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Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH)

Hong-Jeng Yu, Alex Tong-Long Lin[1], Stephen Shei-Dei Yang[2], Ke-Hung Tsui[3], Hsi-Chin Wu[4], Chen-Li Cheng[5], Hong-Lin Cheng[6], Tony T. Wu[7] and Po-Hui Chiang[8]

Department of Urology, National Taiwan University Hospital, [1]Department of Urology, Taipei Veterans General Hospital and National Yang-Ming University, [2]Division of Urology, Department of Surgery, Buddhist Tzu Chi General Hospital, Taipei Branch, [3]Department of Urology, Chang Gung Memorial Hospital- Linkou, Taipei, [4]Department of Urology, China Medical University Hospital, [5]Department of Urology, Taichung Veterans General Hospital, Taichung, [6]Department of Urology, National Cheng Kung University Hospital, Tainan, [7]Department of Urology, Kaohsiung Veterans General Hospital, and [8]Department of Urology, Chang Gung Memorial Hospital- Kaohsiung, Kaohsiung, Taiwan

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Study Type – Therapy (RCT)
Level of Evidence 1b

What's known on the subject? and What does the study add?
Silodosin administered by 4 mg twice daily is as effective as tamsulosin 0.2 mg daily in treating patients with LUTS associated with BPH.

Relative to tamsulosin, silodosin has less cardiovascular side effects as judged by the minimal changes of blood pressure and pulse rats after treatment.

OBJECTIVE

- To test the hypothesis that the efficacy of silodosin would not be inferior to tamsulosin in treating patients with lower urinary tract symptoms associated with benign prostate hyperplasia (BPH).

PATIENTS AND METHODS

- At nine medical centres, 209 patients with an International Prostate Symptom Score (IPSS) of ≥13 were randomized to silodosin (4 mg twice daily) or tamsulosin (0.2 mg once daily) for 12 weeks.
- The primary efficacy measure was the mean change from baseline to endpoint in IPSS.
- The non-inferiority margin of the IPSS change was set at 1.0.
- Secondary efficacy measures included change in maximal urinary flow rate (Q_{max}) and health-related quality of life (HRQL) score.

RESULTS

- Of the 170 (81.3%) patients who completed the study, 86.2% in the silodosin group vs 81.9% in the tamsulosin group achieved a ≥25% decrease in IPSS ($P = 0.53$).
- The mean difference (silodosin minus tamsulosin) in IPSS change from baseline was −0.60 (95% confidence interval −2.15, 0.95), inferring the non-inferiority of silodosin to tamsulosin.
- The mean changes in the Q_{max} and HRQL score from baseline were comparable between the groups (both, $P > 0.05$).
Although patients receiving silodosin had a significantly higher incidence of abnormal ejaculation (9.7% vs tamsulosin 1.0%, $P = 0.009$), only 1.9% discontinued treatment.
- Tamsulosin treatment resulted in a significant reduction in mean systolic blood pressure (−4.2 mmHg, within-group $P = 0.004$) relative to the negligible change of silodosin (−0.1 mmHg, within-group $P = 0.96$)

CONCLUSION

- The trial shows the non-inferiority of silodosin 4 mg twice daily to tamsulosin 0.2 mg once daily in patients with symptoms of BPH.

KEYWORDS

benign prostatic hyperplasia (BPH), silodosin, non-inferiority test, tamsulosin

INTRODUCTION

BPH is the most common benign neoplasm in ageing men, which leads to LUTS including storage, voiding and post-micturition symptoms [1] that adversely affect health-related quality of life (HRQL) by interfering with normal daily activities and sleep patterns. Treatment of BPH is directed at improving patients' symptoms and HRQL, as well as relieving the resultant sequelae, such as acute urinary retention, bladder stones, and deteriorated renal function. Treatment options range from watchful waiting, medical therapies, to various surgical interventions. Each option is associated with a different balance of risks, benefits, and levels of uncertainty about the long-term outcome [2]. The main medical therapies for BPH include α_1-adrenoceptor (α_1-AR) blockers and 5α-reductase inhibitors. The former relieves the smooth muscle tension within the prostate and bladder neck by antagonizing these receptors, thereby increasing urinary flow and reducing LUTS. As smooth muscle contraction of human prostate and urethra is mainly regulated by α_{1A}-subtype whereas muscle contraction of peripheral vasculature is mainly regulated by α_{1B}-subtype, agents such as tamsulosin that has preferential selectivity for α_{1A}-AR has gained wide popularity due to its lower incidence of cardiovascular side-effects [3].

