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Efficacy of Continuous Dosing of Tadalafil Once Daily vs Tadalafil On Demand in Clinical Subgroups of Men With Erectile Dysfunction: A Descriptive Comparison Using the Integrated Tadalafil Databases

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Abstract

Introduction—Various factors play a role in the development of erectile dysfunction (ED).

Aim—To provide a descriptive comparison of erectile function response for tadalafil on-demand (PRN) and once-daily (OAD) dosing regimens in patients with common comorbid conditions, treatments, or risk factors that can be considered when treating ED.

Methods—In total, 17 PRN and 4 OAD placebo-controlled studies were included in the integrated database in these pooled analyses. Data were analyzed from patients treated with placebo, tadalafil 10 mg (low dose), and 20 mg (high dose) for the PRN studies and placebo, tadalafil 2.5 mg (low dose), and 5 mg (high dose) for the OAD studies.

Main Outcome Measures—The effects of tadalafil were measured using the International Index of Erectile Function administered from baseline to week 12. A descriptive comparison of the efficacy of tadalafil PRN vs OAD was examined in the clinical populations.

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SUPPLEMENTARY DATA

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Results—Baseline characteristics of 4,354 men were comparable between the PRN and OAD groups, with differences seen only in the variables of race, body mass index (BMI) of at least 30 kg/m^2, and alcohol use. Tadalafil was efficacious at improving erectile function for all clinical populations, except for the low-dose OAD group, which demonstrated a weaker effect vs placebo than the high-dose OAD group, and the low- and high-dose PRN groups vs placebo for patients with BMI of at least 30 kg/m^2 for patients without a cardiovascular disorder, smokers, patients with ED duration shorter than 1 year, and patients without previous phosphodiesterase type 5 inhibitor use. Tadalafil was efficacious for patients with or without diabetes mellitus, arterial hypertension, hyperlipidemia, and alcohol use at baseline.

Conclusion—Tadalafil OAD and PRN regimens showed efficacy in patients with ED. No clinical populations of patients with ED seemed to benefit overwhelmingly from one dose regimen over the other.

Keywords

Erectile Dysfunction; Phosphodiesterase Type 5 Inhibitors; Tadalafil; Data Pooling; Treatment Efficacy

INTRODUCTION

Numerous factors such as age, weight, diabetes mellitus, cardiovascular disorders, smoking, arterial hypertension, and alcohol use can play a role in the development of erectile dysfunction (ED).[1–6] Owing to the various physical and psychosocial aspects of ED,[7] treatment of ED extends beyond improving erectile function (EF) response and satisfaction.[8–11]

Phosphodiesterase type 5 (PDE5) inhibitors represent the first-line drug treatment for ED.[12,13] The PDE5 inhibitor tadalafil, with on-demand (PRN)[14–17] and once-daily (OAD)[18–22] dosing regimens, has demonstrated efficacy and safety in the treatment of ED. Psychosocial outcomes, spontaneity, and time concerns have shown significant improvement after treatment with long-acting compared with short-acting PDE5 inhibitors.[23,24] Treatment with tadalafil OAD has improved EF in patients with mild and mild to moderate impairments in EF after PRN PDE5 inhibitor therapy.[21,25] Other studies have shown that the OAD dosing regimen leads to high treatment satisfaction for the patient and his partner[19,25–27] and allows patients to have spontaneous sexual activity, thereby changing the requirement for dosing and sexual activity to be linked. An OAD dosing regimen also improves the patient's ability to achieve and maintain erections and improves treatment satisfaction and psychosocial outcomes.[28] In addition, early initiation of the tadalafil OAD regimen protects against penile length loss after nerve-sparing radical prostatectomy.[29]

Few clinical trials have compared the OAD and PRN regimens in the same study directly. Some researchers have reported the tadalafil OAD regimen is more efficacious in treating ED compared with the PRN dosing regimen,[30,31] whereas others have reported no significant differences between tadalafil OAD and PRN dosing regimens in improving erection and sexual satisfaction of patients with ED.[32] In 2014, Porst et al[33] reported on an integrated analysis of data from six placebo-controlled studies (OAD 2.5 or 5 mg) in patients

with different ED characteristics and comorbidities and determined that treatment with the tadalafil OAD regimen resulted in clinically important improvements in patients with mild, moderate, or severe ED. In that study, there was an improvement in International Index of Erectile Function erectile function domain (IIEF-EF) scores in patients with arterial hypertension, cardiac disorder, or hyperlipidemia after treatment with tadalafil 2.5 or 5 mg; however, patients who were obese, smokers, and those with psychogenic ED reached a minimal clinically important difference (MCID; defined as mean improvement in IIEF-EF scores of at least four points[34]) only after treatment with tadalafil 5 mg. Lewis et al[35] evaluated the efficacy of tadalafil in men with ED by demographic and ED characteristics and determined that the tadalafil PRN dosing regimen improved EF across a broad range of patients with ED, including patients with different comorbid conditions.

To our knowledge, there are no published integrated analyses that have looked at the efficacy of tadalafil PRN and OAD dosing regimens in the same context. Clinicians often seek prescribing information and guidance on the two regimens to provide the patient with information to assist in making appropriate treatment decisions.

AIM

In this article, we provide a descriptive comparison of EF and orgasmic function (OF) response to tadalafil PRN and OAD dosing regimens using the integrated tadalafil clinical trial databases. The purpose of this report is to offer this descriptive comparison of pooled data from tadalafil ED studies in patients with common comorbid conditions, treatments, or risk factors that might be considered when treating ED.

METHODS

Studies

In total, 17 PRN[14–17,36] and 4 OAD[19–21,37] placebo-controlled studies in men with ED were included in the integrated (March 2013) database that was used in these pooled analyses. Tadalafil studies in men with lower urinary tract symptoms associated with benign prostatic hyperplasia were excluded from these analyses owing to differences in the study population. Details about the general study design for these studies have been published.[14–17,19–21,36,37] For the 17 PRN studies that had identical study designs, data were analyzed from patients treated with placebo, tadalafil 10 mg (low dose), and tadalafil 20 mg (high dose). For the OAD studies, data were analyzed from patients treated with placebo, tadalafil 2.5 mg (low dose), and tadalafil 5 mg (high dose). The 5-mg PRN dose was not included in the analyses for this report because it is not a globally approved dose by regulatory authorities for the treatment of ED; therefore, for this report, the 10-mg PRN dose is considered low-dose PRN. Two studies were OAD registration studies that included men with ED,[19,20] and one study determined the impact of OAD treatment for men with ED on the sexual quality of life of their female partners.[21] One study evaluated OAD treatment in PDE5 inhibitor-naive men with ED.[37]

Patient Population

Patients were men (≥18 years old) with at least a 3-month history of ED who remained sexually active with the same heterosexual partner. Some exclusion criteria included a history of certain cardiovascular diseases (eg, unstable angina, recent myocardial infarction, recent myocardial revascularization, and poorly controlled blood pressure), a history of radical prostatectomy with subsequent failure to achieve erections, and patients who had penile implants or deformities, clinically significant renal or hepatic insufficiency, and current treatment with nitrates, cancer chemotherapy, or antiandrogens. The details about the inclusion and exclusion criteria for some of these studies have been published.[14–17,19–21,36,37]

Clinical Populations

Using the IIEF-EF and IIEF-OF outcomes, we completed analyses according to the following subgroups (referred to as clinical populations): age (<50, 50–64, or ≥65 years), baseline BMI (<30 vs ≥30 kg/m^2), diabetes mellitus at baseline (yes vs no), baseline cardiovascular disorder (yes vs no), baseline hypertension (yes vs no), baseline hyperlipidemia (yes vs no), smoking or current use of tobacco (yes vs no), current use of alcohol (yes vs no), previous PDE5 inhibitor use (yes vs no), number of antihypertensive medications (none, one, or more than one), and ED duration (<1 vs ≥1 year). Some cardiovascular disorders included cardiomyopathy, myocardial infarction, angina, arrhythmia, tachycardia, atrioventricular block, cardiac failure, congenital cardiac conditions, pulmonary hypertension, pulmonary infarction, abnormal blood pressure, ventricular failure, aortic aneurysm, or arteriosclerosis.

