REVITALISE: A Large Observational Study Assessing the Safety and Effectiveness of Vardenafil in Men With Erectile Dysfunction and Metabolic Syndrome

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ABSTRACT

Introduction: Erectile dysfunction (ED) is prevalent in men with metabolic syndrome (MetS); therefore, it is important to characterize ED treatments in this population.

Aims: To investigate the safety and effectiveness of vardenafil in men with ED and MetS in a clinical setting.

Methods: REVITALISE is an international, prospective, single-arm, observational study in men with ED and MetS newly prescribed vardenafil. Vardenafil was prescribed at the discretion of the treating physician in line with the marketing authorization. Treatment effectiveness (International Index of Erectile Function [IIEF]) and health-related quality of life (Aging Males' Symptoms Scale) were assessed at treatment initiation, at an optional dose adjustment visit after approximately 4 weeks, and at the end of the observation period (approximately 12 weeks).

Main Outcome Measures: The primary outcome was an intraindividual improvement in erectile function (EF), defined as an increase of at least four points in the EF domain of the IIEF. Secondary outcomes included assessing normal EF (IIEF-EF score $\geq$ 26), mild ED (IIEF-EF score = 22−25), and health-related quality of life. Treatment-emergent adverse events were monitored.

Results: In the intent-to-treat population (n = 1,832, mean age = 54.0 years, mean body mass index = 31.82 kg/m^2, Asian 36.8%, white 49.9%, 20.4% with severe ED, 75.6% with mild or moderate ED, 4.0% without ED), 82.4% reported an increase of at least four points in IIEF-EF score. Median IIEF-EF score increased from 15.0 (baseline) to 25.0 at 12 weeks ($P < .0001$). After treatment, 45.4% and 29.4% (intent-to-treat population) had normal EF and mild ED, respectively. Improvements in the sexual, psychological, and somatic subscales of the Aging Males' Symptoms Scale were found ($P < .0001$). Treatment-emergent adverse events were reported by 7.19% of patients; there were no serious adverse events related to vardenafil.

Conclusion: In a clinical setting, men with ED and MetS treated with vardenafil reported improvements in EF and health-related quality of life; and the safety profile of vardenafil was acceptable. REVITALISE demonstrates that vardenafil represents a good treatment option for men with ED and MetS.

Key Words: Erectile Dysfunction; Metabolic Syndrome; Phosphodiesterase Type 5 Inhibitor; Vardenafil

INTRODUCTION

Erectile dysfunction (ED) is estimated to affect more than 150 million men worldwide and is known to be more prevalent in men with metabolic syndrome (MetS) and related conditions such as hypertension and diabetes compared with the general population.[1-6] A recent analysis found that approximately 40% of patients with ED also have MetS, and ED is almost twice as prevalent in patients with MetS compared with those without it.[7] Furthermore, evidence suggests that the relative risk and severity of ED increase as the number of MetS components increases.[1,2] Owing to the large proportion of patients with ED and MetS, it is important that the safety and effectiveness of ED treatments are fully evaluated in this population.

Phosphodiesterase 5 (PDE5) inhibitors, such as vardenafil, are currently the first-line pharmacologic treatment for ED.[8-10]

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Several studies have demonstrated that vardenafil is a safe and effective treatment for patients with ED.[11-17] It also has been found highly effective in men with ED and underlying comorbidities, such as diabetes, hypertension, and dyslipidemia.[18-23] The first prospective study to examine vardenafil use in men with MetS was a small-scale 12-week placebo-controlled study of 145 men with ED and MetS in Germany.[24] It demonstrated that vardenafil was well tolerated and improved erectile function (EF) compared with placebo[24]; however, further evidence form larger-scale studies is required. This non-interventional observational study is the first large-scale international trial to investigate prospectively the effectiveness of vardenafil in patients with ED and MetS.

AIM

The TheRapeutic Effectiveness of VardenafIl in ED patients with the meTAboLIc SyndromE in daily clinical practice (REVITALISE) study was designed to investigate the effectiveness and safety of newly prescribed vardenafil in men with ED and MetS in the clinical setting.

