

Vardenafil, a New Phosphodiesterase Type 5 Inhibitor, in the Treatment of Erectile Dysfunction in Men With Diabetes

A multicenter double-blind placebo-controlled fixed-dose study

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OBJECTIVE — This study evaluated the efficacy and safety of vardenafil treatment for erectile dysfunction (ED) in men with diabetes.

RESEARCH DESIGN AND METHODS — In this prospective multicenter double-blind placebo-controlled fixed-dose parallel-group phase III trial, 452 patients with diabetes (type 1 or type 2) and ED were randomized to take 10 or 20 mg vardenafil or placebo as needed for 12 weeks. Efficacy responses were assessed by International Index of Erectile Function domain scores, rates of vaginal penetration and successful intercourse, and a global assessment question (GAQ) about erection improvement during the previous 4 weeks.

RESULTS — After 12 weeks of treatment, a dose-dependent ($P = 0.02$) improvement in erections was noted for the GAQ, with 57 and 72% of men taking 10 mg or 20 mg vardenafil, respectively, reporting improved erections, in contrast to 13% after taking placebo ($P < 0.0001$). For the erectile function domain, dose-dependent ($P = 0.03$) final scores for the 10- and 20-mg dose were 17.1 and 19.0 compared with 12.6 for placebo ($P < 0.0001$). Both vardenafil doses significantly enhanced the rates of successful penetration ($P < 0.0001$) and successful intercourse ($P < 0.0001$) compared with placebo. Vardenafil treatment was effective in increasing intercourse success rates at all levels of baseline ED severity, at each level of plasma HbA_{1c}, and for type 1 and 2 diabetes. Treatment-emergent adverse events were primarily mild to moderate headache ($\leq 13\%$), flushing ($\leq 10\%$), and rhinitis ($\leq 10\%$).

CONCLUSIONS — Vardenafil statistically improved erectile function and was generally well tolerated in these diabetic patients with ED.

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Abbreviations: ECG, electrocardiogram; ED, erectile dysfunction; EF, erectile function; GAQ, global assessment question; IIEF, International Index of Erectile Function; LOCF, last observation carried forward; PDE5, phosphodiesterase type 5.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Erectile dysfunction (ED), the consistent or recurrent inability to attain and/or maintain a penile erection sufficient for sexual performance (1), can have a significant effect on a patient's quality of life (2–4). ED is a common complication of diabetes because >50% of diabetic men develop ED within 10 years of being diagnosed with diabetes (5). The prevalence of ED increases with age, from 9% in diabetic men ages 20–29 years to 95% in diabetic men >70 years (5), and increases with duration, poor control, and complications of diabetes (such as vascular and microvascular disease and neuropathies) (6).

Diabetic men with ED tend to be less responsive to treatment perhaps because the pathogenesis of diabetes-associated ED is likely to be multifactorial (7,8). Although treatment with phosphodiesterase type 5 (PDE5) inhibitors is less effective in the diabetic patient than in the nondiabetic ED patient, the convenience of an orally formulated PDE5 inhibitor has popularized treatment in a large number of men with diabetes and ED (9,10).

Vardenafil, a new PDE5 inhibitor, is more selective for PDE5 and more biochemically potent than sildenafil in *in vitro* and *in vivo* studies when tested under the same conditions (11–13). These properties suggest that vardenafil may be a highly efficacious oral treatment in the difficult-to-treat ED patients with diabetes. The objective of this study was to assess the efficacy, tolerability, and safety of vardenafil in the treatment of ED in men with diabetes.