Statistical Analyses

Demographics and baseline characteristics were summarized for the tadalafil PRN and OAD low-dose (10 mg for PRN, 2.5 mg for OAD) and high-dose (20 mg for PRN, 5 mg for OAD) groups. Variables examined for baseline characteristics included age (<50, 50–64, or ≥65 years), race, BMI (<30 vs ≥30 kg/ m^2), mean systolic and diastolic blood pressure, ED duration (<1 vs ≥1 year), mean IIEF-EF score, IIEF severity (severe = 1–10, moderate = 11–16, mild ≥ 17), presence or absence of diabetes mellitus, hypertension, hyperlipidemia, or cardiovascular disorders, alcohol use, smoking, previous use of PDE5 inhibitors, use of any antihypertensive medications, and number of antihypertensive medications (none, one, or more than one). Percentages were based on the total number of patients with non-missing data for the specified variables. A descriptive comparison of the efficacy of tadalafil PRN vs OAD regimens was examined in the clinical populations for the IIEF-EF and IIEF-OF domains. The efficacy variables were evaluated at the 12-week study end point, with missing values imputed using the last observation carried forward. Analysis of covariance was used to analyze the IIEF-EF and IIEF-OF domains, including baseline, study (regimen), subgroup, treatment (regimen), and subgroup-by-treatment (regimen) interaction in the model, with the notation of A(B) indicating A nested in B. Placebo-adjusted differences were calculated for tadalafil PRN and OAD doses using their respective placebo groups based on least-squares means from the analysis of covariance model. The clinical relevance of IIEF-EF changes was interpreted using the MCID of at least a four-point change from

baseline to end point[34] and at least 23% change from baseline to end point for Sexual Encounter Profile, question 3 (SEP3)[38]; these threshold values do not exist for IIEF-OF or the other ED indicators. The odds ratio in achieving the MCID was calculated for the tadalafil PRN and OAD dosing regimens vs their respective placebo groups using a logistic regression model, with the same terms as in the analysis of covariance model described earlier. All analyses were exploratory in nature and without multiplicity adjustment. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

MAIN OUTCOME MEASURES

The effects of tadalafil on EF were measured with the IIEF,[39] which is a 15-item questionnaire that assesses domains of male sexual function that include EF, OF, sexual desire, intercourse satisfaction (IS), and overall satisfaction (OS). The IIEF was administered at baseline and at 4-week intervals during the treatment period (after baseline). In this study, patient scores were examined on the EF and OF domains of the IIEF. The EF domain score (sum of questions 1 [erection frequency], 2 [erection firmness], 3 [frequency of partner penetration], 4 [frequency of maintaining erection after penetration], 5 [ability to maintain erection to completion of intercourse], and 15 [confidence in achieving and maintaining erection]) ranges from 1 to 30. The OF domain score (sum of questions 9 [frequency of ejaculation] and 10 [feeling of orgasm and climax frequency]) ranges from 0 to 10. An increase in the EF or OF score indicates an improvement in these IIEF domains. Patient scores also were examined for SEP3 (successful completed intercourse attempts). In addition, patient scores were examined for the IIEF-IS domain (questions 6–8) and IIEF-OS domain (questions 13 and 14; supplement section).

RESULTS

Demographics and Baseline Characteristics

Demographics and baseline illness characteristics for the patient population of 4,354 men (PRN, n = 3,345; OAD, n = 1,009) are presented in Table 1. The baseline characteristics were generally comparable between the PRN and OAD groups for some variables such as age (mean = 54.7 vs 55.6 years), blood pressure (mean systolic = 130.5 vs 130.8 mmHg; mean diastolic = 81.1 vs 79.7 mmHg), ED duration (<1 year = 12.5% vs 11.2%; ≥1 year = 87.5% vs 88.8%), IIEF-EF score (mean = 14.5 vs 14.6), and IIEF severity (mild [≥17] = 39.0% vs 40.6%; moderate [11–16] = 28.3% vs 28.0%; severe [1–10] = 32.7% vs 31.5%). There was a difference between the PRN and OAD groups for the variables of race including Caucasian patients (50.4% vs 84.3%) and Asian patients (39.5% vs 0.4%). Other variables that differed between the PRN and OAD groups included BMI of at least 30 kg/m^2, alcohol use, and diabetes mellitus, with the OAD group having a larger percentage of patients who were obese (27.3% vs 19.1%), more patients who regularly used alcohol (67.5% vs 54.6%), and a larger percentage of patients who did not have diabetes mellitus (84.0% vs 78.4%).

Efficacy

IIEF-EF Domain—Treatment with tadalafil 5 mg (high dose) OAD and 10 mg (low dose) and 20 mg (high dose) PRN demonstrated significantly improved EF as measured by the

placebo-adjusted IIEF-EF LS mean improvements (Figure 1) for all variables examined. Tadalafil 2.5 mg (low dose) did not demonstrate significantly improved EF in several clinical populations (Figure 1). In some clinical subgroups, there was insufficient powering owing to small numbers. The results were consistent across all doses and regimens, with few exceptions. There was a difference in response in the low-dose OAD regimen across different age groups, with a weaker effect seen for the low-dose OAD regimen for patients younger than 50 and at least 65 years old. There was a weaker effect seen in the low-dose OAD regimen for patients with BMI of at least 30 kg/m^2, patients without a cardiovascular disorder, patients who smoked, patients with ED duration shorter than 1 year, and patients without previous PDE5 inhibitor use. Tadalafil was efficacious across all doses and regimens for patients with or without diabetes mellitus, hypertension, hyperlipidemia, and alcohol use at baseline. There was a numerical difference in response for low-dose OAD and PRN regimens compared with high-dose regimens in patients taking more than one antihypertensive agent.

The proportion of patients achieving MCID at end point in the IIEF-EF domain and the odds ratios of tadalafil low-dose (OAD 2.5 mg or PRN 10 mg) and high-dose (OAD 5 mg or PRN 20 mg) groups vs the respective placebo groups are presented in Table 2. The odds ratios were significant for all clinical populations examined, and the results were fairly consistent across all doses and regimens, with the exception of the low-dose OAD regimen in the clinical populations at least 65 years old, with baseline BMI at least 30 kg/m^2, and who smoked.

IIEF-OF Domain—Treatment with tadalafil low-dose and high-dose OAD and PRN regimens demonstrated significantly improved OF as measured by the placebo-adjusted IIEF-OF LS mean improvements (Figure 2) for most clinical subpopulations examined (there is no clinically meaningful cutoff value that has been defined for IIEF-OF or the other ED indicators). The exceptions were with the low-dose OAD regimen in men younger than 50 years, obese men, those who smoked, those who did not have previous PDE5 inhibitor use, those treated with one antihypertensive medication, those with ED duration shorter than 1 year, and those with diabetes mellitus who did not show placebo-adjusted LS mean significant improvements with the low-dose and high-dose OAD regimens. All these groups had insufficient powering, with the exception of the high-dose OAD regimen in patients with diabetes mellitus. There was a difference in response in the low-dose OAD regimen across different age groups, with a greater effect seen for the low-dose OAD regimen in the 50- to 64-year-old group and for patients who had a cardiovascular disorder at baseline. There also was a difference in response in the high-dose OAD regimen across different groups, with a weaker effect seen for patients who had diabetes mellitus at baseline. Tadalafil was efficacious across all doses and regimens for patients with BMI less than 30 or at least 30 kg/m^2 and with or without hypertension, hyperlipidemia, smoking, and alcohol use at baseline.

IIEF Satisfaction Domains—The satisfaction results, IIEF-IS (Supplementary Figure 1) and IIEF-OS (Supplemental Figure 2), showed a similar pattern to the IIEF-EF results. Tadalafil 2.5 mg (low dose) did not demonstrate significantly improved IS as measured by

the placebo-adjusted IIEF-IS score in several clinical populations, including patients younger than 50 and at least 65 years old, patients with BMI of at least 30 kg/m^2, smokers, patients with no alcohol use, those without previous use of PDE5 inhibitors, patients with diabetes, patients without a cardiovascular disorder, patients treated with one or more than one antihypertensive medication, patients with ED duration shorter than 1 year, and patients with hyperlipidemia. Tadalafil 2.5 mg (low dose) did not demonstrate significantly improved OS as measured by the placebo-adjusted IIEF-OS score in several clinical populations, including patients at least 65 years old, patients with BMI at least 30 kg/m^2, smokers, patients with no alcohol use, patients without previous PDE5 inhibitor use, patients treated with one antihypertensive medication, patients with ED duration shorter than 1 year, and patients with diabetes, hypertension, or hyperlipidemia.

Sexual Encounter Profile, Question 3—Treatment with tadalafil low-dose and high-dose OAD or PRN regimens demonstrated significantly improved SEP3 as measured by the placebo-adjusted SEP3 LS mean improvements (Figure 3) for all variables examined with the exception of low-dose OAD in patients who were at least 65 years old, obese patients, patients who smoked, those who were not treated previously with a PDE5 inhibitor, and patients who had ED duration shorter than 1 year (all these groups had insufficient powering).

The proportion of patients achieving MCID at end point in SEP3 and the odds ratios of tadalafil low-dose (OAD 2.5 mg or PRN 10 mg) and high-dose (OAD 5 mg or PRN 20 mg) groups vs the respective placebo groups are presented in Supplementary Table 1. The odds ratios were significant for all clinical populations examined, including age, smoking, alcohol use, and baseline BMI, diabetes, cardiovascular disorder, hypertension, and hyperlipidemia, and the results were fairly consistent across all doses and regimens, with the exception of the low-dose OAD regimen in the clinical populations younger than 50 and at least 65 years old, with baseline BMI of at least 30 kg/m^2, with diabetes mellitus, with no cardiovascular disorder, and those who smoked.