METHODS

Study Design

In this international, multicenter, prospective, single-arm, non-interventional, observational study (NCT01106118), patients were recruited from 171 study centers in 10 countries (Egypt, Israel, Kazakhstan, Kyrgyzstan, Republic of Korea, Lebanon, Russia, Saudi Arabia, Singapore, and Ukraine) from January 2010 to October 2012. Where required, according to local laws and regulations, independent ethics committee or institutional review board approval was gained; and written informed consent from patients was obtained when they agreed to participate.

Inclusion and Exclusion Criteria

Patients with a diagnosis of ED and documented MetS who were newly prescribed vardenafil without prior use of any PDE5 inhibitor within 1 month of study entry were eligible for inclusion. The International Diabetes Federation (IDF) criteria for MetS[1] were strongly recommended: a waist circumference of at least 94 cm in European, sub-Saharan African, Eastern Mediterranean, and Middle East (Arab) populations; at least 90 cm in ethnic South Asians, Chinese, and ethnic South and Central Americans; and at least 82 cm in the Japanese population; and at least two of the following criteria: triglyceride level at least 150 mg/dL or specific treatment for this abnormality, high-density lipoprotein cholesterol level lower than 40 mg/dL or specific treatment for this abnormality, systolic blood pressure (BP) at least 130 mmHg and/or diastolic BP of at least 85 mmHg or previously diagnosed hypertension, and fasting plasma glucose level at least 100 mg/dL or previously diagnosed type 2 diabetes.

The contraindications and warnings of the Summary of Product Characteristics[25] defined the exclusion criteria for the study.

Study Medication

Vardenafil was prescribed in accordance with the marketing authorization and paid for according to standard local practice. The treatment decision was within current practice and no additional diagnostic or monitoring was required for participation in the study. The duration and dose (5-, 10-, or 20-mg tablets) of treatment were determined by the physician.

Study Protocol

Effectiveness was measured using the International Index of Erectile Function (IIEF), the internationally recognized gold standard for assessing ED treatments.[26-28] The Aging Males' Symptoms (AMS) scale[29] (Supplementary File 1) was used to assess health-related quality of life (HRQoL); however, completion of the questionnaire was optional. With the exception of the Russian translation of the AMS scale, the translations of the questionnaire were produced in accordance with the methodologic recommendations for linguistic and cultural adaption of HRQoL measurements.[29-31]

Patients were followed for approximately 12 weeks, with observations recorded at two to three consecutive visits: at vardenafil initiation, at an optional visit after approximately 4 weeks (if dose adjustment was required according to the clinical response of the patient), and at the end of the 12-week observation period.

At the initial enrollment visit, the patients' demographic information, components of MetS, ED history, prescribed vardenafil dose, and concomitant conditions and medications were recorded. ED etiology was classified by the treating physician based on the physician's assessment of the patient and the patient's medical history. The IIEF[26] and AMS scale[29] (optional) questionnaires also were completed.

At the optional dose adjustment visit, the IIEF questionnaire was completed and the physician recorded the prescribed vardenafil dose, the number of tablets taken since the first visit (as reported by the patient), changes in concomitant medication, and adverse events (AEs). At the final visit, at the end of the study or at discontinuation of therapy (whichever was sooner), the IIEF and AMS scale (optional) questionnaires and global assessment question were completed. The physician recorded the prescribed vardenafil dose, the number of tablets taken since the last visit (as reported by the patient), concomitant medication, and AEs. Patients could discontinue the study at any time; if discontinuation occurred before the 12-week assessment, then it was considered the final visit. Patients who withdrew from the study were not replaced and were not permitted to re-enter.