RESEARCH DESIGN AND METHODS

Study design

The study was a randomized double-blind fixed-dose parallel-group trial conducted at 47 centers in the U.S. and

Canada. Baseline characteristics were assessed after a 4-week unmedicated phase during which time patients had to have attempted intercourse on at least 4 separate days and had to have been unsuccessful in at least half of these attempts. Lack of success was defined as failure to penetrate their partner or to maintain an erection to successful intercourse. Patients were then randomized to 10 or 20 mg vardenafil or placebo treatment arms for 12 weeks. Patients were instructed to take the study drug as needed, but no more than once a day and ~1 h before intercourse. No specific instructions were given with regard to food or alcohol use. Efficacy and safety data were collected at 4-week intervals. After the active treatment phase, patients had the option of participating in a 12-week extension phase in which all patients received either 10 or 20 mg vardenafil. Safety and efficacy from the extension phase will be reported elsewhere. Vardenafil hydrochloride (vardenafil) was supplied by Bayer AG.

Inclusion and exclusion criteria

Men over age 18 years who were in a stable heterosexual relationship, who had a clinical diagnosis of type 1 or type 2 diabetes, and who had experienced ED for longer than 6 months were included. Their HbA_{1c} had to be ≤12%. Patients were excluded if their ED was the result of radical prostatectomy, primary hypoactive sexual desire, or spinal cord injury. Patients with previous myocardial infarction, stroke, ischemia by electrocardiography, or life-threatening arrhythmia were allowed to participate if these events had not occurred in the 6 months before the trial. Specific exclusion criteria at screening included uncontrolled atrial tachyarrhythmia, unstable angina pectoris, severe chronic liver disease, clinically significant chronic hematological disease or bleeding disorder, resting hypotension or hypertension, symptomatic postural hypotension within 6 months before screening, retinitis pigmentosa, proliferative diabetic retinopathy that progressed within 6 months before screening, autonomic (but not peripheral sensory) neuropathy associated with clinically significant gastroparesis, hypo- or hyperthyroidism, and recent severe uncontrolled migraine headaches. According to the protocol, previous exposure to sildenafil was allowable. However, if patients had discontinued sildenafil because of

significant side effects or because of dissatisfaction with its efficacy, they were excluded. Nitrate medication was strictly contraindicated. Anti-androgens, anti-coagulant androgens, and trazodone hydrochloride were not allowed.

Efficacy variables

The primary measures of efficacy were the erectile function (EF) domain of the validated International Index of Erectile Function (IIEF) questionnaire (14) and two diary questions concerning sexual encounter: "Were you able to insert your penis in your partner's vagina?" and "Did your erection last long enough for you to have successful intercourse?" The secondary efficacy variable reported here is the global assessment question (GAQ), "Has the treatment you have been taking over the past 4 weeks improved your erections?"

Safety

The safety population included all patients who took at least one dose of study medication and who had any postrandomization safety data collected. Blood chemistries, vital signs, and 12-lead electrocardiograms (ECGs) were evaluated at 0, 4, and 12 weeks of treatment. In ~61–75 men in each group, the vital signs and ECGs were obtained within 11 min and 5 h after taking the drug when pharmacologically active plasma concentrations of vardenafil would be expected. Treatment-emergent adverse events were recorded at 4-week intervals. Events were determined by each blinded investigator to be probably, possibly, unlikely, or not related to the study drug. Patients who did not enter the extension study were followed for 7 days after the last dose to record any serious adverse events and for 30 days after the last dose to record any deaths.

Statistics

The intent-to-treat population, defined as individuals who took at least one dose of study medication and who had baseline and any post-baseline efficacy data, was used to calculate all the efficacy variables. For EF domain scores, the last observation carried forward (LOCF) approach was used to account for missing values. For both diary questions, the mean success rate of each individual patient over the entire treatment period was averaged across all patients and is reported as the mean success rate for each man. For the

GAQ, values were obtained from patients who completed 12 weeks of treatment; an LOCF value was also calculated.

The primary efficacy variables were analyzed with ANCOVA, with baseline response as a covariate and with terms for center and treatment. The GAQ was analyzed using logistic regression with terms for center and treatment.