DISCUSSION

The results of these analyses of men with ED demonstrate that diabetes mellitus, arterial hypertension, hyperlipidemia, and alcohol use at baseline do not appear to have a major impact on the effect of tadalafil treatment on EF with either dose or regimen as measured by the mean change from baseline to end point in the IIEF-EF score in these clinical populations. For the group with baseline diabetes mellitus, there were small patient numbers for the low-dose OAD group; however, because patients with diabetes are usually more difficult to treat, the results suggest efficacy of low-dose OAD in this clinical subgroup. This confirmed the findings from previous studies that demonstrated that OAD and PRN dosing are efficacious across a broad spectrum of clinical subgroups.[33,35]

The results were not comparable for the categories of baseline age: there was a weaker (worse) effect seen with the low-dose OAD regimen for patients younger than 50 and at least 65 years old vs placebo compared with the high-dose OAD regimen and low- and high-dose PRN regimens vs placebo. Although it is difficult to compare these groups because of

various confounding factors, there might be a signal in patients at least 65 and younger than 50 years old indicating that the tadalafil low-dose OAD regimen might not be optimum for this subpopulation. However, because the patient numbers are small (smaller than the sample size requirement of 64 patients per group to achieve 80% power), it is important to interpret these results with caution. The results from the low-dose OAD regimen in patients who were not treated previously with a PDE5 inhibitor, patients with ED duration shorter than 1 year, and patients who are smokers also have small numbers, making their interpretation less robust. A smaller effect was seen in the low-dose OAD group for patients with BMI of at least 30 kg/m^2; however, given the relatively few patients in this category, strong statements cannot be made. This could be of interest for further investigation. The data showed a weaker effect for the low dose for the PRN and OAD regimens in patients with BMI of at least 30 kg/m^2. The response in the low-dose group with BMI of at least 30 kg/m^2 is predictable compared with the group with BMI less than 30 kg/m^2 or compared with patients taking the higher dose, because a high BMI correlates with the presence of diabetes mellitus, arterial hypertension, hyperlipidemia, and other confounding factors linked to obesity, making this one of the more difficult-to-treat subpopulations. Studies have shown that in obese patients, EF improves after weight loss induced by bariatric surgery or lifestyle intervention.[40,41] There was a weaker effect seen in the low-dose OAD regimen for patients who did not have a cardiovascular disorder and for patients who smoked. Normal erection depends on penile vascular endothelial function, and smoking can have an adverse effect on vascular endothelium and lead to an increased risk for ED.[42–44] Therefore, the weaker effect seen in smokers in this study is not surprising; however, the numbers were small in this subpopulation of patients (<64 patients), so this result should be interpreted with caution.

The results suggest low-dose OAD and PRN regimens can have a smaller effect than high-dose regimens in patients taking more than one antihypertensive agent, although this is not conclusive owing to the small patient numbers. Further investigation could be of interest in this clinical subgroup.

The SEP3 results followed a similar pattern to those of the IIEF-EF, in which treatment with tadalafil low-dose and high-dose OAD or PRN regimens demonstrated significant improvement in SEP3 for all variables examined except for low-dose OAD in some clinical populations.

Orgasmic function has not routinely been reported in PDE5 inhibitor studies. In this study, for patients with diabetes mellitus, there was a smaller effect on OF with the high-dose OAD regimen compared with the PRN regimen, suggesting that patients with diabetes mellitus might respond to PRN treatment more than to OAD treatment. This observation should be interpreted with caution, because the low-dose OAD arm was not sufficiently powered. There also was a noticeable difference in the placebo response arms between the different treatment regimens in the diabetes mellitus population.

The baseline characteristics were comparable between the PRN and OAD groups for the variables of age, blood pressure, ED duration, IIEF score, and IIEF severity. There was a difference in the percentage of patients by race between the PRN and OAD groups, with a larger percentage of white patients in the OAD group and a larger percentage of Asian

patients in the PRN group. This difference in race reflects the differences in geographic locations where the trials were carried out. Most PRN studies were conducted in Asian countries such as Taiwan, Korea, India, mainland China, Philippines, Singapore, Hong Kong, Indonesia, and Malaysia, which resulted in the discrepancy of 39.5% vs 0.4% of patients being Asian in the PRN vs OAD groups. In addition, some OAD studies were conducted primarily in Europe and the United States, resulting in most men being white in the OAD studies. Studies have shown that ethnicity can be a contributing factor in how men experience patterns of recovery of sexual function after radical prostatectomy[45] and in how they perceive improvements in erection.[35] The differences in race and ethnicity between the OAD and PRN groups in these analyses need to be considered when results are interpreted. Other baseline characteristics that differed between the individual groups included BMI, with more patients classified as obese in the OAD group than in the PRN group, and alcohol use, with heavier use in the OAD group than in the PRN group. In addition, there was a larger percentage of patients who did not have diabetes mellitus in the OAD group than in the PRN group.

This study examined EF response in patients with ED and provided the first descriptive comparison of tadalafil OAD and PRN low-dose and high-dose regimens in multiple clinical populations. However, the study is limited by several variables. Because of the inclusion and exclusion criteria inherent to enrolling patients in clinical trials, patients in these analyses might not completely represent the general population. It is difficult to draw conclusions and make robust inferences for some subgroups with small patient numbers, particularly for those in the low-dose OAD group (a simple power calculation showed 64 patients per group were required to achieve 80% power assuming a 0.5 effect size). In addition, the difference in race in the clinical studies across the tadalafil regimens discussed can introduce bias. A direct comparison between the two regimens is not possible because the PRN and OAD regimens were not studied head-to-head in the same study. Moreover, indirect comparisons were not possible because the placebo treatments were not shared in all studies owing to differences in formulation and regimen. With many potential measured or unmeasured confounders, it is not practically feasible to use a model-based approach, adjusting for those confounding factors, to compare doses across regimens. With all these considerations, we resorted to a descriptive comparison between regimens.

In conclusion, tadalafil OAD and PRN regimens, at low and high doses, showed efficacy in patients with ED across the clinical subpopulations examined. We did not find clear evidence of clinical populations of patients with ED in which PRN performed meaningfully better than an OAD dosing regimen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Derby CA, Mohr BA, Goldstein I, et al. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology. 2000; 56:302–306. [PubMed: 10925098]
2. Fonseca J, Tomada N, Magalhães A, et al. Effect of aging and cardiovascular risk factors on receptor tie1 expression in human erectile tissue. J Sex Med. 2015; 12:876–886. [PubMed: 25487286]
3. Glina S, Sharlip ID, Hellstrom WJ. Modifying risk factors to prevent and treat erectile dysfunction. J Sex Med. 2013; 10:115–119. [PubMed: 22971247]
4. Korhonen PE, Ettala O, Kautiainen H, et al. Factors modifying the effect of blood pressure on erectile function. J Hypertens. 2015; 33:975–980. [PubMed: 25668346]
5. Lewis RW, Fugl-Meyer KS, Bosch R, et al. Epidemiology/risk factors of sexual dysfunction. J Sex Med. 2004; 1:35–39. [PubMed: 16422981]
6. Stokes VJ, Anderson RA, George JT. How does obesity affect fertility in men—and what are the treatment options? Clin Endocrinol (Oxf). 2015; 82:633–638. [PubMed: 25138694]
7. Althof SE, O'Leary MP, Cappelleri JC, et al. US and International SEAR Study Group. Self-esteem, confidence, and relationships in men treated with sildenafil citrate for erectile dysfunction: results of two double-blind, placebo-controlled trials. J Gen Intern Med. 2006; 21:1069–1074. [PubMed: 16836626]
8. Althof S. Sexual therapy in the age of pharmacotherapy. Annu Rev Sex Res. 2006; 17:116–132.
9. Araujo AB, Durante R, Feldman HA, et al. The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. Psychosom Med. 1998; 60:458–465. [PubMed: 9710291]
10. Brock G, Chan J, Carrier S, et al. The treatment of erectile dysfunction study: focus on treatment satisfaction of patients and partners. BJU Int. 2007; 99:376–382. [PubMed: 17155989]
11. McCabe MP, Althof SE. A systematic review of the psychosocial outcomes associated with erectile dysfunction: does the impact of erectile dysfunction extend beyond a man's inability to have sex? J Sex Med. 2014; 11:347–363. [PubMed: 24251371]
12. Briganti A, Salonia A, Gallina A, et al. Drug insight: oral phosphodiesterase type 5 inhibitors for erectile dysfunction. Nat Clin Pract Urol. 2005; 2:239–247. [PubMed: 16474835]
13. Tsertsvadze A, Fink HA, Yazdi F, et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and metaanalysis. Ann Intern Med. 2009; 151:650–661. [PubMed: 19884626]
14. Chen KK, Jiann BP, Lin JS, et al. Efficacy and safety of on-demand oral tadalafil in the treatment of men with erectile dysfunction in Taiwan: a randomized, double-blind, parallel, placebo-controlled clinical study. J Sex Med. 2004; 1:201–208. [PubMed: 16422975]
15. Choi HK, Ahn TY, Kim JJ, et al. A double-blind, randomised-placebo, controlled, parallel group, multicentre, flexible-dose escalation study to assess the efficacy and safety of sildenafil administered as required to male outpatients with erectile dysfunction in Korea. Int J Impot Res. 2003; 15:80–86. [PubMed: 12789384]
16. Guo YL, Zhu JC, Pan TM, et al. Efficacy and safety of on-demand tadalafil for the treatment of erectile dysfunction in South-East Asian men. Int J Urol. 2006; 13:721–727. [PubMed: 16834650]
17. Yip WC, Chiang HS, Mendoza JB, et al. Efficacy and safety of on demand tadalafil in the treatment of East and Southeast Asian men with erectile dysfunction: a randomized double-blind, parallel, placebo-controlled clinical study. Asian J Androl. 2006; 8:685–692. [PubMed: 16855765]
18. Hatzichristou D, Gambla M, Rubio-Aurioles E, et al. Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. Diabet Med. 2008; 25:138–146. [PubMed: 18290855]
19. Porst H, Giuliano F, Glina S, et al. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5 mg and 10 mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. Eur Urol. 2006; 50:351–359. [PubMed: 16766116]