AEs were recorded at each visit and coded using the Medical Dictionary for Regulatory Activities version 15.1. An AE was

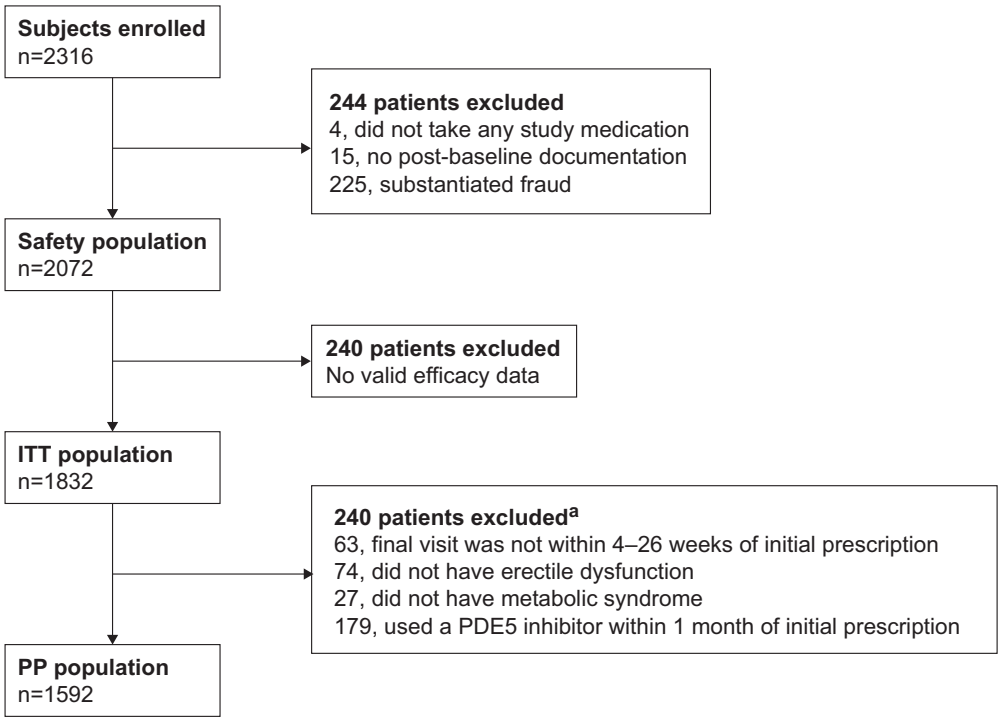

Figure 1. Study populations. [a]Multiple responses were possible. ITT = intent-to-treat; PDE5 = phosphodiesterase type 5; PP = per-protocol.

considered a treatment-emergent AE (TEAE) if it began from the date of the first prescription to 7 days after the final study visit.

Patient Populations

A patient was included in the safety analysis if at least one dose of study medication was taken or was considered taken in cases in which any post-baseline data were documented but information on study medication intake was missing. Patients valid for safety analysis, that is, who had valid efficacy data at their first dose of vardenafil and at either dose adjustment or final visit, were included in the intent-to-treat (ITT) population. Valid efficacy data were defined as a valid score (0, 1, 2, 3, 4, or 5) for all six items of the IIEF-EF. Patients valid for ITT were excluded from the per-protocol (PP) population if they were younger than 18 years, had no ED (IIEF-EF score $\geq$ 26 at initial visit), or did not have MetS as defined by the IDF, World Health Organization,[32] the European Group for the Study of Insulin Resistance,[33] the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III),[34] or IDF and NCEP ATP III consensus.[35]

MAIN OUTCOME MEASURES

The primary objective was to determine a clinically relevant, intraindividual improvement in EF, defined as an increase of at least four points in IIEF-EF score after approximately 12 weeks of treatment.

The secondary objectives were to determine an increase of at least five points in IIEF-EF score and to assess normal EF (IIEF-EF score $\geq$ 26 points), mild ED (IIEF-EF = 22—25 points), and the effect of vardenafil on HRQoL using the AMS Scale after approximately 12 weeks of treatment. Subgroup analyses of changes in IIEF-EF were performed for race, body mass index (BMI), age, and alcohol consumption.

Safety was assessed according to TEAEs.

Statistical Analyses

Approximately 2,000 patients were considered sufficient to detect a percentage of patients with at least four-point improvement of 72% within a 95% CI $\pm$ 2.5% (primary outcome).

Descriptive analysis of the data was performed using summary statistics for categorical and quantitative (continuous) data. Continuous data were described by the number of non-missing values, median, mean, SD, minimum, and maximum and 1, 5, 25, 75, 95, and 99 percentile quantiles. Frequency tables were generated for categorical data and missing was included as a category.