Retrospective analyses were performed to evaluate efficacy in different patient subgroups. Rates of successful intercourse were analyzed according to baseline severity (EF domain scores: mild 22–25, mild to moderate 17–21, moderate 16–11, severe <11) (14), according to HbA_{1c} levels (≤6, >6 to <8, and ≥8%), and according to type of diabetes. Analyses by baseline severity of ED, HbA_{1c} levels, and type of diabetes were performed using an ANCOVA model with model terms for center, treatment, subgroup, baseline, and treatment by subgroup interaction.

RESULTS

Disposition and demographics

A total of 452 male patients with diabetes and ED were randomized to take placebo (*n* = 150), 10 mg vardenafil (*n* = 153), or 20 mg vardenafil (*n* = 149) during a 12-week double-blind multicenter study measuring the safety and efficacy of vardenafil in diabetic patients. The intent-to-treat population included 430 patients (placebo, *n* = 140; 10 mg vardenafil, *n* = 149; 20 mg vardenafil, *n* = 141). The 73 patients who prematurely discontinued the study were evenly distributed across treatment groups. Five patients in the placebo group and three patients in the 10 mg treatment group discontinued treatment because of insufficient therapeutic effect. No such discontinuations occurred in the 20 mg group. Eleven patients discontinued treatment because of adverse events (two in the placebo group, four in the 10 mg vardenafil group, and five in the 20 mg vardenafil group). All other discontinuations were due to loss to follow-up, consent withdrawal, patient noncompliance, or protocol violation.

Demographic and baseline characteristics were distributed similarly among patient populations (Table 1). The mean patient age at enrollment was 57 years. Most patients (88%) had type 2 diabetes and poor glycemic control. The mean duration of ED since diagnosis was 3.5 years,

Table 1—Demographic and baseline characteristics (safety population)

| | Placebo | 10 mg vardenafil | 20 mg vardenafil |
|--|----------|------------------|------------------|
| <i>n</i> | 143 | 152 | 144 |
| Age (mean in years) | 56.8 | 58.0 | 56.9 |
| Race | | | |
| Caucasian | 113 (79) | 124 (82) | 113 (78) |
| Black | 15 (10) | 14 (9) | 12 (8) |
| Hispanic | 10 (7) | 10 (7) | 15 (10) |
| Other* | 5 (3) | 4 (3) | 4 (3) |
| BMI (mean in kg/m ²) | 31.5 | 30.6 | 30.2 |
| Duration of ED since first diagnosis (mean in years) | 3.7 | 3.4 | 3.3 |
| Etiology | | | |
| Organic | 118 (83) | 125 (83) | 115 (80) |
| Psychogenic | 0 (0) | 2 (1) | 0 (0) |
| Mixed | 25 (17) | 24 (16) | 28 (20) |
| Severity of ED | | | |
| Severe (<11) | 82 (57) | 88 (58) | 70 (49) |
| Moderate (11–16) | 35 (24) | 30 (20) | 37 (26) |
| Mild to moderate (17–21) | 19 (13) | 26 (17) | 23 (16) |
| Mild (22–25) | 5 (3) | 8 (5) | 13 (9) |
| Normal (≥26) | 2 (1) | —(—) | 1 (1) |
| Duration of diabetes (mean in years) | 12.0 | 10.0 | 10.5 |
| Type of diabetes | | | |
| Type 1 | 14 (10) | 17 (11) | 20 (14) |
| Type 2 | 128 (90) | 135 (89) | 124 (86) |
| With neural manifestation | 10 (7) | 8 (5) | 7 (5) |
| With eye manifestation | 8 (6) | 7 (5) | 7 (5) |
| With another manifestation† | 1 (<1) | 3 (2) | 4 (3) |
| HbA _{1c} levels | | | |
| ≤6.0 | 3 (2) | 5 (3) | 4 (3) |
| >6.0 to <8.0 | 60 (42) | 66 (43) | 66 (46) |
| ≥8.0 | 79 (55) | 80 (53) | 73 (51) |
| Medical history | | | |
| Hypertension | 82 (57) | 83 (55) | 66 (46) |
| Depressive disorder | 11 (8) | 14 (9) | 20 (14) |
| Concomitant medication‡ | | | |
| β-Blockers | 14 (10) | 16 (11) | 22 (15) |
| Renin-angiotensin system acting agents | 76 (53) | 70 (46) | 64 (44) |
| Calcium-channel blockers | 22 (15) | 24 (16) | 20 (14) |
| Serum lipid-reducing agents | 50 (35) | 49 (32) | 47 (33) |
| Diuretics | 25 (17) | 27 (18) | 19 (13) |
| Other antihypertensive agents | 10 (7) | 20 (13) | 10 (7) |
| Insulin | 51 (36) | 54 (36) | 47 (33) |
| Glucose-lowering drugs | 108 (76) | 110 (72) | 100 (69) |
| Prior sildenafil use | 78 (55) | 91 (60) | 87 (60) |