Silodosin is a novel highly selective α_{1A}-AR blocker recently developed in Japan. The affinity for the α_{1A}-AR over α_{1B}-AR subtype was 583-fold for silodosin, in contrast to the about 15-fold for tamsulosin [4]. Uroselectivity (selectivity for the human prostate) of silodosin has been found to be ≈200-fold higher than its selectivity for the aorta, in comparison to the ≈10-fold of tamsulosin [5,6]. Several clinical studies [7–9] have shown the clinical efficacy of silodosin in men with LUTS associated with BPH, including a notable decrease in both storage, voiding symptoms, and HRQL score [7] In addition, silodosin was shown to have early onset and sustained positive effects on urodynamic parameters [9].

To date, clinical studies comparing the safety and efficacy between silodosin and other α_1-AR blockers remains sparse. To evaluate whether the high selectivity of silodosin for the α_{1A}-AR in human prostate can translate into a clinical advantage relative to other available α_1-AR blockers, we performed a randomized, multicentre, double-blind, parallel-group comparison study to compare the safety and efficacy of silodosin and tamsulosin in treating patients with LUTS associated with BPH. However, the standard tamsulosin dosage used in clinical practice in the USA and Europe ranges from 0.4 to 0.8 mg/day. On the contrary, several studies have shown that low-dose tamsulosin (0.2 mg/day) is an effective treatment for Asian men with LUTS/BPH, and is generally well tolerated as well. The proposed reasons for this may be explained by relatively smaller transitional zone growth and bodyweight in Asian men [10–12]. Considering the population in Taiwan is similar to that in other Asian countries, we adopted the recommended dose of tamsulosin 0.2 mg once daily for comparison.

PATIENTS AND METHODS

This was a 12-week, randomized, double-blind, multicentre study conducted at nine medical centres in Taiwan from July 2007 to September 2008. Men aged ≥40 years with an IPSS of ≥13, a HRQL score of ≥3, a prostate volume of ≥20 mL, and a maximal urinary flow rate (Q_{max}) of <15 mL/s with a voided volume of ≥100 mL were eligible for enrolment. Key exclusion criteria were previous prostate surgery, a history of prostate cancer, neurogenic bladder, bladder neck constriction, urethral stricture, bladder calculus, active UTI, a postvoid residual urine volume of >250 mL, exposure to sex hormone within 3 months prior to the washout period, renal dysfunction (serum creatinine of >2.0 mg/dL), a history of severe liver impairment, severe cardiovascular diseases, severe hypotension, and known hypersensitivity or history of active substance abuse (including alcohol) within the past 2 years. All procedures were performed in compliance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Investigational Review Boards at all participating sites reviewed and approved the protocol. All patients provided written informed consent before enrolment. After completing 7-day 'washout' and 7-day observation periods, patients were randomized to receive oral silodosin (4 mg twice daily) or tamsulosin (0.2 mg in the morning and one placebo capsule in the evening) for 12 weeks. Both investigators and patients were 'blinded' to treatment.

