

# Vardenafil (Levitra) for erectile dysfunction: a systematic review and meta-analysis of clinical trial reports

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**Trials of the efficacy and safety of vardenafil in the treatment of male erectile dysfunction (ED) were meta-analysed. All available databases were searched (January 1, 2001–November 30, 2003). Trials were eligible if they included men with ED, compared vardenafil with placebo, were randomized, were at least of 12 weeks duration, and assessed clinically relevant outcomes. Two reviewers independently evaluated study quality and extracted data in a standardized fashion. Nine trials (6809 men) met the inclusion criteria. In results pooled from seven fixed-dose trials, vardenafil increases the Erectile Function domain of the International Index of Erectile Function questionnaire by 6.18 units (weighted mean difference (WMD)). Vardenafil also increases the percentage of erections firm enough to allow vaginal penetration (WMD: 26) and the percentage of sexual attempts that were successful per participant (WMD: 29.8). The percentage of men agreeing with the statement that ‘the treatment they have been taking over the past 4 weeks improved their erections’, is also in favour of vardenafil (relative risk (RR): 3). These efficacy variables appeared greater at higher doses, although there are no significant differences between 10 and 20 mg dose. The same results were extracted for the two flexible ‘as needed’ dosing trials. Discontinuations are greater at the vardenafil groups compared to placebo (RR: 2.25). Specific adverse events with vardenafil included flushing, dyspepsia, headache, and rhinitis. Vardenafil was not significantly associated with serious cardiovascular events or death. Vardenafil, in all treatment regimens, shows to possess superior efficacy to placebo in the treatment of patients with erectile dysfunction. More data is needed on patients’ subgroups.**

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## Introduction

Erectile dysfunction (ED) has been defined by the National Institutes of Health Consensus Development Panel on Impotence and the American Urological Association as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance.<sup>1,2</sup> ED is a common medical disorder that has a negative impact on the quality of life and self-esteem and can create difficulties in partner relationships.<sup>1</sup> A variety of organic, psychogenic, and lifestyle factors have been implicated in

the etiology of ED.<sup>3</sup> Moreover, ED is strongly age-related (but not age-dependent), with an estimated prevalence rate of 39% in men who are 40 years old, increasing to 67% in men who are 70 years old.<sup>4</sup>

Penile erection is a vascular process that involves relaxation of the smooth muscle cells of the corpus cavernosum and associated arterioles.<sup>5</sup> Evidence suggests that a major component of the process of smooth muscle relaxation is mediated by nitric oxide (NO) through cyclic guanosine monophosphate (cGMP).<sup>6,7</sup> In response to sexual stimulation, NO is released by nerve endings and endothelial cells and increases the production of cGMP by guanylate cyclase, resulting in relaxation of cavernosal smooth muscle cells and penile erection.<sup>6–9</sup> Subsequently, cGMP is catabolized by cGMP-specific phosphodiesterase type 5 (PDE5), resulting in restoration of quiescent muscle tone and detumescence.

Further understanding of the mechanism of penile erection has led to the development of sildenafil citrate (Viagra<sup>®</sup>, Pfizer Inc.), a novel orally active

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agent that selectively inhibits cGMP-specific PDE5, the predominant isozyme responsible for catabolism of cGMP in the human corpus cavernosum.<sup>10</sup> As a selective inhibitor of cGMP catabolism in the corpus cavernosum, sildenafil restores cGMP-induced penile erectile activity in subjects with ED, but only under conditions where sexual stimulation occurs. Sildenafil and the substances vardenafil (Levitra<sup>®</sup>, Bayer AG/Glaxo Smith Kline)<sup>11</sup> and tadalafil (Cialis<sup>®</sup>, Lilly ICOS LLC),<sup>12</sup> which were developed later, are known as PDE5 inhibitors. The development of the newer PDE5 inhibitors vardenafil and tadalafil now prompts the question of whether and how these two substances differ in terms of efficacy and adverse effects from sildenafil.

Vardenafil has already been released in Europe and was recently approved by the Food and Drug Administration (FDA) advisory panel for marketing in the USA. Since physicians and patients ask for efficacy and Adverse Events (AEs) of this new substance, it is now time to write a review based on the information available.

## Methods

### Literature search

Trials were identified by searching the MEDLINE, Embase, CINAHL, Current Contents, and Cochrane Library electronic databases (January 1, 2001–November 30, 2003). We also checked the proceedings of the US FDA advisory panel related to the relevant approval applications. We did the same by searching the European Agency for the evaluation of Medical Products. The search strategy included the key terms ‘impotence’ or ‘erectile dysfunction’, combined with ‘vardenafil’, ‘Levitra’, and ‘NDA-21400’, and limited by combination with the terms ‘clinical trial’, ‘controlled trial’, and ‘randomized controlled trial’. We entered frequently cited papers into Science Citation Index to retrieve reports, which have cited them, manually searched conference proceedings and text books, and screened reference lists of all obtained papers. Finally, we asked content experts for relevant references.