20. Rajfer J, Aliotta PJ, Steidle CP, et al. Tadalafil dosed once a day in men with erectile dysfunction: a randomized, double-blind, placebo-controlled study in the US. Int J Impot Res. 2007; 19:95–103. [PubMed: 16871272]
21. Rubio-Aurioles E, Kim ED, Rosen RC, et al. Impact on erectile function and sexual quality of life of couples: a double-blind, randomized, placebo-controlled trial of tadalafil taken once daily. J Sex Med. 2009; 6:1314–1323. [PubMed: 19473285]
22. Seftel AD, Buvat J, Althof SE, et al. Improvements in confidence, sexual relationship and satisfaction measures: results of a randomized trial of tadalafil 5 mg taken once daily. Int J Impot Res. 2009; 21:240–248. [PubMed: 19536128]
23. Rubio-Aurioles E, El-Meliegy A, Abdulwahed S, et al. Decision tree analyses of key patient characteristics in Middle Eastern/ North African and Latin American men treated with long-acting and short-acting PDE5 inhibitors for erectile dysfunction. Curr Med Res Opin. 2015; 31:367–378. [PubMed: 25068906]
24. Sontag A, Ni X, Althof SE, et al. Relationship between erectile function and sexual self-confidence: a path analytic model in men being treated with tadalafil. Int J Impot Res. 2014; 26:7–12. [PubMed: 23864107]
25. Burns PR, Rosen RC, Dunn M, et al. Treatment satisfaction of men and partners following switch from on-demand phosphodiesterase type 5 inhibitor therapy to tadalafil 5 mg once daily. J Sex Med. 2015; 12:720–727. [PubMed: 25615445]
26. Carson CC, Rajfer J, Eardley I, et al. The efficacy and safety of tadalafil: an update. BJU Int. 2004; 93:1276–1281. [PubMed: 15180622]
27. Skoumal R, Chen J, Kula K, et al. Efficacy and treatment satisfaction with on-demand tadalafil (Cialis) in men with erectile dysfunction. Eur Urol. 2004; 46:362–369. [PubMed: 15306109]
28. Porst H, Brock GB, Kula K, et al. Effects of once-daily tadalafil on treatment satisfaction, psychosocial outcomes, spontaneous erections, and measures of endothelial function men with erectile dysfunction but naïve to phosphodiesterase type 5 inhibitors. J Androl. 2012; 33:1305–1322. [PubMed: 22790642]
29. Brock G, Montorsi F, Costa P, et al. Effect of tadalafil once daily on penile length loss and morning erections in patients after bilateral nerve-sparing radical prostatectomy: results from a randomized controlled trial. Urology. 2015; 85:1090–1096. [PubMed: 25813656]
30. Jamshidian H, Borhan A, Kooraki S, et al. Evaluation of the efficacy of once-daily use of tadalafil vs on-demand use. Is there a cumulative effect? J Pak Med Assoc. 2012; 62:1195–1198. [PubMed: 23866410]
31. Kang DH, Lee JY, Chung JH, et al. Comparison of efficacy for erectile function and lower urinary tract symptoms of tadalafil 20 mg on-demand and 5 mg once daily in patients with erectile dysfunction. Int J Clin Pract. 2012; 66:813–820. [PubMed: 22805273]
32. Tang YX, Zhou HB, Peng SL, et al. Effects of tadalafil on erectile dysfunction: on-demand versus once-daily dosing. Zhonghua Nan Ke Xue. 2012; 18:472–474. in Chinese. [PubMed: 22741449]
33. Porst H, Gacci M, Büttner H, et al. Tadalafil once daily in men with erectile dysfunction: an integrated analysis of data obtained from 1913 patients from six randomized, double-blind, placebo-controlled, clinical studies. Eur Urol. 2014; 65:455–464. [PubMed: 24119319]
34. Rosen RC, Allen KR, Ni X, et al. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol. 2011; 60:1010–1016. [PubMed: 21855209]
35. Lewis RW, Sadovsky R, Eardley I, et al. The efficacy of tadalafil in clinical populations. J Sex Med. 2005; 2:517–531. [PubMed: 16422847]
36. [Accessed March 24, 2016] Cialis (LY450190). Clinical study results for Cialis (LY450190). Available at: http://lillytrials.com/results/cialis.pdf
37. Montorsi F, Aversa A, Moncada I, et al. A randomized, double-blind, placebo-controlled, parallel study to assess the efficacy and safety of once-a-day tadalafil in men with erectile dysfunction who are naïve to PDE5 inhibitors. J Sex Med. 2011; 8:2617–2624. [PubMed: 21707928]
38. Araujo AB, Allen KR, Ni X, et al. Minimal clinically important differences in the vaginal insertion and successful intercourse items of the sexual encounter profile. J Sex Med. 2012; 9:169–179. [PubMed: 21981744]

39. Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile function. Urology. 1997; 49:822–830. [PubMed: 9187685]
40. Gupta BP, Murad MH, Clifton MM, et al. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med. 2011; 171:1797–1803. [PubMed: 21911624]
41. Reis LO, Favaro WJ, Barreiro GC, et al. Erectile dysfunction and hormonal imbalance in morbidly obese male is reversed after gastric bypass surgery: a prospective randomized controlled trial. Int J Androl. 2010; 33:736–744. [PubMed: 20039972]
42. Harte CB. Concurrent relations among cigarette smoking status, resting heart rate variability, and erectile response. J Sex Med. 2014; 11:1230–1239. [PubMed: 24576257]
43. Kovac JR, Labbate C, Ramasamy R, et al. Effects of cigarette smoking on erectile dysfunction. Andrologia. 2015; 47:1087–1092. [PubMed: 25557907]
44. Shabsigh R, Fishman IJ, Schum C, et al. Cigarette smoking and other vascular risk factors in vasculogenic impotence. Urology. 1991; 38:227–231. [PubMed: 1887536]
45. Namiki S, Kwan L, Kagawa-Singer M, et al. Sexual function following radical prostatectomy: a prospective longitudinal study of cultural differences between Japanese and American men. Prostate Cancer Prostatic Dis. 2008; 11:298–302. [PubMed: 17909566]

Conflict of Interest

Gerald Brock is a member of the advisory board and speaker's bureau for Eli Lilly, Pfizer, JNJ, AMS, Coloplast, Ferring, and Astellas and owns stock at Eli Lilly, Pfizer and JNJ. Matthias Oelke is a consultant, speaker, and/or trial participant for Bayer Healthcare, Eli Lilly, and Pfizer. John Mulhall has a leadership position relationship with the Alliance for Fertility Preservation and the Association of Peyronie's Disease Advocates, has a scientific study or trial relationship with Pfizer, has a consultant or advisor relationship with Eli Lilly, Nexmed, Absorption Pharmaceuticals, Meda, and has a consultant or advisor, scientific study or trial relationship with AMS and Vivus. Matt Rosenberg is a consultant for Eli Lilly and is the Section Editor of Urology at the *International Journal of Clinical Practice*. Allen Seftel has a paid position on the editorial board of the *Journal of Urology*. Deborah D'Souza is an employee of inVentiv Health Clinical, LLC. Jane Barry is an employee and minor stockholder of Eli Lilly. Xiao Ni is a former employee and minor stockholder of Eli Lilly.