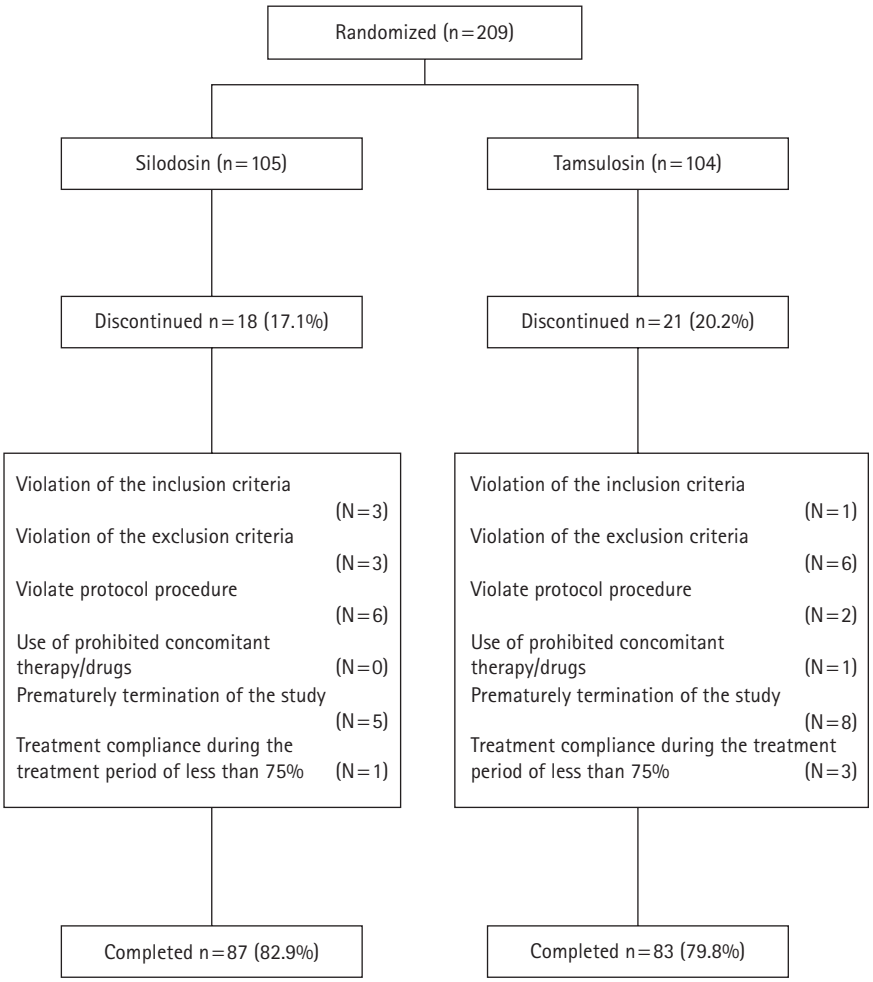
All randomized patients attended clinic at 0 (initiation of treatment), 2, 4, 8, and 12 weeks. During each visit, subjective symptoms (IPSS and HRQL scores) were recorded. Uroflowmetry and postvoid residual urine were measured at 0, 4 and 12 weeks. The primary endpoint for efficacy was the change in the IPSS from baseline. Patients who achieved a ≥25% reduction in the IPSS from baseline were considered as responders. The main secondary end points were change in Q_{max} and HRQL from baseline. The changes in IPSS subscores (voiding and storage symptom scores) were also analysed.

Blood pressure and pulse rate was measured at 0, 2, 4, 8 and 12 weeks of the treatment period (or at withdrawal); clinical laboratory tests including haematology, biochemistry and urine analysis were performed at 0, 4 and 12 weeks (or at withdrawal). All adverse events (AEs) were recorded and assessed for severity and causal relationship with taking the study drugs by the investigators.

Analysis of non-inferiority was conducted using the confidence limit approach [13,14]. The difference in IPSS change between silodosin and tamsulosin from baseline to 12 weeks was calculated. The non-inferiority margin was set at 1.0 [15], i.e. non-inferiority could be shown if the upper limit of two-sided 95% CI for the difference of the change in the IPSS falls below 1.0. Based on this assumption, the number of patients required to verify the non-inferiority of silodosin to tamsulosin with a one-sided statistical significance level of 2.5% and a power of 80% was calculated as 80 patients per group. It was anticipated that up to 10% of randomized patients was ineligible for the clinical per protocol (PP) population. Therefore, ≈ 200 patients were recruited to provide 160 PP evaluable patients.

Within-group comparisons between efficacy parameters at endpoint and at baseline were conducted using the single-sample *t*-test. Between-group comparisons in efficacy parameters were analysed using the analysis of covariance including treatment and study site as fixed effects, and the baseline measure of that efficacy parameter as the covariate. The percentage of IPSS responders and the frequency of AEs between the treatment groups were compared using Fisher's exact test. For all tests, a $P \leq 0.05$ was considered to indicate statistical significance.