Data are *n* (%) unless otherwise indicated. *Asian, Native American, or unknown. †renal or ketoacidosis; ‡patients using a medication any time after the start of dosing with the study drug and up to 30 days after the last dose of the study drug, regardless of their use before starting the study drug, except for rates of insulin and glucose-lowering drug use, which were measured at randomization; patients could be on more than one medication.

and a majority of men (55%) reported severe ED. The mean duration of treatment was ~78 days in each treatment group. The mean number of doses per patient per week was 1.8 for the placebo group

and 2.1 and 2.0 for the 10 and 20 mg vardenafil groups.

Efficacy

Treatment with vardenafil compared with treatment with placebo improved EF in

diabetic men. After 12 weeks, changes from baseline in the EF domain of the IIEF with vardenafil treatment (5.9 and 7.8 for 10 and 20 mg vardenafil, respectively) were significantly greater ($P < 0.0001$) than with placebo treatment (1.4 for placebo) (Fig. 1A). Final scores reached 19.0 with the highest dose compared with 12.6 with placebo. A dose response was noted for the EF domain ($P = 0.03$). The other primary efficacy variables (patient diary recordings) also showed significant improvement with treatment compared with placebo ($P < 0.0001$) (Fig. 1B and C); however, no dose response was noted. The mean ability of each man to maintain erections until completion of intercourse was 54% with 20 mg vardenafil treatment compared with 23% with placebo. The overall responder rate, as measured by the proportion of men reporting improved erections on the GAQ at 12 weeks, was 72% in the 20 mg vardenafil group and 54% for the 10 mg patients and was significantly higher than the 13% of men treated with placebo ($P < 0.0001$) (Fig. 1D). The LOCF values were similar to those of the completers: 70% for 20 mg, 54% for 10 mg, and 13% for placebo. The response rate at 20 mg was significantly higher than that at 10 mg in both LOCF and completer analyses ($P \leq 0.02$).

The rate of successful intercourse was also evaluated based on the baseline severity of ED. More than half the patients had severe ED at baseline and, as expected, they rarely had successful intercourse (0.9–2.5%) before treatment. After treatment with vardenafil, however, the average success rate for each man with severe ED reached 40% in the 20 mg treatment group (Fig. 2) compared with 11% in the placebo group ($P < 0.0001$). In the mild ED category, although baseline intercourse success rates were higher (35–47%), the average success rate was 75% in the 20 mg group compared with 47% in the placebo group ($P < 0.09$). Success rates were also examined for the proportion of men who reached a certain threshold of success, such as three of four times (i.e., the proportion of men with 75% per patient success rate). According to this criterion, there were not as many men who reached this relatively high level of success in the severe ED group (25% for 20 mg vardenafil and 5% for placebo) compared with those in the mild to moderate ED category (73% for 20 mg vard-