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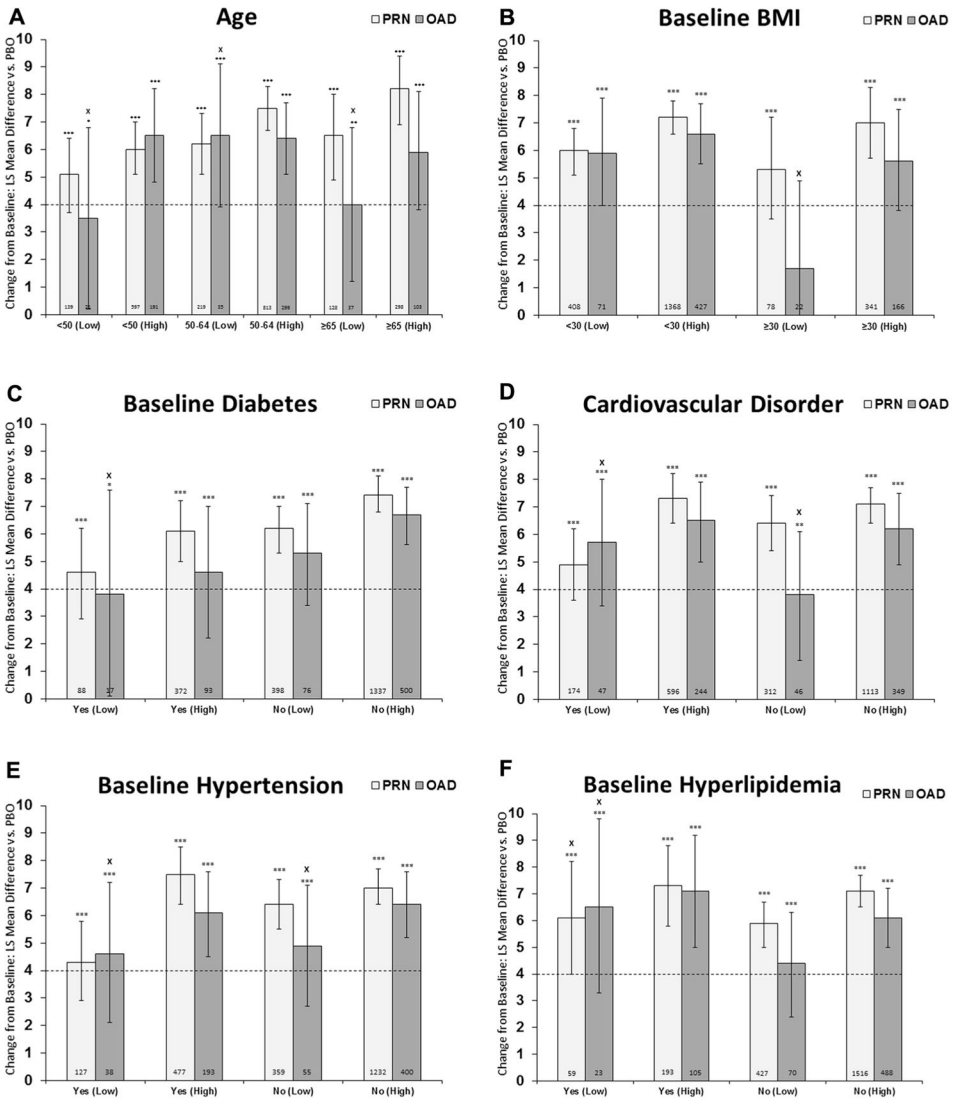


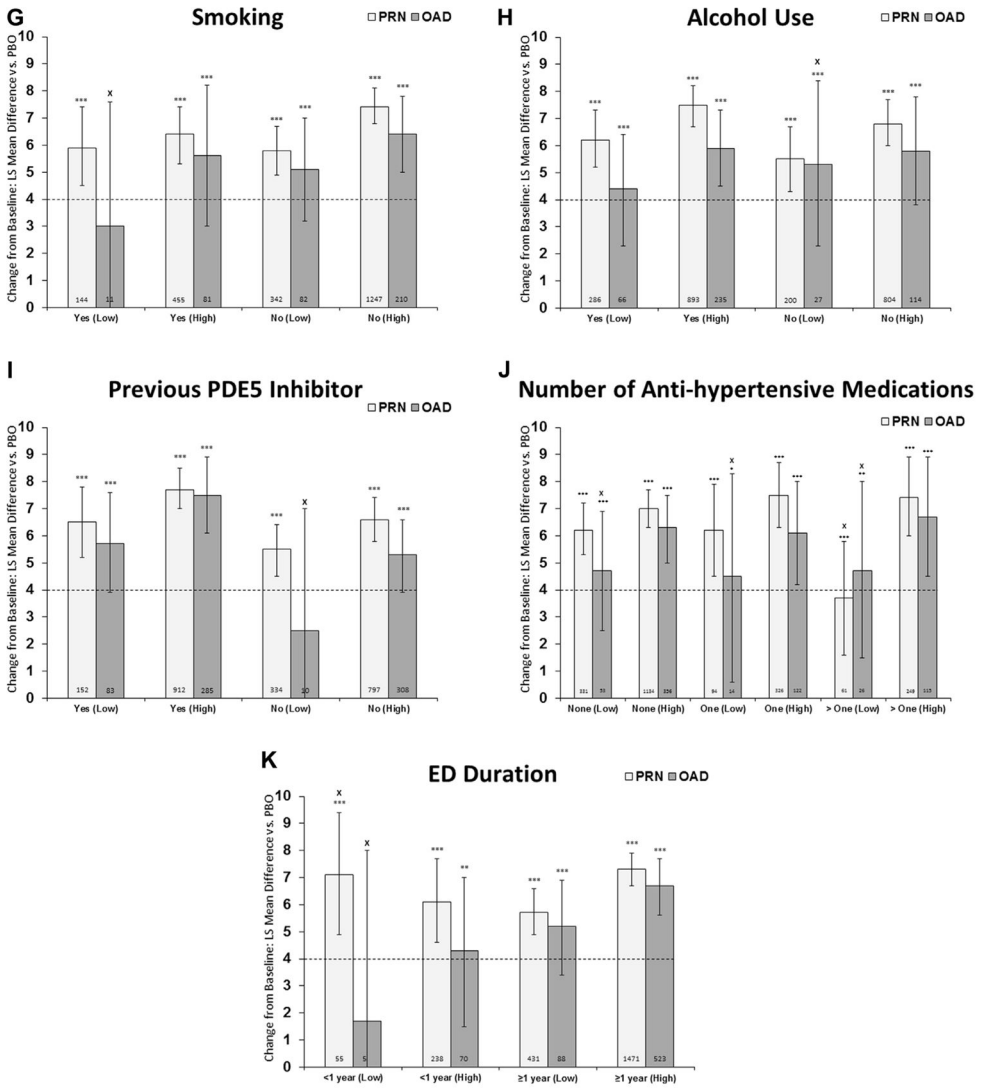
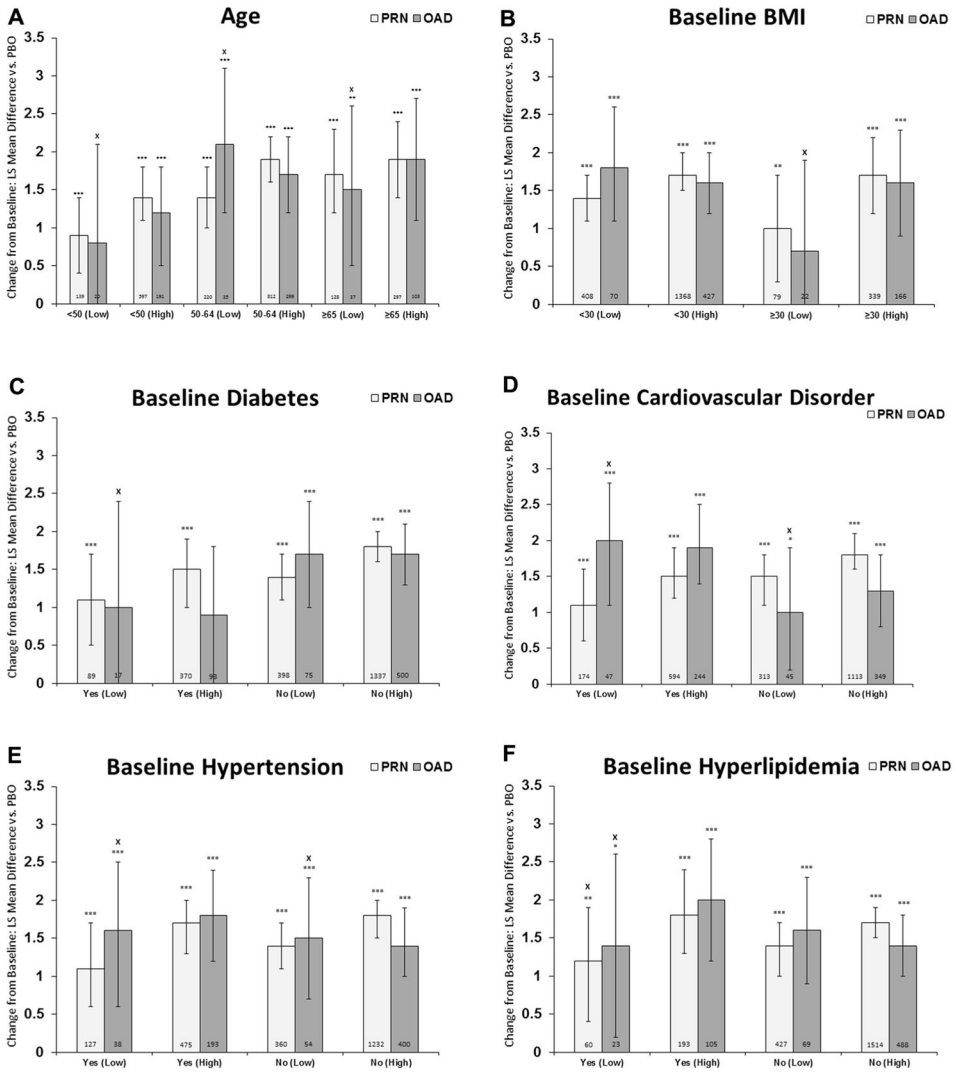


Figure 1.