FIG. 1. Flow diagram of patient disposition.



Variable	Silodosin	Tamsulosin	*P*
Number patients	87	83	
Mean (SD):			
Age, years	67.5 (9.3)	65.0 (8.8)	0.08
Body mass index, kg/m^2	25.0 (2.7)	24.5 (2.9)	0.20
Prostate volume, mL	44.8 (24.2)	38.2 (16.7)	0.02
IPSS-Total	19.3 (4.5)	19.8 (4.5)	0.41
IPSS-Voiding	12.1 (3.3)	13.0 (3.3)	0.10
IPSS-Storage	7.1 (3.1)	6.9 (3.1)	0.59
HRQL score	3.8 (0.8)	3.7 (0.8)	0.21
Q_{max}, mL/s	10.3 (2.8)	10.6 (2.8)	0.45

TABLE 1 Baseline demographic characteristics

RESULTS

In all, 209 patients were recruited and randomized to receive silodosin (105) or tamsulosin (104). Of these patients, only 170 (81.3%) completed the study, including 87 in the silodosin group and 83 in the tamsulosin group. The proportion of patients discontinued from study were comparable ($P = 0.463$) between the groups. The flow diagram of patient disposition is depicted in Fig. 1. The groups were well compatible in baseline characteristics (Table 1), except that patients in the silodosin group had a larger prostate volume (ean [SD] 44.8 [24.2] mL vs tamsulosin 38.2 [16.7] mL, $P = 0.02$) and had a marginally higher incidence of previous acute urinary retention (8.7% vs tamsulosin 2.9%, $P = 0.063$). Hypertension was the most frequently reported concomitant disease in both groups.

EFFICACY MEASUREMENT

The mean changes of primary and secondary efficacy variables at 2 and 12 weeks from baseline are summarized in Table 2. The change in IPSS over time is also depicted in Fig. 2. The percentage of patients achieving a ≥25% reduction in IPSS at the end of treatment was comparable between the groups (silodosin 86.2% vs tamsulosin 81.9%, $P = 0.53$). After treatment, patients in both groups achieved a significant reduction in IPSS (silodosin −7.2 and tamsulosin −6.7) at 2 weeks (both $P < 0.001$ for within-group comparisons). There was further improvement, albeit to a lesser degree, over the study period (Fig. 2) and the mean change from baseline in IPSS at the end of treatment was −10.6 for silodosin and −10.0 for tamsulosin. Comparisons between silodosin and tamsulosin at 2 and 12 weeks both showed no significant differences ($P = 0.53$ at 2 weeks and $P = 0.44$ at 12 weeks).

The mean difference in IPSS change over the 12-week treatment between the groups was −0.6 (silodosin had a larger reduction than tamsulosin) in the PP cohort, with the 95% CI ranging from −2.15 to 0.95 (Fig. 3). The upper 97.5% confidence limit for the difference between two groups was 0.95, which was lower than the pre-specified 1.0 margin. Analysis using the intent-to-treat (ITT) cohort also obtained similar results (difference −1.0, 95% CI −2.57, 0.56). Thus, the non-inferiority of silodosin to tamsulosin in IPSS improvement could be confirmed.

For the secondary endpoint variables, both silodosin and tamsulosin achieved significant improvements at the end of treatment in voiding symptom score, storage symptom score, Q_{max}, and HRQL score from baseline (Table 2, within-group comparison, all $P <$ 0.001). Between-group comparisons for the mean change at 12 weeks from baseline in voiding symptom score (silodosin −7.1 vs tamsulosin −6.7, $P = 0.47$), storage symptom score (silodosin −3.5 vs tamsulosin −3.3, $P = 0.55$), HRQL score (silodosin −1.4 vs tamsulosin −1.2, $P = 0.45$), and Q_{max} (silodosin 0.9 mL/s vs tamsulosin 1.6 mL/s, $P = 0.25$)

were not statistically significantly different (Table 2).