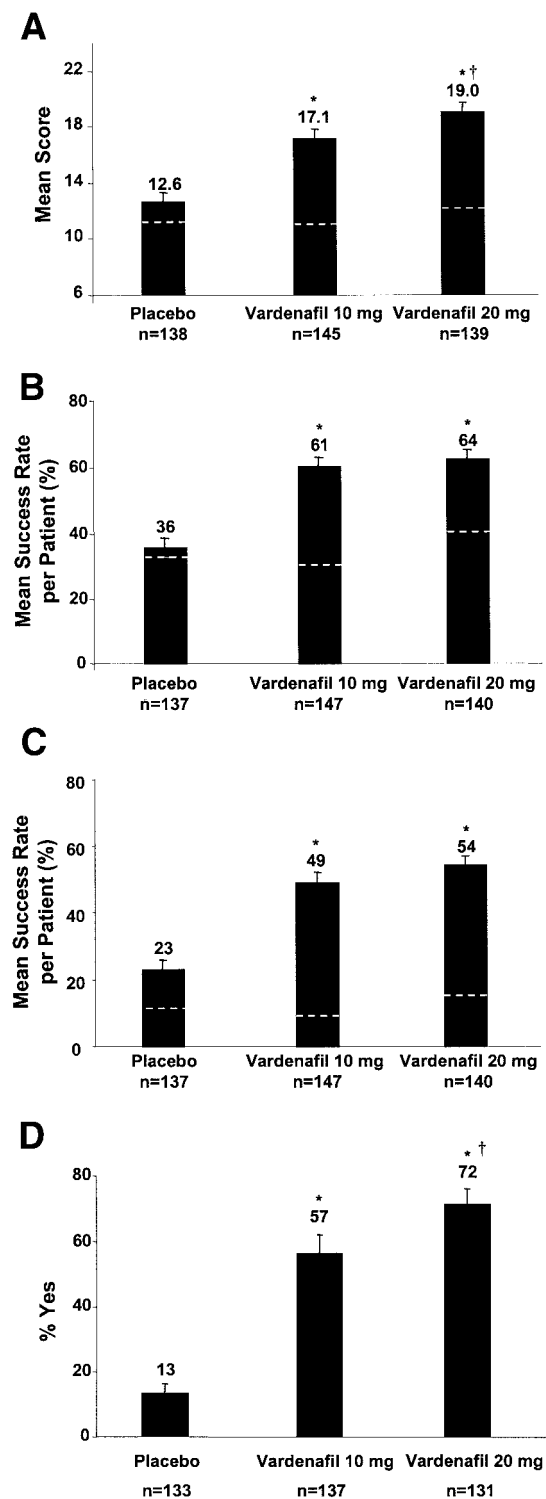


Figure 1—Primary and secondary efficacy variables. A: EF domain of the IIEF: mean scores (least square) at 12 weeks (LOCF). A score <11 is severe, 11–17 is moderate, 18–25 is mild, and ≥ 26 is normal. B: Sexual encounter profile (SEP) 2: “Were you able to insert your penis in your partner’s vagina?” C: SEP3: “Did your erection last long enough for you to have successful intercourse?” For SEPs, patients recorded their answer (“yes” or “no”) in a diary. Results are the mean (least square) per patient value for success rate for all attempts over the course of the 12-week treatment. D: GAQ: “Has the treatment you have been taking over the past 4 weeks improved your erections?” Results are the mean value for patients completing 12 weeks of treatment. Dashed lines represent baseline values. Black bars represent efficacy values after 12 weeks. * $P < 0.0001$ compared with placebo; † $P < 0.03$ compared with 10 mg vardenafil.

enafil and 44% for placebo). Nevertheless, compared with the placebo responses in the severe ED group, a substantial proportion of men achieved a success rate of 75% on treatment with vardenafil.