### Selection criteria

Trials were eligible if they (a) included men with ED, (b) were randomized, (c) compared vardenafil with placebo, (d) were at least 12 weeks in duration, and (e) assessed the following clinical outcomes related to ED:

- Erectile function domain of the International Index of Erectile Function questionnaire (EF-IIEF)<sup>13</sup>

- Sexual Encounter Profile–Q2 (SEP2)
- Sexual Encounter Profile–Q3 (SEP3), and
- Global Assessment Question (GAQ).

For each trial, two of the authors (SAM, PP) assessed study eligibility. Differences in assessment were resolved by reaching a consensus.

### Outcome measures

Information on trial characteristics, patient demographics, inclusion and exclusion criteria, dropouts, treatment efficacy, and adverse events were extracted in a standardized form. The primary measures of efficacy after 12 weeks of treatment were the EF-IIEF domain score (questions 1–5 and 15) and two diary questions concerning sexual encounter profile: ‘Were you able to insert your penis in your partner’s vagina?’ (SEP2) and ‘Did your erection last long enough for you to have successful intercourse?’ (SEP3). While the EF score was considered as a continuous variable *a priori*, the mean success rate per patient was calculated from the two diary questions. Thus, SEP2 and 3 were also considered as continuous variables.

The secondary efficacy variable reported herein was the response of patients completing 12 weeks of treatment to the following Global Assessment Question: ‘Has the treatment you have been taking over the past 4 weeks improved your erections?’ This variable, answered by yes/no, was measured as a dichotomous variable.

AEs of vardenafil treatment were also sought. Evaluation included the number of men with any treatment-related AEs, those discontinuing through dissatisfaction, protocol violation or AEs, and information on particular AEs.

### Assessment of methodologic quality

We assessed the quality of randomized treatment by recording all the characteristics of the trials, such as randomization, double blindness, description of withdrawals and dropouts, and whether or not randomization and blinding were appropriate.<sup>14</sup> Moreover, we assessed whether trials used an intention-to-treat analysis for the outcomes they described.<sup>15</sup>

### Statistical analysis

For evaluation of continuous outcomes (EF-IIEF, SEP2, SEP3), we estimated the weighted mean differences (WMDs) and their 95% confidence intervals (CIs). For evaluation of dichotomous outcome (GAQ), we calculated the weighted relative risk (RR) and the 95% CIs. For adverse events and

withdrawals, we determined the percentage of men achieving each outcome according to treatment assignment and the weighted RR and 95% CIs.

For measurement, we used the random effects method. Calculations were performed using the RevMan 4.0 software.<sup>16</sup> The results were tested for heterogeneity at a significance level of  $P < 0.01$ .