SAFETY EVALUATION

During the treatment period, 52.4% of patients in the silodosin group and 43.7% of those in the tamsulosin group reported at least one AE, respectively ($P = 0.26$). Most of the AEs in both groups were mild and well tolerated. The percentage of patients reporting at least one moderate or severe AE was similar between the treatment groups (silodosin 8.7% vs tamsulosin 11.7%, $P = 0.49$). The two most common AEs were abnormal ejaculation (silodosin 9.7% vs tamsulosin 1.0%, $P = 0.009$) and dizziness (silodosin 7.8% vs tamsulosin 2.9%, $P = 0.21$). Regardless of the high incidence (9.7%) of abnormal ejaculation in the silodosin group, only two (1.9%) patients discontinued treatment.

The mean (SD) change in systolic blood pressure (SBP) from baseline to the end of treatment was significantly higher (between-group $P = 0.02$) in the tamsulosin group (–4.2 [14.5] mmHg, within-group $P = 0.004$) relative to the negligible change in the silodosin group (–0.1 [14.2] mmHg, within-group $P = 0.96$). The change in diastolic blood pressure (DBP) was also marginally higher in the tamsulosin group (–2.0 [10.3] mmHg vs silodosin 0.2 (9.9) mmHg, $P = 0.06$), although it did not reach statistical significance. There was a significant decrease in pulse rate in patients receiving tamsulosin (–1.9 [9.4] beats/min bpm, within-group $P = 0.04$), but not in those receiving silodosin (1.0 [11.8] beats/min, within-group $P = 0.83$). The mean changes of standing/sitting BP and pulse rate between silodosin and tamsulosin groups are detailed in Table 3. In summary, there were significant changes in intra-group comparisons in sitting SBP (all post-baseline evaluation points), standing SBP (at 8 weeks), sitting DBP (at 2 weeks, 8 weeks, end of study), standing DBP (at 8 weeks), and pulse rate (at end of study) in the Tamsulosin group. All of these findings were minor and none of them was clinically significant. On the other hand, the comparison between the silodosin group and tamsulosin group had significant differences in sitting SBP ($P = 0.02$) and in pulse rate at 12 weeks ($P = 0.03$).

DISCUSSION

The present study showed that silodosin 4 mg twice daily was not inferior to tamsulosin 0.2 mg once daily in patients with symptoms of BPH. The changes in IPSS, HRQL score and Q_{max} after treatment were all comparable between the groups. Although tamsulosin is used in higher doses in Western countries (0.4–0.8 mg daily), a dose of 0.2 mg daily is recommended in Asian countries [16,17]. The present result is consistent with previously published data from a phase 3 study conducted on 475 Japanese patients [15]. In that study, comparable efficacy was shown between silodosin and tamsulosin in improving LUTS associated with BPH. However, silodosin showed faster onset of treatment response, as it elicited a significantly larger decrease in IPSS than tamsulosin did at 2 weeks [15]. Recently, an extended study also showed that the efficacy and safety of silodosin were sustained for 1 year [18].Combined data from two phase 3 studies conducted in the USA that treated 923 patients either with silodosin or placebo for 12 weeks showed similar safety and efficacy of silodosin 8 mg once daily in LUTS associated with BPH [3]. The pooled data analysis also showed that the clinical effects of silodosin occurred fairly early: significant improvement in urinary flow could occur at 2–6 h and significant reductions in urinary symptoms by 3–4 days after the initiation of treatment [7]. Furthermore, the clinical effectiveness was seen not only in patients with mild symptoms, but also in those with severe symptoms. These results have clinical implications: the early onset of treatment effect may lead to better adherence to medication by patients, whereas the effectiveness in patients with severe