The relationship of each patient’s re-

sponse to vardenafil (success rate in maintaining an erection) and baseline HbA_{1c} is shown graphically in Fig. 3. In the analysis of SEP-3 overall, the addition of HbA_{1c} by treatment interaction to the model (which already contained terms for treatment, center, and baseline) increased the

R^2 by 0.0042 (total $R^2 = 0.42$), with a P value for the interaction term of 0.4435; therefore, after adjusting for other terms, there was no incremental information provided by HbA_{1c}. This finding indicates that there was no clear relationship between response to vardenafil and glyce-mic control. Successful intercourse rates for patients treated with 20 mg vardenafil were 50% in the >6 to <8% HbA_{1c} subgroup ($n = 64$) and 54% in the $\geq 8\%$ HbA_{1c} subgroup ($n = 71$) compared with 20 and 23% in placebo-treated patients in the >6 to <8% ($n = 56$) and $\geq 8\%$ ($n = 77$) HbA_{1c} subgroups, respectively. Responses were significantly superior to placebo for both vardenafil doses in both HbA_{1c} subgroups.

There were 10–14% of patients in each treatment arm who had type 1 diabetes. For these men, the least-square mean per patient response for success rate in maintenance of erection to successful intercourse was 10, 48, and 65% for placebo, 10 mg, and 20 mg, respectively. For type 2 diabetic patients, these responses were 25, 49, and 52%, respectively. Responses to 10 and 20 mg vardenafil in both type 1 and type 2 diabetic subgroups were statistically better than responses to placebo ($P \leq 0.005$). There appeared to be a slight difference in both placebo and 20-mg responses between type of diabetes, but the smaller representation of patients with type 1 diabetes makes statistical comparison difficult.

For the subset of men who were naive to sildenafil, the responses were similar to those from patients who had taken sildenafil previously. For men naive to sildenafil, the mean per patient success rates in maintenance of erection to successful intercourse were 22, 47, and 49% for placebo, 10 mg vardenafil, and 20 mg vardenafil, respectively. These results compared with 20, 48, and 55% for patients who had previously taken sildenafil in the placebo, 10 mg, and 20 mg groups, respectively. The subgroups were not significantly different from each other, but within subgroups, both treatments were significantly better than placebo.

Safety

In this fixed dose study, adverse events were few and generally mild to moderate and transient in nature. The most frequent were headache, cutaneous flushing, and rhinitis. A maximum of 13% of men reported any one of these adverse

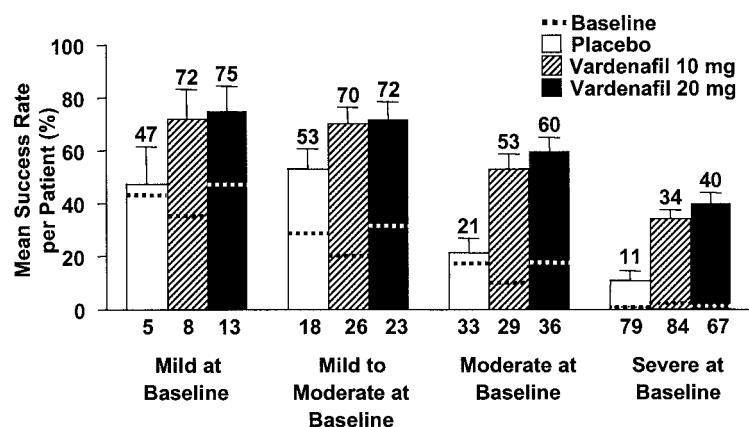


Figure 2—Efficacy by baseline severity of ED. Rate of successful intercourse (“Did your erection last long enough for you to have successful intercourse?”) was determined based on patient baseline ED severity (EF domain scores: mild 22–25, mild to moderate 17–21, moderate 16–11, severe <11) (14). Results presented are the mean (least square) success rates per patient calculated for all attempts over the course of treatment.

events after treatment with 10 mg or 20 mg vardenafil compared with 7% in the placebo group (Table 2). No color disturbances in vision were noted.