## Results

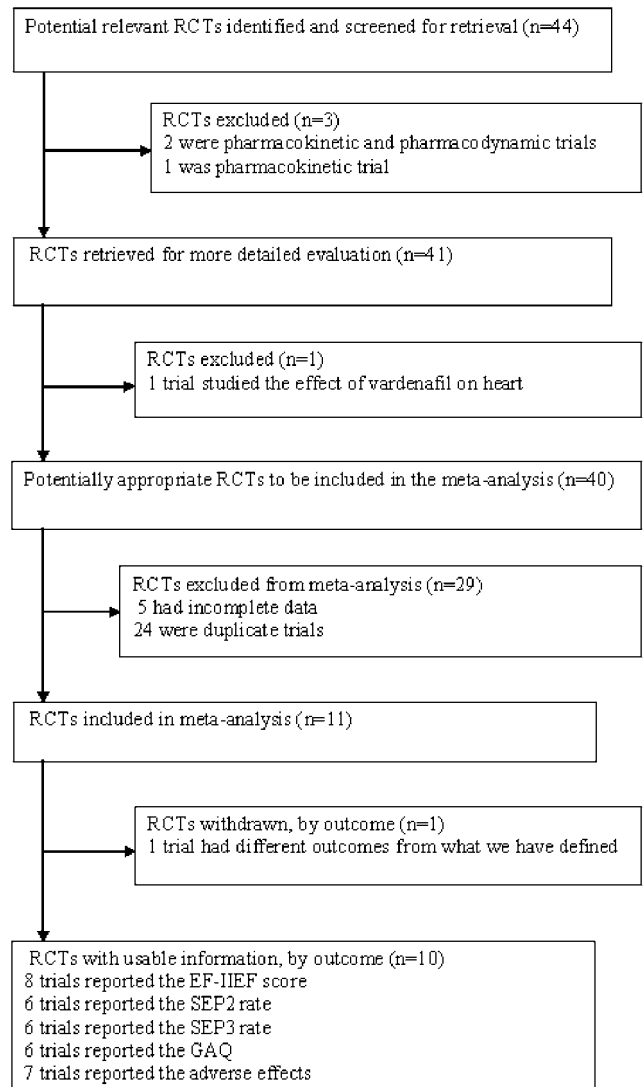
### Characteristics of trials

A total of 44 potentially relevant trials were identified and screened for retrieval. The screening was performed according to the QUOROM statement (Figure 1).<sup>17</sup>

A total of 10 trials involving 6809 men met all the eligibility criteria and were included in this systematic review (Table 1).<sup>18–27</sup> Five trials were published in peer-reviewed journals,<sup>18–22</sup> but one of them was a reanalysis of a previous trial<sup>18</sup> focusing on patient subgroups.<sup>22</sup> One trial was submitted by the sponsor (Bayer AG) to the FDA for approval of the drug.<sup>27</sup> Four trials were presented in conference meetings and were published as abstracts.<sup>23–26</sup> Eight reported that they were randomized, double blind and placebo-controlled,<sup>18–25,27</sup> and one was reported only as randomized and placebo-controlled.<sup>26</sup> However, only two trials described the generation of allocation sequences.<sup>19,21</sup> None of them reported if a concealment of treatment assignment was done and how the allocation was implemented. There were also no details of blinding with the exemption of one trial.<sup>18</sup>

In six trials, there was a description of withdrawals and dropouts. All trials were multicenter, parallel in design and the treatment regimen included a taken 'as needed' fixed (seven trials) or flexible dose (two trials). All papers, but one,<sup>25</sup> described the results to be analyzed as according to the intent-to-treat (ITT) principle. However, as generally interpreted, ITT principle was inadequately described and applied.<sup>15</sup> The authors defined the ITT population as consisting of all patients who had received at least one dose of study medication and at least one efficacy assessment, and used the last-observation-carried-forward (LOCF-ITT) method to account for missing data. Such an approach is inconsistent with the basic meaning of the ITT principle.

Power calculations for detecting difference responses in primary outcome were detailed in three trials.<sup>18,19,21</sup> Two papers reported the exact nature of  $P$ -values;<sup>21,25</sup> in the others, for the purpose of our meta-analysis,  $P$ -values were considered two-sided. All studies were financially supported or at least one of the authors was affiliated with a commercial



**Figure 1** Progress through the stages of the meta-analysis for vardenafil RCTs.

body. There was no information on whether the commercial body was involved in planning, conduct, analysis, or writing up.

In seven trials, the treatment duration was 12 weeks and in two 26 weeks. Common trial inclusion criteria were men 18 years of age or older experiencing ED, which was defined as the inability to achieve or maintain a penile erection sufficient for satisfactory sexual intercourse for more than 6 months in duration. General exclusion criteria were anatomic abnormalities of the penis that could impair EF, hypoactive sexual desire, ED after spinal cord injury, retinitis pigmentosa, unstable angina pectoris, uncontrolled atrial tachyarrhythmia, or any myocardial infarction, stroke, electrocardiographic ischemia, life-threatening arrhythmia within the previous 6 months. Patients were excluded if they had symptomatic postural hypotension within 6 months prior to screening, resting hypotension

**Table 1** Characteristics of included vardenafil trials

Study and year	Men randomized (dropouts)	Design	Treatment regimen (vardenafil, mg)	Treatment duration (weeks)	Characteristics of participants
Porst <i>et al</i> (2001) <sup>18</sup> Porst <i>et al</i> (2003) <sup>22 a</sup> Hellstrom <i>et al</i> (2002) <sup>19</sup>	601 (95)	Parallel	Fixed dose (5, 10, 20)	12	General population (excluded radical prostatectomy)
Porst <i>et al</i> (2002) <sup>25</sup>	805 (297)	Parallel	Fixed dose (5, 10, 20)	26	General population (excluded radical prostatectomy)
Goldstein <i>et al</i> (2003) <sup>20</sup>	1401 <sup>b</sup>	Parallel	Fixed dose (5, 10, 20)	26	General population and patients taking antihypertensive medications
Brock <i>et al</i> (2003) <sup>21</sup>	452 (73)	Parallel	Fixed dose (10, 20)	12	Diabetic men (excluded radical prostatectomy)
Montorsi <i>et al</i> (2003) <sup>23</sup>	440 (110)	Parallel	Fixed dose (10, 20)	12	Men with radical retropubic prostatectomy; neurovascular bundle sparing, 73 % bilateral
Hatzichristou <i>et al</i> (2003) <sup>26</sup>	1479 (400)	Parallel	Fixed dose (5, 10, 20)	12	General population (excluded radical prostatectomy)
Hatzichristou <i>et al</i> (2003) <sup>24</sup>	323 <sup>b</sup>	Parallel	Flexible dose, starting dose 10 mg	12	General population
Clinical trial 10128 (2001) <sup>27</sup>	463 <sup>b</sup>	Parallel	Flexible dose, starting dose 10 mg	12	Men with sildenafil nonresponse histories
	845 (127)	Parallel	Fixed dose (5, 10, 20)	12	General population (excluded radical prostatectomy)