TABLE 2 Efficacy outcome measures

Outcome measure	Mean (SD) change from baseline: Silodosin	Tamsulosin	Difference silodosin vs tamsulosin, adjusted mean (95% CI)	*P*
IPSS-Total at:				
2 weeks	–7.2 (5.2)	–6.7 (5.2)	–0.50 (–2.06, 1.06)	0.53
12 weeks	–0.6 (5.1)	–10.0 (5.1)	–0.60 (–2.15, 0.95)	0.44
IPSS-Voiding at:				
2 weeks	–5.1 (3.8)	–4.8 (3.8)	–0.31 (–1.46, 0.84)	0.59
12 weeks	–7.1 (3.8)	–6.7 (3.9)	–0.43 (–1.60, 0.74)	0.47
IPSS-Storage at:				
2 weeks	–2.1 (2.5)	–1.9 (2.5)	–0.22 (–0.97, 0.52)	0.55
12 weeks	–3.5 (2.2)	–3.3 (2.2)	–0.20 (–0.85, 0.45)	0.55
HRQL Score at:				
2 weeks	–0.9 (1.0)	–0.8 (1.0)	–0.15 (–0.45, 0.16)	0.34
12 weeks	–1.4 (1.1)	–1.2 (1.1)	–0.20 (–0.52, 0.12)	0.45
Q_{max} at:				
12 weeks	0.9 (4.2)	1.6 (4.2)	–0.74 (–2.01, 0.52)	0.25
% patients with ≥25% improvement in IPSS	**86.2**	**81.9**	**–**	**0.53**

FIG. 2. The change in IPSS over time.

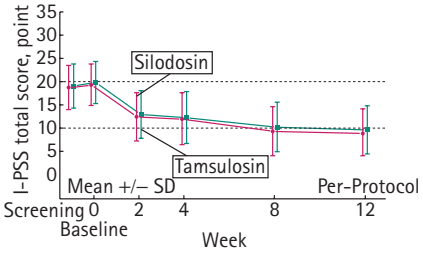
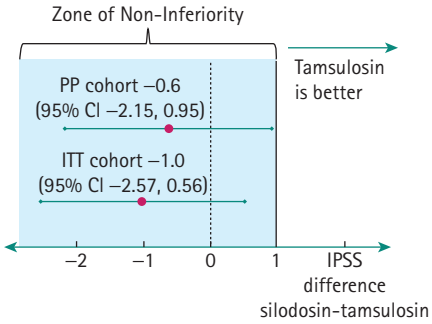


FIG. 3. Analysis of non-inferiority for IPSS change between silodosin and tamsulosin. Non-inferiority to tamsulosin of silodosin was confirmed by the upper limit of the 95% CI of 0.95 at 12 weeks in the PP cohort, and of 0.56 at 12 weeks in the ITT cohort.



Variable	Mean (SD) change from baseline		P
	Silodosin	Tamsulosin	
Sitting SBP at:			
Baseline	132.4 (16.48)	131.4 (15.82)	0.64
12 weeks	−0.1 (14.20)	−4.2 (14.58)	0.02
Standing SBP at:			
Baseline	133.4 (16.36)	130.3 (16.59)	0.17
12 weeks	0.1 (14.32)	−2.1 (14.01)	0.09
Sitting DBP at:			
Baseline	79.6 (9.35)	79.2 (10.04)	0.70
12 weeks	0.2 (9.88)	−2.0 (10.27)	0.06
Standing DBP at:			
Baseline	81.5 (10.56)	81.0 (11.05)	0.71
12 weeks	−0.4 (10.11)	−1.3 (9.12)	0.39
Pulse rate at:			
Baseline	75.0 (11.40)	75.2 (10.97)	0.89
12 weeks	1.1 (11.76)	−1.9 (9.43)	0.03

TABLE 3
Mean changes in BP and pulse rate between the silodosin and tamsulosin groups

symptoms may reduce the likelihood of undergoing surgery.

Given the placebo effect may reduce urinary symptoms by up to 20% in medical therapy for BPH [19], only patients achieving a ≥25% decrease in the IPSS after treatment were considered as responders. In the present study, the percentage of responders was high and comparable (silodosin 86.2% vs tamsulosin 81.9%, $P = 0.53$) between the treatment groups. The non-inferiority margin of 1.0 was chosen according to previous studies which showed the difference in the IPSS change after treatment was ≈2.0 between placebo and tamsulosin. Therefore, half of this value 1.0 was chosen as the non-inferiority margin [15]. The mean difference (silodosin minus tamsulosin) in IPSS change between the groups at the end of treatment was −0.6 (95% CI −2.15, 0.95) in the PP cohort and −1.0 (95% CI −2.57, 0.56) in the ITT cohort, confirming the non-inferiority of silodosin to tamsulosin. A larger sample size is required to ascertain whether silodosin is equivalent or even better than tamsulosin in improving LUTS.