Efficacy of tadalafil PRN vs OAD in various clinical populations as demonstrated by IIEF-EF: (A) age, (B) baseline BMI, (C) baseline diabetes, (D) cardiovascular disorder, (E) baseline hypertension, (F) hyperlipidemia, (G) smoking, (H) alcohol use, (I) previous PDE5 inhibitor use, (J) number of antihypertensive medications, (K) ED duration.The lower dose is 10 mg for PRN and 2.5 mg for OAD, and the higher dose is 20 mg for PRN and 5 mg for OAD.The numbers within the bars indicate the number of patients with non-missing data at baseline and at least one visit after baseline. The x indicates fewer than 64 patients in the subgroup. The dotted line represents the minimal clinically important difference of at least 4 change from baseline to end point (no clinically meaningful cutoff value has been defined for International Index of Erectile Function orgasmic function domain or other ED indicators; hence, dotted lines are not included in the other figures). The error bars represent 95% CIs. *P <.05; **P <.01; ***P <.001. BMI = body mass index; ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function erectile function domain;

LS =least squares; OAD =once daily; PBO =placebo; PDE5 =phosphodiesterase type 5; PRN =on demand.



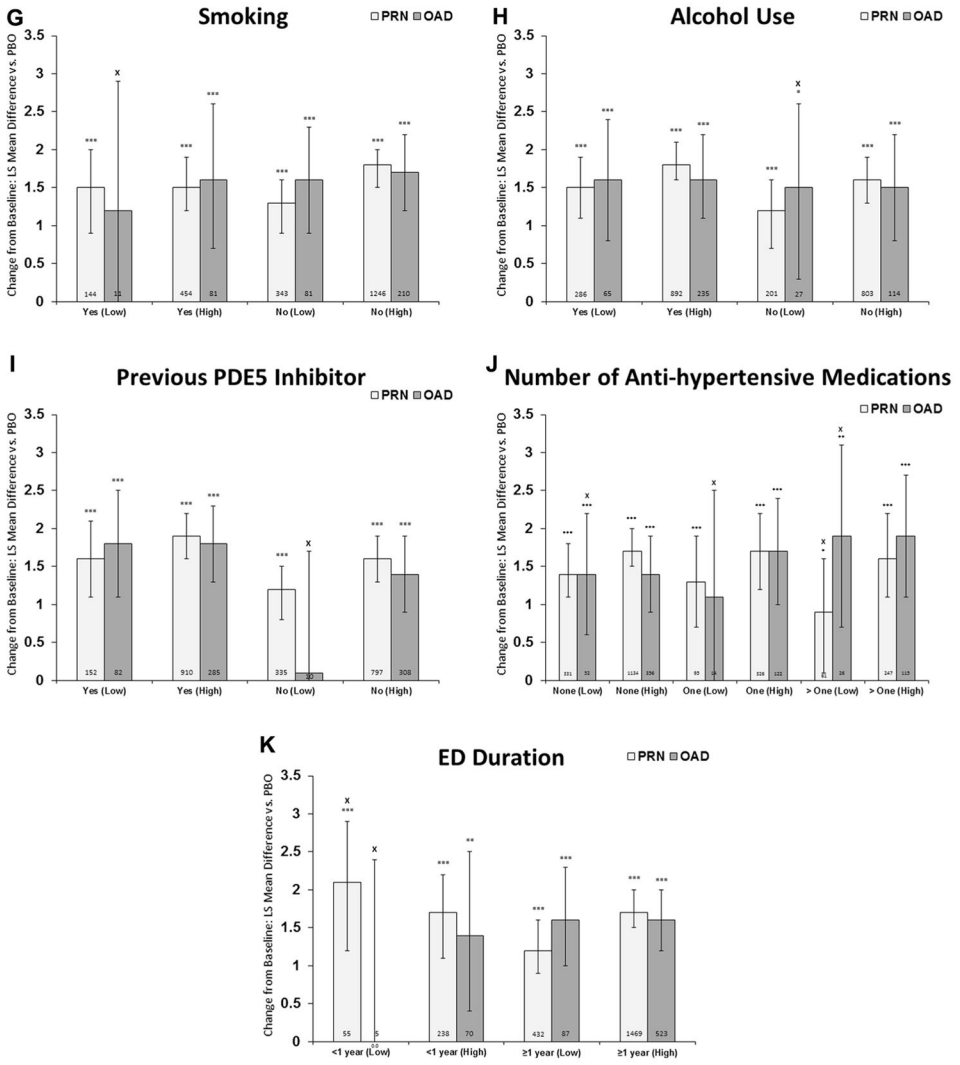
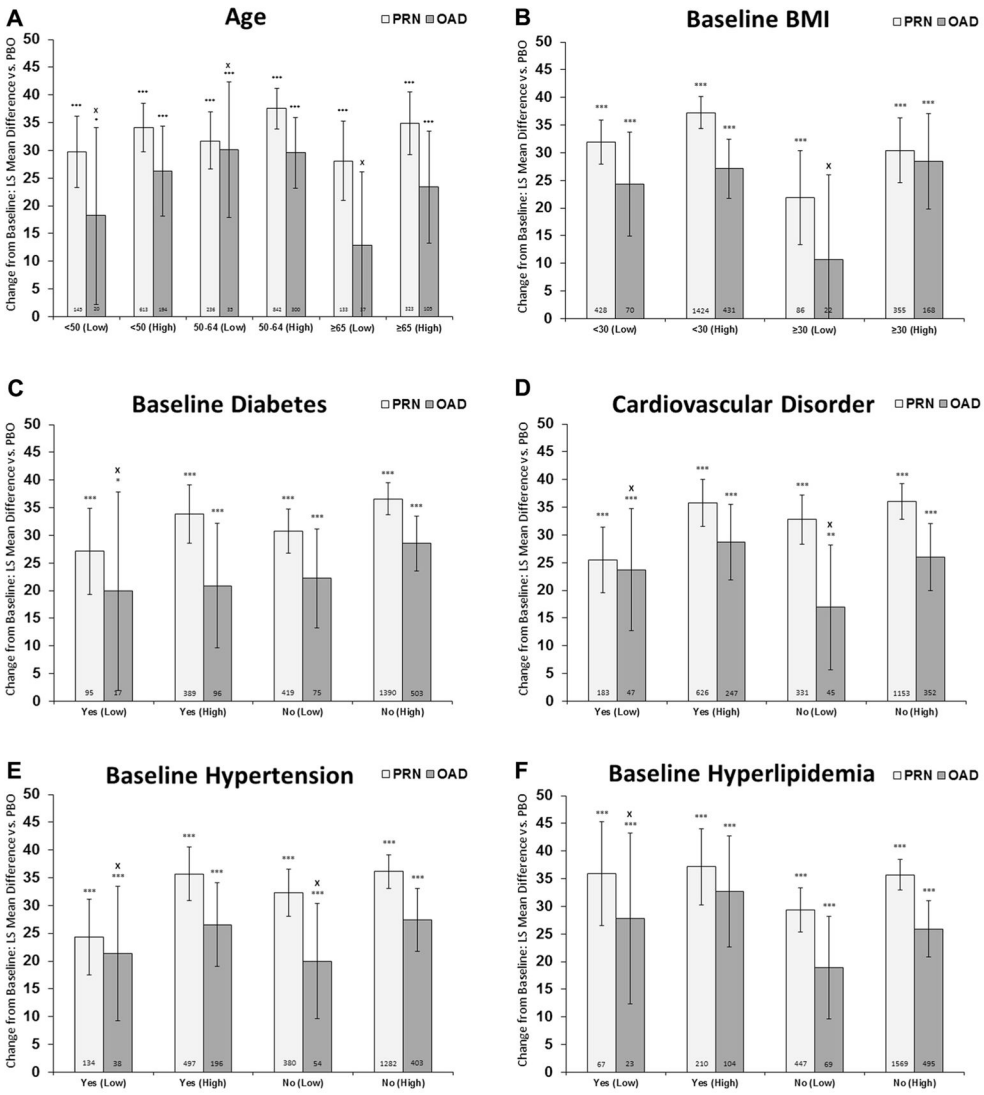


Figure 2.