<sup>a</sup>Same trial as Porst (2001) with more data on patient subgroups.

<sup>b</sup>Dropouts are not reported.

(systolic blood pressure (SBP)  $\leq$  90 mmHg), hypertension (resting SBP  $\geq$  170 mmHg or diastolic blood pressure  $\geq$  110 mmHg), a history of hepatitis B surface antigen or hepatitis C, severe chronic liver disease or abnormalities such as, chronic hematologic disease, bleeding disorder, poorly controlled diabetes mellitus (hemoglobin A1c  $>$  12%), inadequately treated hyperthyroidism or hypothyroidism, or a history of peptic ulcer disease within 1 year before screening. Patients with a history of malignancy within the previous 5 years, low serum testosterone levels (defined as the lower limit of normal, according to the range of laboratories that participated in the study, which was at least 10 nmol/l), serum creatinine values higher than 2.5 mg/dl, any investigational drug usage within 30 days of screening, and sildenafil or other therapy for ED within 7 days before screening were also excluded. Intake of antiandrogens, anticoagulants, androgens, and trazodone hydrochloride were additional reasons for exclusion. Radical prostatectomy was an exclusion criterion in five trials. A 'history of unresponsiveness to sildenafil' was an exclusion criterion in five trials.<sup>18–20,23,27</sup> A history of significant side effects with sildenafil use was an exclusion criterion in two trials.<sup>20,21</sup> Some trials published in abstracts did not report exclusion criteria.<sup>24–26</sup> One trial, a phase IIb study, was enrolling generally healthier patients than the other trials.<sup>18</sup>

### Demographics of patients

Men in these trials had a mean age of 56 years (Table 2). The mean ED duration was 3.8 years.

Baseline ED severity was estimated from scores of enrolled participants ( $n = 3182$ ) on the EF domain score. Men scoring 0–10 were stated as having severe ED (46%), those scoring 11–25 were rated as having mild to moderate (51%), and those scoring 26–30 were considered to have no ED (3%). A total of 55% of the men had purely organic ED, 12% had purely psychogenic ED, and 33% had a mixture of these two. The prevalent comorbid conditions were hypertension (36%), diabetes mellitus (38%), and depression (23%).

### Efficacy analysis

Vardenafil doses of 5, 10, and 20 mg were clinically and statistically superior to placebo in the treatment of ED. The results of the efficacy analysis for the primary and the secondary end points are analyzed in Figure 2. All three-dose regimens produced clear statistically significant improvements in the EF-IIEF domain score. EF ranged, in fixed-dose trials, from 5.06 to 6.91 and was related to dose, with the greatest benefit for the 20 mg dose. The pool from the two flexible doses shows an increase of 7.45 in the EF score (7.45; 95% CI, 3.97–10.92). However, while the change in EF for the 20 mg dose (6.91; 95% CI, 6.11–7.70) was greater numerically than the 5 mg dose (5.06; 95% CI, 3.67–6.45), there was no great difference from the 10 mg dose (6.16; 95% CI, 5.25–7.07). The test for heterogeneity yields a result of  $P = 0.11$ .

The other primary efficacy variables, SEP2 and SEP3, derived from patient diary recordings, also