Several studies have shown that treatment with selective α_{1A}-AR blockers is associated with considerable disturbances in ejaculatory function especially retrograde ejaculation. Possible mechanisms include impaired bladder neck closure leading to retrograde ejaculation [20] and insufficient contraction of the vas deferens or seminal vesicle [21], as both prostate urethra and vas deferens are predominately innervated by α_{1A}-ARs. The reported rate of abnormal ejaculation ranged from 22.3% to 28% [22] for silodosin therapy, significantly higher than the 5–10% for tamsulosin therapy [19]. This difference could be at least in part be attributed to the relatively higher uroselectivity and α_{1A}-AR affinity of silodosin relative to tamsulosin. While the present study also showed a significantly higher incidence of abnormal ejaculation among patients treated with silodosin (9.7% vs tamsulosin 1.0%, $P = 0.009$), the incidence in both groups was much lower than previous reports [16,20]. Also, the rate of the discontinuation from treatment was very low. A plausible explanation is that a substantial proportion of the older Taiwanese men do not engaged in sexual activity any longer and thus sexual satisfaction is not considered as a major concern. Of note, *post hoc* analyses using data obtained from a large phase 3 clinical study of silodosin showed that patients with abnormal ejaculation was associated with much larger improvements in LUTS [23]. Irrespective of this finding, abnormal ejaculation may remain to be a relevant issue for young patients.

It is estimated that asymptomatic hypotension occurs in 7% with tamsulosin therapy [3,24], and in an animal study, it has been shown that tamsulosin caused a greater reduction of BP in older dogs, while silodosin had a less hypotensive effect in all age groups [25]. This finding coincides with the present study, as tamsulosin resulted in a significant reduction in mean SBP compared with a negligible change with silodosin. This finding may be explained by the fact that silodosin has a higher affinity for α_{1A}-AR over α_{1B}-AR, as compared with tamsulosin [4]. A hypotensive effect may pose a significant problem among the older population because it may lead to serious morbidity, e.g. falls and fractures.

The major drawback of this study is that the regimen, 0.2 mg dose of tamsulosin, which is the recommended dose in Asia, limits the application of the findings to Western countries where 0.4–0.8 mg of tamsulosin is prescribed. Recently, the European Silodosin Study Group reported a large-scale trial which enrolled 1228 men and compared the efficacy of silodosin (8 mg once daily), tamsulosin (0.4 mg once daily) and placebo [26]. The results showed that the overall efficacy of silodosin is not inferior to tamsulosin, which is consistent with our present study.

In conclusion, silodosin, a highly selective α_{1A}-AR blocker, administered at 4 mg twice daily was not inferior to tamsulosin 0.2 mg once daily in patients with moderate-to-severe LUTS associated with BPH. Although abnormal ejaculation occurred more often in patients receiving silodosin, it rarely resulted in discontinuation of treatment. In addition, the effect on cardiovascular effect was negligible. Thus, silodosin can be considered an effective and safe treatment for BPH.

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CONFLICT OF INTEREST

Hong-Jeng Yu, Alex Tong-Long Lin, Stephen Shei-Dei Yang, Ke-Hung Tsui, His-Chin Wu, Chen-Li Cheng, Hong-Lin Cheng, Tony T. Wu and Po-Hui Chiang are all study investigators for Synmosa. Source of funding: Synmosa Pharmaceutical Company, Taiwan.

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Correspondence: Hong-Jeng Yu, Department of Urology, National Taiwan University Hospital, No.7, Chung-Shan South Road, Taipei, Taiwan.
e-mail: yhj5251@ntu.edu.tw

Abbreviations: **Q_{max}**, maximal urinary flow rate; **HRQL**, health-related quality of life; **AR**, adrenoceptor; **AE**, adverse event; **PP**, per protocol; **ITT**, intent-to-treat; **(S)(D)BP**, (systolic) (diastolic) blood pressure.