Serious adverse events were rare and distributed similarly between treatment groups ($n = 4$ [3%] for placebo, $n = 3$ [2%] for 10 mg vardenafil, and $n = 4$ [3%] for 20 mg vardenafil). No individual event type was reported in more than one patient per treatment group. All serious adverse events considered to be possibly or probably related to vardenafil treatment resolved. One patient with extensive comorbidities and taking multiple concomitant medications experienced

chest pain, dyspnea, larynx edema, and asthma. In the rest of the patients with serious adverse events, ST depression, hypesthesia, or moderate amnesia was noted. No patient died during the double-blind treatment period after the randomization visit. Adverse events that led to discontinuation were two (1%) in placebo, four (3%) in the 10 mg group, and five (3%) in the 20 mg group. The most common reasons were headache ($n = 2$ in the 20 mg group), cutaneous flushing ($n = 2$ in the 10 mg group, $n = 1$ in the 20 mg group), rhinitis ($n = 1$ in the 20 mg group), and unspecified abnormal vision ($n = 1$ in the 20 mg group).

Overall, laboratory abnormalities and mean changes in heart rate were similar for all three treatment groups. A slight decrease in mean blood pressure (systolic blood pressure: -1.4 to -4.5 mmHg; diastolic blood pressure: -2.0 to -3.9 mmHg) in the vardenafil treatment groups compared with the placebo group (systolic blood pressure: 0.3 – 0.6 mmHg; diastolic blood pressure: 1.4 – 1.5 mmHg) was noted when measured between 11 min and 5 h after taking the medication. ECG abnormalities were of minor clinical significance, and no new myocardial infarctions were noted. The ECGs of four patients (one placebo, one 10 mg vardenafil, and two 20 mg vardenafil) were interpreted as abnormal and clinically significant. These events were sinus bradycardia, first-degree atrioventricular block, or ST and/or T wave abnormalities. Because of the small number of abnormal observations, the relationship to treatment could not be assessed.

CONCLUSIONS— In the present study, vardenafil treatment significantly improved EF in diabetic men at each level of baseline ED severity and whether they had poor or poorer glycemic control. Compared with placebo treatment, vardenafil treatment at the fixed doses of 10 and 20 mg produced a dose-dependent clinically meaningful statistically significant improvement in the three primary efficacy measures of EF: the EF domain

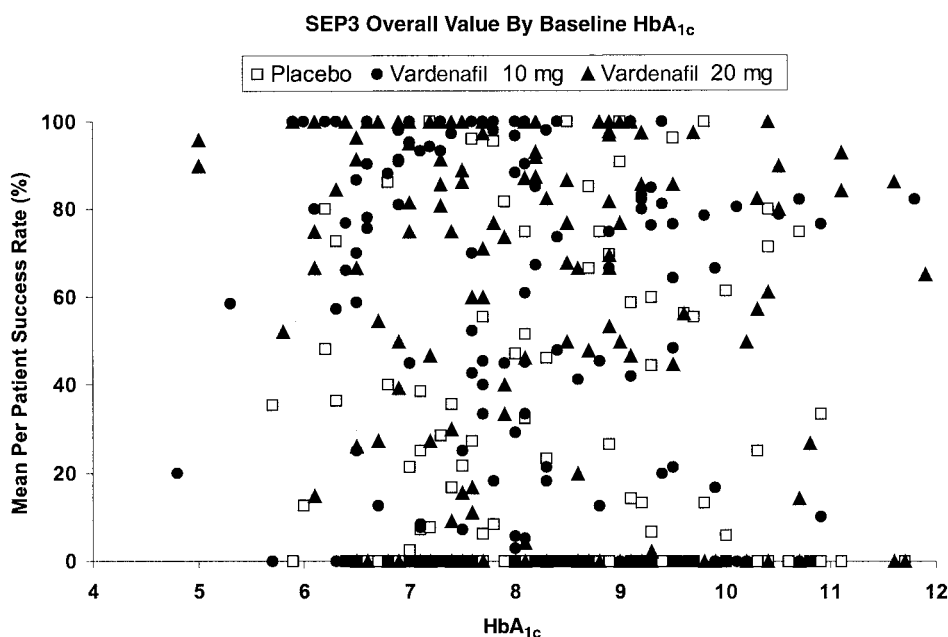


Figure 3—Relationship between response to treatment and baseline plasma HbA_{1c} levels. There was no correlation between individual success rate of erections with a duration sufficient to complete intercourse from diary question sexual encounter profile 3 (SEP3) and baseline plasma levels of HbA_{1c} . Contribution to $R^2 = 0.0042$ and $P = 0.44$.