**Table 2** Baseline characteristics of 4286 participants

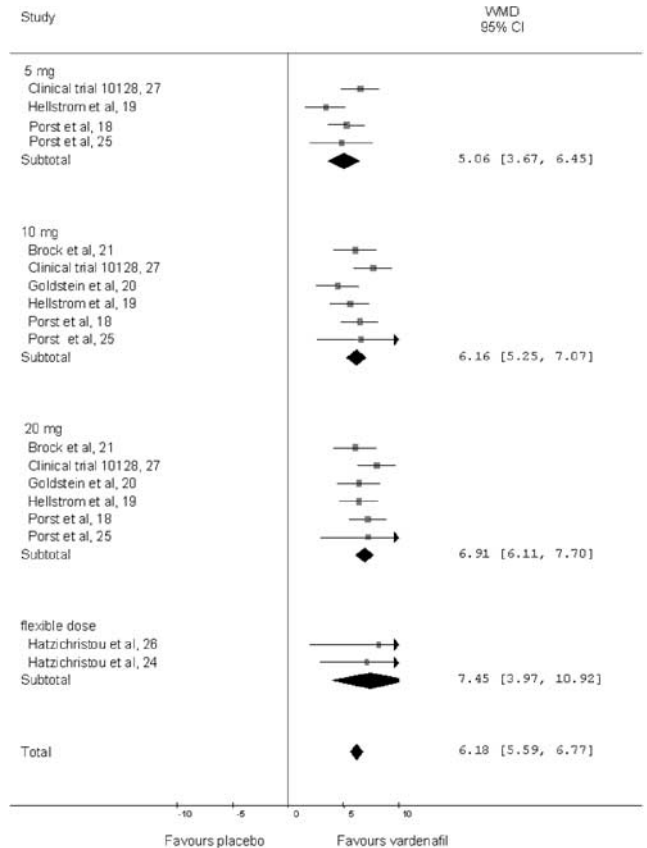
Characteristic	Vardenafil group—all arms (n = 3164)	Placebo group (n = 1122)
Age (mean) <sup>18–21,23,27</sup>	55.9	56.2
Race (%)		
White <sup>19–21,23,27</sup>	76.6	76.3
Black <sup>20,23</sup>	2.9	8.9
Asian <sup>23</sup>	2.7	3.5
BMI <sup>19–21,23</sup>	28.2	28.5
ED duration (mean, y) <sup>18–20,23</sup>	4	3.6
ED severity (%) <sup>18–21</sup>		
Severe	47.2	45
Mild to moderate	52.4	50.3
None	0.4	4.7
ED cause (%) <sup>18–20</sup>		
Organic only	54.7	56.3
Psychogenic only	11.9	13
Mixed	33.4	30.7
Comorbid conditions (%)		
Hypertension <sup>19–21,23</sup>	36.8	34.2
Diabetes mellitus <sup>19–21,23</sup>	37.2	39.6
Ischemic heart disease <sup>19</sup>	3.1	4.9
Depression <sup>19,20</sup>	20.9	28.9

showed significant improvement with treatment, compared to placebo (Figures 3 and 4). Again, a dose response is noticed with the greater increase in 20 mg, in the fixed-dose trials. However, the differences between the 10 and 20 mg are too small to be clinically meaningful. The flexible-dose studies also showed a great difference with the placebo but only one trial evaluated SEP3.

Overall, there was an increase of 26% (95% CI, 22.89–29.11) in the success rate for penetration and an increase of 29.8% (95% CI, 26.47–33.06) in the success rate for maintaining erection during intercourse compared to placebo. The test for heterogeneity yields a result of  $P=0.05$  for SEP 2 and  $P=0.06$  for SEP3.

The GAQ, which evaluated whether the quality of erections has improved while on treatment, demonstrated a marked increase in all vardenafil-treated groups (Figure 5).

All vardenafil groups were significantly greater than placebo ( $P<0.00001$ ). A total of 69% of men receiving vardenafil reported that treatment improved their erections compared with 26% of men allocated to the placebo group (RR, 3; 95% CI, 2.4–3.7). Greater improvement was observed for 20 mg dose (RR, 3.6; 95% CI, 2.2–6) and 10 mg dose (RR, 3.2; 95% CI, 2–5.2). The 5 mg dose had the smaller RR risk from the fixed-dose regimen (RR, 1.9; 95% CI, 1.5–2.5). In the two trials that used a flexible-dose regimen, the RR was also in favor of vardenafil