Efficacy of tadalafil PRN vs OAD in various clinical populations as demonstrated by IIEF-OF: (A) age, (B) baseline BMI, (C) baseline diabetes, (D) cardiovascular disorder, (E) baseline hypertension, (F) hyperlipidemia, (G) smoking, (H) alcohol use, (I) previous PDE5 inhibitor use, (J) number of antihypertensive medications, (K) ED duration. The lower dose is 10 mg for PRN and 2.5 mg for OAD, and the higher dose is 20 mg for PRN and 5 mg for OAD. The numbers within the bars indicate the number of patients with non-missing data at baseline and at least one visit after baseline. The x indicates fewer than 64 patients in the subgroup. The error bars represent 95% CIs. *$P < .05$; **$P < .01$; ***$P < .001$. BMI = body mass index; ED = erectile dysfunction; IIEF-OF = International Index of Erectile Function orgasmic function domain; LS = least squares; OAD = once daily; PBO = placebo; PDE5 = phosphodiesterase type 5; PRN = on demand.



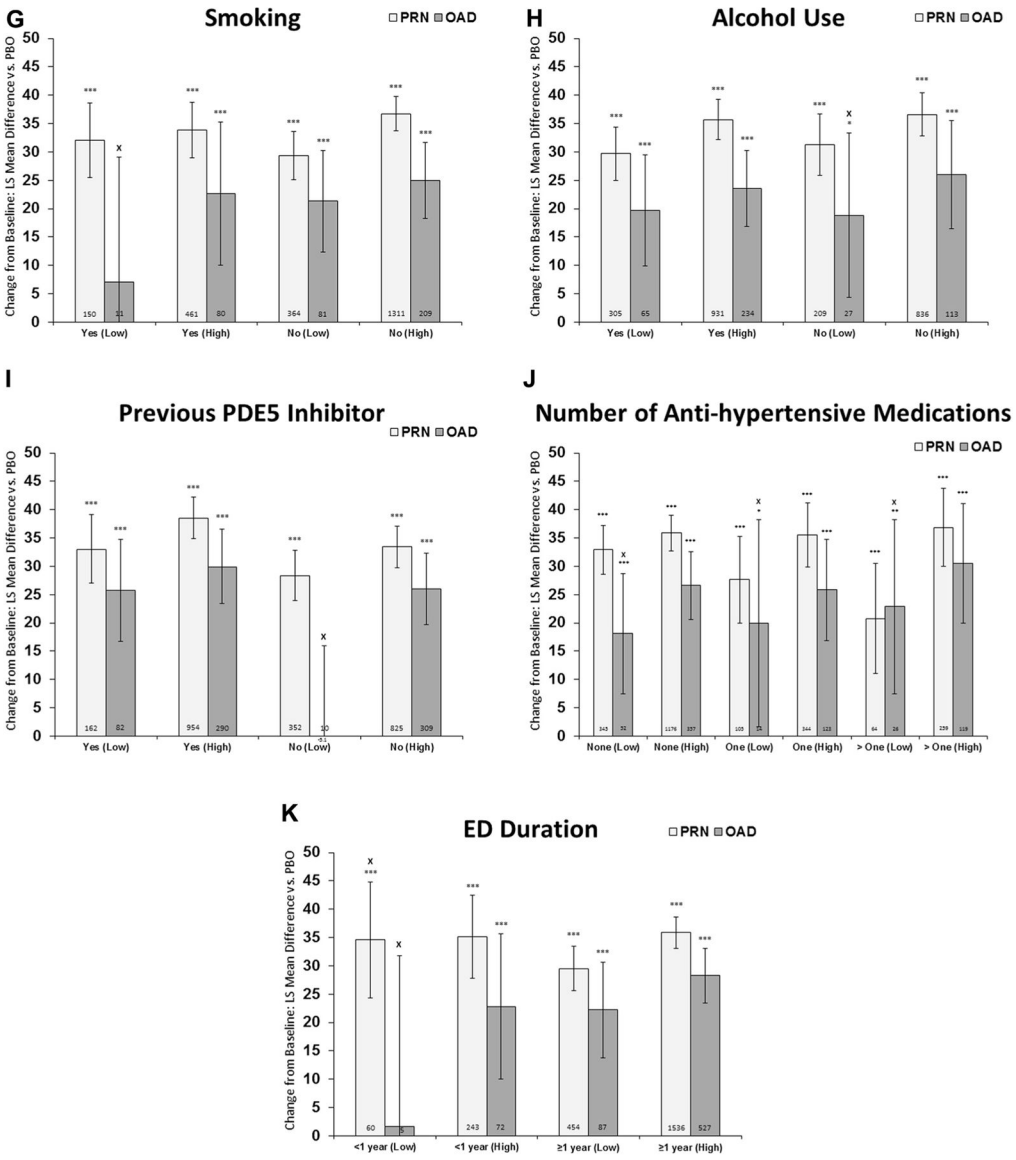


Figure 3.

Efficacy of tadalafil PRN vs OAD in various clinical populations as demonstrated by SEP3: (A) age, (B) baseline BMI, (C) baseline diabetes, (D) cardiovascular disorder, (E) baseline hypertension, (F) hyperlipidemia, (G) smoking, (H) alcohol use, (I) previous PDE5 inhibitor use, (J) number of antihypertensive medications, (K) ED duration. The lower dose is 10 mg for PRN and 2.5 mg for OAD, and the higher dose is 20 mg for PRN and 5 mg for OAD. The numbers within the bars indicate the number of patients with non-missing data at baseline and at least one visit after baseline. The x indicates fewer than 64 patients in the subgroup. The error bars represent 95% CIs. *$P < .05$; **$P < .01$; ***$P < .001$. BMI = body mass index; ED = erectile dysfunction; IIEF-IS = International Index of Erectile Function intercourse satisfaction domain; LS = least squares; OAD = once daily; PBO = placebo,

PDE5 = phosphodiesterase type 5; PRN = on demand; SEP3 = Sexual Encounter Profile, question 3.

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Table 1

Demographics and baseline characteristics*

Variable	PRN				OAD			
	Placebo (N = 1,002)	Low dose (10 mg; N = 527)	High dose (20 mg; N = 1,816)	Total (N = 3,345)	Placebo (N = 296)	Low dose (2.5 mg; N = 96)	High dose (5 mg; N = 617)	Total (N = 1,009)
Age (y), mean (SD)	55.0 (11.2)	56.5 (11.5)	54.1 (11.4)	54.7 (11.4)	55.5 (11.2)	59.8 (11.5)	55.1 (10.8)	55.6 (11.1)
Age group, n (%)								
<50 y	320 (31.9)	149 (28.3)	625 (34.4)	1,094 (32.7)	86 (29.1)	22 (22.9)*	199 (32.3)	307 (30.4)
50–64 y	485 (48.4)	241 (45.7)	855 (47.1)	1,581 (47.3)	150 (50.7)	36 (37.5)*	309 (50.1)	495 (49.1)
≥65 y	197 (19.7)	137 (26.0)	335 (18.5)	669 (20.0)	60 (20.3)*	38 (39.6)*	109 (17.7)	207 (20.5)
Race, n (%)								
White	473 (47.2)	235 (44.6)	979 (53.9)	1,687 (50.4)	256 (86.5)	80 (83.3)	515 (83.5)	851 (84.3)
Black	16 (1.6)*	3 (0.6)*	61 (3.4)*	80 (2.4)	6 (2.0)*	9 (9.4)*	12 (1.9)*	27 (2.7)*
Asian	443 (44.2)	274 (52.0)	603 (33.2)	1,320 (39.5)	1 (0.3)*	0 (0.0)*	3 (0.5)*	4 (0.4)*
Other	70 (7.0)	15 (2.8)*	173 (9.5)	258 (7.7)	33 (11.1)*	7 (7.3)*	87 (14.1)	127 (12.6)
BMI (kg/m^2), mean (SD)	26.7 (4.1)	26.6 (4.3)	26.9 (4.3)	26.8 (4.2)	28.2 (4.4)	28.5 (3.9)	28.2 (4.5)	28.2 (4.4)
BMI group, n (%)								
<30 kg/m^2	817 (81.5)	439 (83.3)	1,451 (79.9)	2,707 (80.9)	214 (72.3)	73 (76.0)	447 (72.4)	734 (72.7)
≥30 kg/m^2	185 (18.5)	88 (16.7)	365 (20.1)	638 (19.1)	82 (27.7)	23 (24.0)*	170 (27.6)	275 (27.3)
Systolic BP (mmHg), mean (SD)	130.4 (14.5)	129.9 (14.6)	130.8 (15.0)	130.5 (14.8)	130.4 (13.8)	127.6 (13.3)	131.4 (13.9)	130.8 (13.9)
Diastolic BP (mmHg), mean (SD)	81.3 (8.5)	80.5 (8.6)	81.2 (8.3)	81.1 (8.4)	79.6 (9.1)	78.4 (8.6)	79.9 (9.0)	79.7 (9.0)