Table 2—Incidence of treatment-emergent adverse events occurring in $\geq 5\%$ of any treatment group

| | Placebo | Vardenafil 10 mg | Vardenafil 20 mg |
|----------------------|---------|---------------------|---------------------|
| n | 143 | 152 | 144 |
| Headache | 10 (7) | 20 (13) | 16 (11) |
| Flushing | 1 (<1) | 14 (9) | 14 (10) |
| Rhinitis | 7 (5) | 8 (5) | 15 (10) |
| Sinusitis | 1 (<1) | 2 (1) | 9 (6) |
| Accidental injury | 4 (3) | 12 (8) | 3 (2) |

Data are n (%).

score of the IIEF and two diary questions addressing rates of vaginal penetration and successful intercourse. Similar levels of efficacy were observed irrespective of whether patients had type 1 or type 2 diabetes. The responder rate was high because 72% of men taking 20 mg vardenafil responded that their erections had improved after treatment for 3 months. Intercourse success rates were significantly increased by vardenafil in all patient subgroups, including those with severe baseline ED, although the higher absolute success rate in the mild ED group in part may be explained by the higher success rate at baseline.

The disease burden of the diabetic population included in this study was severe because more than half of the men had severe ED at baseline and/or poor glycemic control. The high responder rate observed in this study describes the response of a population considered difficult to treat successfully. This finding is consistent with previous clinical studies in which vardenafil improved erections in up to 85% of men with ED with a broad etiology (15). As in this previous study (15), vardenafil was also effective regardless of baseline severity, although the absolute success rate was lower in the severe group because the men started at a much reduced success rate. Treatment with 20 mg vardenafil for 12 weeks resulted in a marked improvement in sexual function, because mean intercourse success rates in men with severe ED increased from <2.5% at baseline to 40%. Treatment with 20 mg vardenafil for men with mild ED at baseline resulted in average per patient success rates of 75%. Efficacy across different degrees of ED severity in men with diabetes is crucial because ED worsens with duration of diabetes (3).

It could be argued that exclusion of patients who had previously discontinued sildenafil because of efficacy or intolerance may have improved the response rate to vardenafil. However, although they were not supposed to participate in this study, 3% of patients were included who later admitted to past discontinuation of sildenafil treatment. Although it is unclear how many men had not considered entry before screening, only 12 of 174 (6%) were rejected during the baseline screening period because of previous sildenafil discontinuation. Approximately 40% of men were naive to sildenafil, and the similar success rates for vardenafil patients, whether previous users or not, suggests that this exclusion criterion did not affect the efficacy observed in this study. A clearer comparison of efficacy with other therapeutic agents would be derived from head-to-head studies in the same population with enough patients to show significant differences.

Vardenafil was generally well tolerated. Treatment-emergent adverse events were mostly mild and moderate headache, cutaneous flushing, or rhinitis. The lack of reported color/vision changes during this trial using these dosages was consistent with previous trials. However, transient vision changes, such as haziness, were noted infrequently. This safety profile is consistent with the adverse event profile of a highly selective PDE5 inhibitor (11).

Complications of diabetes such as vascular disease and neuropathies render diabetic men more difficult to successfully treat (16). This study demonstrated marked improvement from baseline after treatment with vardenafil indicating a robust response to treatment in this population. With the growing prevalence of diabetes and the difficulties associated with the treatment of ED in this population, it is important to have options for treating this common and serious complication of diabetes. This study suggests that vardenafil treatment, to which many men respond, provides an effective and generally well tolerated treatment for ED in men with diabetes.

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