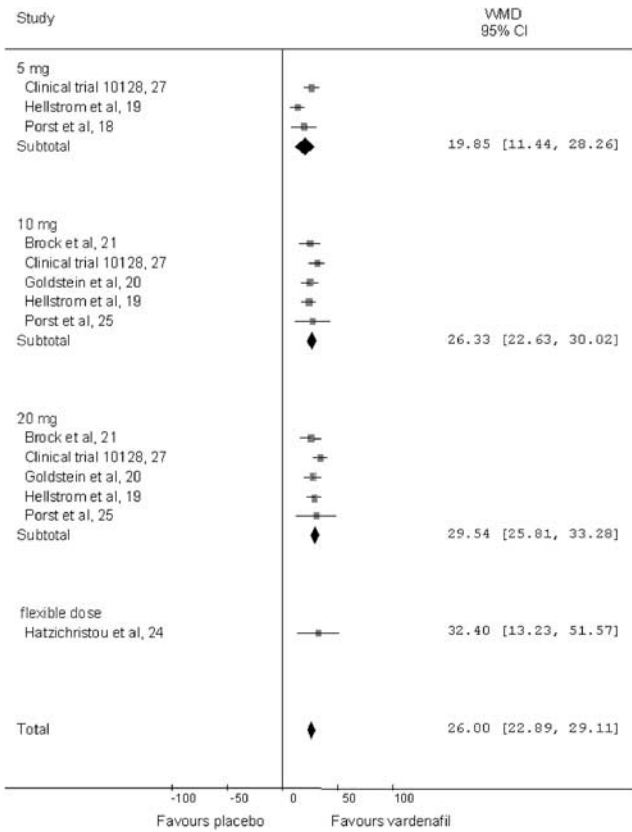


**Figure 2** WMDs for the Erectile Function domain of the International Index of Erectile Function questionnaire (CI: confidence interval).

treatment (RR, 3.2; 95% CI, 1.8–5.8). The test for heterogeneity yields a result of  $P<0.00001$ .

### Safety

The primary evaluation of the safety of vardenafil was derived from seven placebo-controlled trials. A total of 4374 patients were evaluated and of these, 2660 patients received vardenafil. In these studies, 50.4% of patients reported AEs. The incidence rates of treatment-emergent AEs in the vardenafil treatment group were greater than in the placebo group. AEs that occurred at least twice as often on vardenafil than on placebo were headache, flushing, rhinitis–sinusitis, and dyspepsia. The incidence of treatment-emergent AEs reported by  $\geq 2\%$  of patients taking vardenafil is shown in Table 3. The incidence rates of treatment-emergent AEs in the placebo-controlled flexible trials were markedly higher than those in the fixed-dose studies. Data from fixed-dose trials indicated that all AEs were more frequent at higher doses. Overall, discontinuations were greater in the vardenafil group compared to placebo, while the discontinuation rate in flexible-dose trials was lower in comparison to fixed-dose trials.

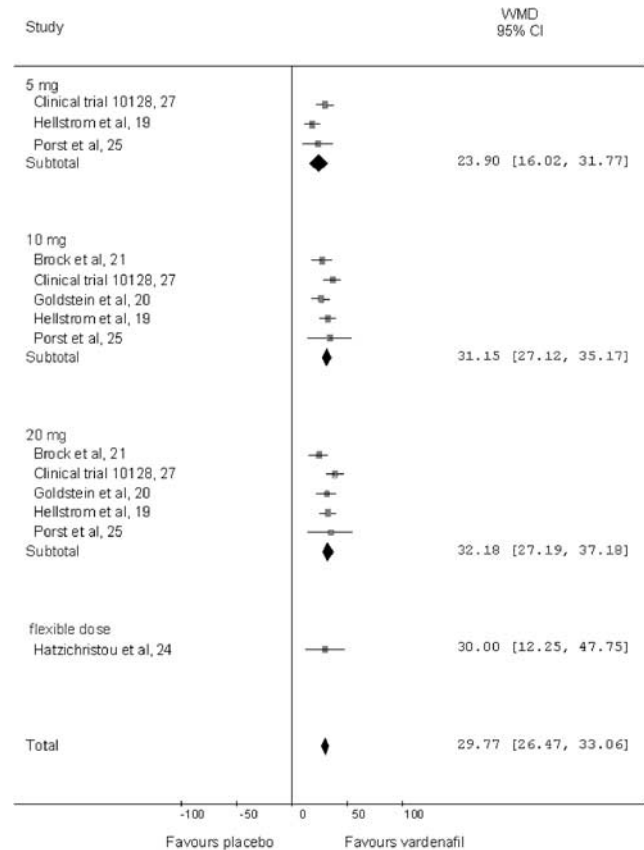


**Figure 3** WMDs in the percentage of erections firm enough for intercourse (CI: confidence interval).

The incidence of death and serious cardiovascular events, such as angina pectoris and myocardial infarction, were seldom in patients recruited in these randomized studies. In data available from the FDA approval package,<sup>27</sup> the combined outcome of angina or chest pain, in patients without history of cardiovascular disease (CVD), was reported by 1.4% of men receiving vardenafil compared with 1% of men taking placebo (Fisher's exact test,  $P=0.4$ ). The incidence rate of angina or chest pain in patients with a history of CVD was 2.7% and 0.9, respectively (Fisher's exact test,  $P=0.42$ ). Similarly, the myocardial infarction incidence rate was 0.5/0.0% (Fisher's exact test,  $P=1$ ) and 0.0/0.1% (Fisher's exact test,  $P=0.35$ ) for patients with and without CVD, respectively. Five deaths in patients taking vardenafil and one in placebo-treated patients were reported. Four of these deaths appeared unrelated to the use of the drug. In the fifth case, a causal relationship with vardenafil cannot be ruled out.