Variable	PRN				OAD			
	Placebo (N = 1,002)	Low dose (10 mg; N = 527)	High dose (20 mg; N = 1,816)	Total (N = 3,345)	Placebo (N = 296)	Low dose (2.5 mg; N = 96)	High dose (5 mg; N = 617)	Total (N = 1,009)
ED duration, n (%)								
<1 y	109 (10.9)	60 (11.4)*	248 (13.7)	417 (12.5)	36 (12.2)*	5 (5.2)*	72 (11.7)	113 (11.2)
≥1 y	893 (89.1)	467 (88.6)	1,568 (86.3)	2,928 (87.5)	260 (87.8)	91 (94.8)	545 (88.3)	896 (88.8)
IIEF-EF score, mean (SD)	14.4 (6.3)	14.2 (6.2)	14.6 (6.2)	14.5 (6.2)	14.6 (6.5)	13.1 (6.5)	14.9 (6.1)	14.6 (6.3)
IIEF severity, n (%)								
Mild	380 (38.0)	202 (38.4)	721 (39.7)	1,303 (39.0)	119 (40.3)	33 (34.4)*	254 (41.6)	406 (40.6)
Moderate	284 (28.4)	147 (27.9)	515 (28.4)	946 (28.3)	82 (27.8)	24 (25.0)*	174 (28.5)	280 (28.0)
Severe	336 (33.6)	177 (33.7)	580 (31.9)	1,093 (32.7)	94 (31.9)	39 (40.6)*	182 (29.8)	315 (31.5)
Diabetes, n (%)								
Yes	227 (22.7)	98 (18.6)	399 (22.0)	724 (21.6)	46 (15.5)*	17 (17.7)*	98 (15.9)	161 (16.0)
No	775 (77.3)	429 (81.4)	1,417 (78.0)	2,621 (78.4)	250 (84.5)	79 (82.3)	519 (84.1)	848 (84.0)
Hypertension, n (%)								
Yes	274 (27.3)	138 (26.2)	506 (27.9)	918 (27.4)	110 (37.2)	39 (40.6)*	203 (32.9)	352 (34.9)
No	728 (72.7)	389 (73.8)	1,310 (72.1)	2,427 (72.6)	186 (62.8)	57 (59.4)*	414 (67.1)	657 (65.1)
Hyperlipidemia, n (%)								
Yes	149 (14.9)	68 (12.9)	217 (11.9)	434 (13.0)	64 (21.6)	23 (24.0)*	111 (18.0)	198 (19.6)
No	853 (85.1)	459 (87.1)	1,599 (88.1)	2,911 (87.0)	232 (78.4)	73 (76.0)	506 (82.0)	811 (80.4)
Cardiovascular disorder, n (%)								
Yes	358 (35.7)	187 (35.5)	638 (35.1)	1,183 (35.4)	135 (45.6)	48 (50.0)*	255 (41.3)	438 (43.4)

Variable	PRN				OAD			
	Placebo (N = 1,002)	Low dose (10 mg; N = 527)	High dose (20 mg; N = 1,816)	Total (N = 3,345)	Placebo (N = 296)	Low dose (2.5 mg; N = 96)	High dose (5 mg; N = 617)	Total (N = 1,009)
No	644 (64.3)	340 (64.5)	1,178 (64.9)	2,162 (64.6)	161 (54.4)	48 (50.0) *	362 (58.7)	571 (56.6)
Alcohol use, n (%)								
Yes	554 (55.5)	312 (59.2)	953 (52.8)	1,819 (54.6)	144 (66.1)	68 (70.8)	238 (67.4)	450 (67.5)
No	444 (44.5)	215 (40.8)	851 (47.2)	1,510 (45.4)	74 (33.9)	28 (29.2) *	115 (32.6)	217 (32.5)
Smoking, n (%)								
Yes	266 (26.7)	156 (29.6)	476 (26.3)	898 (26.9)	38 (19.5) *	12 (12.5) *	83 (28.2)	133 (22.7)
No	732 (73.3)	371 (70.4)	1,333 (73.7)	2,436 (73.1)	157 (80.5)	84 (87.5)	211 (71.8)	452 (77.3)
Previous PDE5 inhibitor, n (%)								
Yes	441 (44.0)	165 (31.3)	977 (53.8)	1,583 (47.3)	148 (50.0)	86 (89.6)	300 (48.6)	534 (52.9)
No	561 (56.0)	362 (68.7)	839 (46.2)	1,762 (52.7)	148 (50.0)	10 (10.4) *	317 (51.4)	475 (47.1)
Any antihypertensive medication, n (%)								
Yes	324 (32.3)	173 (32.8)	614 (33.8)	1,111 (33.2)	131 (44.3)	41 (42.7) *	248 (40.2)	420 (41.6)
No	678 (67.7)	354 (67.2)	1,202 (66.2)	2,234 (66.8)	165 (55.7)	55 (57.3) *	369 (59.8)	589 (58.4)
Antihypertensive medications, n (%)								
0	678 (67.7)	354 (67.2)	1,202 (66.2)	2,234 (66.8)	165 (55.7)	55 (57.3) *	369 (59.8)	589 (58.4)
1	199 (19.9)	108 (20.5)	352 (19.4)	659 (19.7)	81 (27.4)	15 (15.6) *	126 (20.4)	222 (22.0)
>1	125 (12.5)	65 (12.3)	262 (14.4)	452 (13.5)	50 (16.9) *	26 (27.1) *	122 (19.8)	198 (19.6)

BMI = body mass index; BP = blood pressure; ED = erectile dysfunction; IIEF = International Index of Erectile Function; IIEF-EF = International Index of Erectile Function erectile function domain; N = number of randomized subjects; n = number of subjects with non-missing data; OAD = once a day; PDE5 = phosphodiesterase type 5 inhibitor; PRN = as needed.

* Fewer than 64 patients in subgroup.

Table 2

Proportion of patients achieving minimal clinically important difference (change ≥ 4 from baseline to end point) at end point (week 12, last observation carried forward) in the international index of erectile function erectile function domain*

	PRN						OAD					
	Low dose (10 mg; n = 527)			High dose (20 mg; n = 1,816)			Low dose (2.5 mg; n = 96)			High dose (5 mg; n = 617)		
Variable	**N**	**n**	**OR (TAD vs PBO)**	**N**	**n**	**OR (TAD vs PBO)**	**N**	**n**	**OR (TADA vs PBO)**	**N**	**n**	**OR (TAD vs PBO)**
Age (y)												
<50	139	96	3.34§	597	456	4.24§	21*	13	3.00†	191	151	5.27§
50–64	219	146	5.20§	813	613	6.72§	35*	22	4.25§	299	207	4.65§
≥65	128	82	4.99§	298	217	6.56§	37*	16	2.47	103	68	6.22§
Baseline BMI (kg/m^2)												
<30	408	279	4.68§	1,368	1,027	5.70§	71	42	3.84§	427	314	5.64§
≥30	78	45	3.47§	341	260	5.73§	22*	9	1.37	166	112	3.62§
Baseline diabetes												
Yes	88	51	3.93§	372	246	4.41§	17*	9	3.78†	93	55	3.78§
No	398	273	4.61§	1,337	1,041	6.30§	76	42	2.99§	500	371	5.34§
Baseline cardiovascular disorder												
Yes	174	100	3.32§	596	434	5.51§	47*	26	3.70§	244	163	5.15§
No	312	224	5.36§	1,113	853	5.79§	46*	25	2.31†	349	263	4.88§
Baseline hypertension												
Yes	127	68	2.80§	477	345	5.35§	38*	18	2.84†	193	126	4.90§
No	359	256	5.36§	1,232	942	5.87§	55*	33	3.04§	400	300	5.00§

	PRN						OAD					
	Low dose (10 mg; n = 527)			High dose (20 mg; n = 1,816)			Low dose (2.5 mg; n = 96)			High dose (5 mg; n = 617)		
Variable	N	n	OR (TAD vs PBO)	N	n	OR (TAD vs PBO)	N	n	OR (TADA vs PBO)	N	n	OR (TAD vs PBO)
Baseline hyperlipidemia												
Yes	59†	42	6.05§	193	141	5.77§	23*	12	3.64†	105	72	5.92§
No	427	282	4.30§	1,516	1,146	5.69§	70	39	2.86§	488	354	4.70§
Smoking												
Yes	144	100	4.32§	455	346	4.94§	11*	5	1.04	81	58	2.44†
No	342	224	4.50§	1,247	937	6.02§	82	46	3.50§	210	148	5.57§
Alcohol use												
Yes	286	197	5.07§	893	681	6.28§	66	34	2.95§	235	172	5.62§
No	200	127	3.87§	804	597	5.20§	27*	17	2.94†	114	79	3.03§

BMI = body mass index; N = number of subjects with baseline and end-point results; n = number of subjects achieving minimal clinically important difference at study end point; PBO = placebo; OAD = once a day; OR = odds ratio; PRN = as needed; TAD = tadalafil.

*Fewer than 64 patients in subgroup.

†$P \leq .05$.

§$P \leq .001$.