value of <15 ml/s was an indication of voiding difficulty or risk for urinary retention; aside from the fact that solving the typical symptoms of OAB e.g., urgency or decreased inter-void interval is more clinically relevant rather than focusing on the uroflowmetry improvement[23-25]. The increase in PVR volume was also more remarkable in mirabegron although both arms showed statistically meaningful values[19-22,26]. This result partially portrayed a decrease in bladder overactivity, as more urine is more likely to be stored in the bladder rather than uncontrollably voided. However, the interpretation of this increase is debatable, considering the higher increase in PVR could also mean that the administration of both agents should be carefully done among patients with a progressive bladder's reorganization due to the bladder outlet obstruction (BOO)[27,28]. Therefore, a thorough identification of patient's complaint in storage or voiding symptoms is mandatory since an increase of PVR in BOO patients may represent the underlying chronic urinary retention.

We also observed some increase in MCC volume after the administration of both agents, with a higher MD in the mirabegron arm even though the difference to the antimuscarinics was not statistically significant[20,22,26]. This result implied that mirabegron will more likely increase the overall

bladder capacity after several time periods hence reducing the frequency of symptoms rate accordingly. It might also mean that the bladder is progressively getting better at storing urine at a higher volume closer to the normal MCC range of 300 to 600 mL, although the role of mean cystometric capacity may represent the bladder's capacity even better[29,30]. Interestingly, mirabegron arm exhibited a higher improvement in MVV by 40.29 mL after the completion of follow-up, compared to antimuscarinics agents with only 6.36 mL increase[19,21]. This quantitative evidence can be translated into the hypothesis that the patients might experience a reduced frequency symptoms rate since the more urine is stored in the bladder, the more urine will be voided after a period of time. Nevertheless, increase of MVV is representing an amelioration of the patients' storage symptoms, which were prominently complained among OAB populations[2,31].

Analysis of the data presented by Matsukawa et al[22] and Scaldazza et al[32] regarding the Pdet. Qmax also revealed a converse result compared to the aforementioned outcomes. The study by Scaldazza et al[32] reported that the mirabegron arm failed to show any improvement since the detrusor pressure is evidently increasing. However, the reported improvement by Matsukawa et al[22] might be attributed to its concomitant α1-blocker (silodosin 8 mg) use, which particularly need further investigation in future trials; even though the result is comparable to Scaldazza et al[20] which solely investigate mirabegron *vs*. solifenacin. The influence of prior antimuscarinics or even Botulinum toxin A induction among intervention group remains questionable. In some instances, PVR analysis in the trial by Wang et al[21] disclosed a marked improvement even though its pooled statistical weight is relatively low (3.8-11.4%). Despite variances of pre-intervention details, this review generally scoped that mirabegron is almost consistently better than antimuscarinics in ameliorating pathologic UDS findings in non-neurogenic OAB. We also secondarily evaluated the DO case rate, in which the antimuscarinics arm is disclosing higher RR value compared to mirabegron[20,22]. Therefore, less common DO cases after mirabegron administration can be expected as it might possess better detrusor control during the filling phase. The DO's role in OAB is commonly presented as a co-existing symptom from storing and voiding complaint, thus the association between bladder overactivity, BOO, and abnormal micturition pattern could be concluded by the DO rates since it generally represents the pathophysiology[28,32-34].

Though the UDS practice among global centers is progressively declining, the 2019 recommendation by International Consultation on Incontinence Research Society (ICI-RS) is still advocating a standardized UDS parameter panel to rule-out a potential of missing objectiveness at some extent; yet several guidelines also against UDS to primarily diagnose non-neurogenic OAB[37]. Considering the clinical utility of UDS remains controversial and reckoned as the main limitation of this review strength, its reliability may influence the decision making by confirming the diagnosis within on-board evidence rather than focusing solely to the patient's subjective report[35,36]. Mirabegron and UDS parameter study to estimate its efficacy hold such interesting clinical implication, since both variables were regarded as 'alternative' strategies in OAB. We captured the superiority of mirabegron compared to antimuscarinics in objective measurement through UDS; although pharmacology-based approach is eventually still placed on the 2nd line OAB treatment and variability among centres in conducting UDS parameter analysis should be acknowledged[8,9]. Nevertheless, this study had successfully delivered the main premise of its implicated PICO by confirming the magnitude of mirabegron to positively shift the UDS parameter among the included RCT.

Our study has several limitations, which mainly involved our study size due to strict PICO-reasoning and eligibility criteria to solely focus on UDS parameter improvement. Though this deterrent factor may influence the quality of our conclusion, we believe this is the first study to investigate time sensitive UDS outcomes after a considerably equal intervention. A unique perspective to view our findings is by considering the fact that UDS itself is not a primary diagnostic tool for OAB, and mirabegron is not the first-line pharmacologic treatment as well. Those statements partially explain our limitation of included population size since those trials which focused on class-to-class pharmacologic comparison is relatively novel in functional urologic care. Nevertheless, to answer its review implication and limitation, our study may be able to strengthen both variables' position in OAB management thus incorporating its value on the workup, and treatment should be possible in advance.

A higher heterogeneity rate in this study were observable in several outcomes, possibly caused

by a wide range of reported SD; reflecting a possible mathematical bias though within statistically preventable area by applying REM analysis. Rather than accounting the lack of evidence as the limitation, it is more reasonable to view this investigation as an opportunity and ground-basis to increase the number of UDS-based study among functional urology disease. As we are aiming for more thorough and objective pathologic assessment even though the current role of UDS in OAB workup are limited as an auxiliary diagnostic tool. For that reason, we believe this study will possess a cornerstone role in future functional urology by proposing this statistical model of evaluation, investigating the renewed role of UDS to confirm an agent efficacy, or correlate the UDS-findings with symptoms attenuation.

Conclusions

The emerging role of mirabegron to potentially replace antimuscarinics as the mainstay pharmacologic treatment in non-neurogenic OAB patients has been confirmed in this review. We outline the UDS parameter improvement among mirabegron arm were statistically higher compared to individuals receiving antimuscarinics. Therefore, mirabegron administration may translate into better functional micturition recovery and LUTS amelioration to achieve the major treatment goal. It is still highly recommended to conduct a standardized and larger UDS parameter-based trial to evaluate pharmacologic agents' efficacy, considering its role as a diagnostic workup remain controversial and emphasizing its objective aspect should be pivotal in future functional urology science.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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No funding was received for this study.

Authors' Contribution
All authors contributed equally to the preparation of this manuscript. Though, the proofreading and finalization was performed by the first author (S.M.W.).

Ethics Approval
Ethics Approval is not applicable to our study design since we conducted a review analysis. Therefore, the respective consents or approvals had been granted to the original authors of the literature included.

ORCID ID
Syah Mirsya Warli: 0000-0002-8339-1072; Naufal Nandita Firsty: 0000-0003-1668-6660; Adrian Joshua Velaro: 0000-0002-5871-6728; Debora Natalia: 0000-0001-7418-0620; Zaimah Z. Tala: 0000-0001-7910-4117.

Data Availability
All data and information related to this manuscript preparation is available on request by approaching the first author (S.M.W.) through the mentioned email address.

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