## Discussion

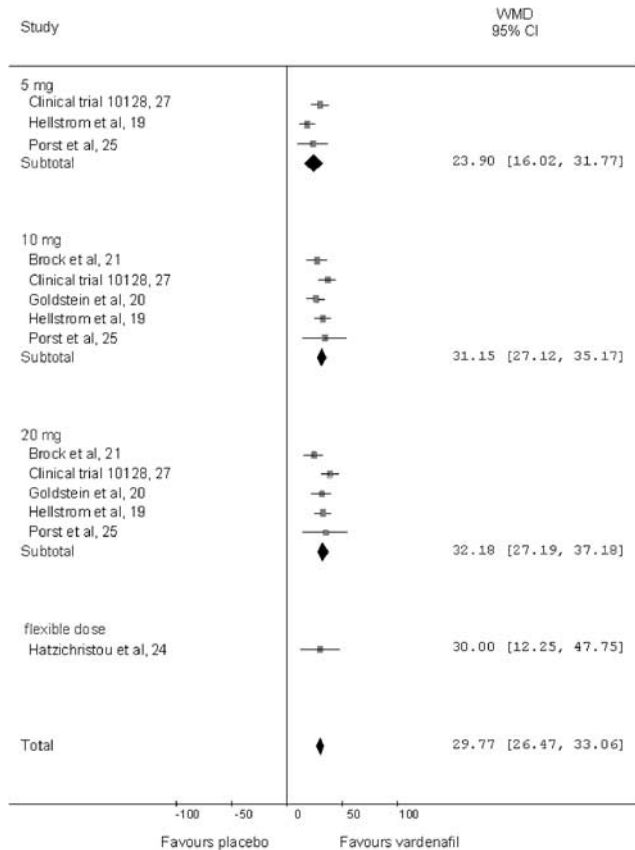
While self-injections still have their place for a limited number of patients,<sup>28</sup> the therapeutic management of ED was revolutionized after the intro-



**Figure 4** Weighted mean differences (WMDs) in the percentage of sexual attempts that were successful per participant (CI: confidence interval).

duction of oral sildenafil for both psychogenic and organic ED.<sup>10</sup> Basic research into ED has demonstrated the importance of the NO/cGMP/PDE5 interactions for the natural erection process.<sup>5-9</sup> The PDE5 inhibition with subsequent cGMP accumulation, caused by sildenafil, has made this mechanism an attractive approach for the relief of erectile disorders. Great efforts to optimize both the efficacy and safety profile in this new therapeutic concept are under way worldwide. Vardenafil hydrochloride, 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.<sup>29-31</sup>

The importance of meta-analysis in drug development and regulatory procedures is being increasingly recognized.<sup>32,33</sup> Therefore, we conducted this systematic review and meta-analysis to estimate the magnitude of treatment benefits and AEs associated with vardenafil treatment in men with ED. Our review identified nine randomized, multicenter, placebo-controlled, parallel-group design trials suitable for meta-analysis. Seven studies implemented fixed-dose and two flexible-dose regimens. The assessed co-primary and secondary parameters can provide clear evidence of the efficacy and safety of



**Figure 5** RR in the percentage of men reporting that 'the treatment they have been taking over the past 4 weeks improved their erections'.

the evaluated medication. The primary time point for all efficacy variables was 12 weeks after randomization.

The results of this meta-analysis demonstrated that 5, 10, and 20 mg of vardenafil showed a statistically and clinically significant improvement compared with placebo in terms of all primary parameters. An increased response was observed across the entire dose range with the greatest efficacy at the 20 mg dose. However, the differences between 10 and 20 mg are minimal. The benefit achieved with vardenafil 20 mg compared to that achieved with 10 mg in the broad spectrum of ED population was not clinically significant. In addition, data from flexible-dose studies came to the same conclusion, that is, vardenafil is clinically and statistically superior to placebo.

The mean difference of effect in IIEF-EF ranged from an improvement over placebo of 5 with vardenafil 5 mg to 6.9 with vardenafil 20 mg. The mean difference in flexible-dose studies was 7.5, probably because the titration to the 20 mg dose of vardenafil achieved more optimal response.

Improvement in success for penetration ranged from 19.9% with vardenafil 5 mg to 29.5% with vardenafil 20 mg, compared to placebo; again the

**Table 3** Discontinuations and adverse events by treatment dose

	Vardenafil group (n = 2660) (%)	Placebo group (n = 1714) (%)	RR (95% CI)
<b>Discontinuations</b>			
Flexible dose	1	<1	1.32 (0.30–5.58)
Fixed dose, 5 mg	4	2	2.00 (1.01–3.97)
Fixed dose, 10 mg	3	2	1.80 (0.96–3.36)
Fixed dose, 20 mg	5	2	3.23 (1.80–5.81)
<b>Any adverse event</b>			
Flexible dose	26	4	7.01 (4.08–12.04)
Fixed dose, 5 mg	29	11	2.66 (2.08–3.41)
Fixed dose, 10 mg	45	12	3.68 (2.82–4.80)
Fixed dose, 20 mg	56	12	4.56 (3.32–6.26)
<b>Headache</b>			
Flexible dose	9	2	4.59 (2.05–10.26)
Fixed dose, 5 mg	14	6	2.94 (1.49–5.91)
Fixed dose, 10 mg	15	5	3.03 (2.18–4.21)
Fixed dose, 20 mg	19	5	3.72 (2.48–5.58)
<b>Vasodilatation—flushing</b>			
Flexible dose	9	<1	9.64 (1.40–66.45)
Fixed dose, 5 mg	7	<1	6.48 (1.82–23.15)
Fixed dose, 10 mg	12	<1	16.77 (7.39–38.06)
Fixed dose, 20 mg	14	<1	18.81 (8.31–42.60)
<b>Dyspepsia</b>			
Flexible dose	3	0	22.50 (1.33–379.64)
Fixed dose, 5 mg	1	<1	2.89 (0.86–9.72)
Fixed dose, 10 mg	5	<1	7.82 (2.78–22.01)
Fixed dose, 20 mg	5	<1	12.66 (4.60–34.85)
<b>Rhinitis—sinusitis</b>			
Flexible dose	7	2	3.99 (1.65–9.67)
Fixed dose, 5 mg	8	4	1.90 (1.21–2.98)
Fixed dose, 10 mg	12	5	2.30 (1.46–3.62)
Fixed dose, 20 mg	15	5	3.32 (2.41–4.59)

flexible-dose studies showed better response (32.4%). Improvement in maintenance of erection for successful completion of intercourse confirmed the superiority of vardenafil, by ranging from 23.9% with 5 mg to 32.2% with 20 mg, as compared to placebo. No safe conclusion can be drawn regarding flexible dose of vardenafil since only one trial used this therapeutic regimen. All, except for EF, primary outcome showed heterogeneity.

The proportion of responders, defined as those in the ITT population, who affirmatively answered the GAQ was significantly higher for all groups of patients treated with vardenafil than for those treated with placebo. For this secondary outcome, there was also a dose-related difference in response between 5, 10, and 20 mg. At 12 weeks, 60.2% of those receiving vardenafil 5 mg, 67.4% of those receiving vardenafil 10 mg, and 73.5% of those receiving vardenafil 20 mg described a positive response to the GAQ. The percentages for the placebo group were 26.2, 18.9, and 18.9%, respectively. The positive responders rate for flexible trials

was 72% for vardenafil vs 23% for placebo. However, for this variable, the trials appeared quite heterogeneous ( $P < 0.00001$ ). The heterogeneity of results of the two primary and one secondary outcome when traced back appears to be clinical in origin, because the population characteristics of the trials (general population, diabetics, radical prostatectomy patients, healthy individuals) may affect the response.

The analysis of the data on safety show that vardenafil has a safety profile which is expected for its pharmacological class, headache and vasodilatation (flushing) being the most frequently reported AEs. There was a dose-dependent increase in the incidence of treatment-related AEs from placebo to 5 mg (29%), 10 mg (58.7%), and 20 mg (56%) for most of the reported AEs. A higher proportion of patients in all vardenafil groups withdrew due to AEs compared to the placebo group. The lower proportion was observed in flexible-dose trials (RR, 1.3). This finding may explain the fact that the adverse event rate was higher in this group, because a larger proportion of patients remained under vardenafil treatment.

In conclusion, the evidence from this systematic review and meta-analysis indicates that in the broad population of men with ED, vardenafil safely and consistently improved all efficacy parameters of EF, improving erections and satisfaction in men treated for 12 weeks. Additional data, however, are needed to more precisely determine the efficacy and safety of vardenafil treatment in patient subgroups, that is, the efficacy according to etiology of ED, the efficacy according to baseline severity of ED, the efficacy according to patient age, and the efficacy according to prior use of sildenafil. Moreover, we need more data that will show the consistency of efficacy over time, since only two trials extend the duration of treatment over 12 weeks. While the direct comparison of the medications for the treatment of ED has started,<sup>34</sup> randomized trials should compare vardenafil with other treatment agents. With these data, the so-called 'phosphodiesterase inhibitor 'war' may come to an end.

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