Efficacy end-point analyses were performed for the ITT and PP populations. The change from baseline IIEF-EF score was tabulated by visit and for the final visit; the last observation carried forward was used for the primary end point only. The increase in IIEF-EF score was analyzed non-parametrically using the Wilcoxon signed rank test (one-sided). The Fisher exact test was used to compare changes in categorized IIEF-EF domain scores and overall satisfaction. The AMS scores were analyzed descriptively by summary statistics for absolute scores and

Table 1. Study population demographics and clinical characteristics of erectile dysfunction

	Safety population (n = 2,072)	ITT population (n = 1,832)
Age, y		
Mean (SD)	53.6 (9.97)	54.0 (9.87)
Range	22–85	22–85
Weight, kg		
Mean (SD)	95.71 (16.98)	95.05 (16.63)
Range	53.5–220.0	53.5–220.0
BMI, kg/m^2		
Mean (SD)	32.03 (5.44)	31.82 (5.35)
Range	19.5–70.8	19.5–70.8
Race, n (%)		
Asian	714 (34.5)	674 (36.8)
White	1,040 (50.2)	915 (49.9)
Black	60 (2.9)	28 (1.5)
Other	144 (6.9)	120 (6.6)
No data	114 (5.5)	95 (5.2)
Nicotine consumption, n (%)		
Never	700 (33.8)	
Former smoker	420 (20.3)	
Current smoker	853 (41.2)	
No data	99 (4.8)	
Alcohol consumption, n (%)		
Abstinent	809 (39.0)	
Light	722 (34.8)	
Moderate	366 (17.7)	
Heavy	52 (2.5)	
No data	123 (5.9)	
Physical exercise, n (%)		
None	1,065 (51.4)	
1 h/wk	360 (17.4)	
2 h/wk	258 (12.5)	
3 h/wk	160 (7.7)	
≥4 h/wk	140 (6.8)	
No data	89 (4.3)	
ED duration, n (%)		
<6 mo	392 (18.9)	
6–12 mo	732 (35.3)	
1–3 y	566 (27.3)	
>3 y	374 (18.1)	
No data	8 (0.4)	
ED etiology, n (%)		
Organic	607 (29.3)	
Psychogenic	166 (8.0)	
Mixed	1,005 (48.5)	
No data	294 (14.2)	
Previous ED treatment, n (%)		
No treatment	1,238 (59.7)	
Sildenafil	406 (19.6)	
Tadalafil	199 (9.6)	
Vardenafil	16 (0.8)	
Other	133 (6.4)	
No data	80 (3.9)	
Concomitant diseases, n (%)*		
Arteriosclerosis	151 (7.3)	
Benign prostatic hyperplasia	413 (19.9)	
Coronary heart disease	70 (3.4)	
Depression	76 (3.7)	
Myocardial infarction	62 (3.0)	
Concomitant cardiovascular medications, n (%)	930 (44.9)	
Agents acting on renin-angiotensin system	392 (18.9)	
Antihypertensives	7 (0.3)	
β-Blockers	292 (14.1)	
Calcium channel blockers	139 (6.7)	
Cardiac therapy	27 (1.3)	
Diuretics	43 (2.1)	
Lipid-modifying agents	508 (24.5)	
Peripheral vasodilators	3 (0.1)	
Vaso-protective agents	10 (0.5)	

BMI = body mass index; ED = erectile dysfunction; ITT = intent-to-treat.
*By prespecified term; reported by at least 3% of the safety population.

changes from baseline; the Wilcoxon signed rank test (one-sided) was used to analyze improvement in total AMS score.

Data management and statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Study Population

Of 2,316 patients enrolled in the study, 2,072 patients were included in the safety population; of these, 1,832 had valid efficacy data and were included in the ITT population and 1,592 were included in the PP population (Figure 1). In the safety population, the mean age was 53.6 years (SD = 9.97), mean weight was 95.71 kg (SD = 16.98), and mean BMI was 32.03 kg/m^2 (SD = 5.44; Table 1). At the initial visit, 374 (20.4%) patients had severe ED, 701 (38.3%) had moderate ED, 494 (27.0%) had mild to moderate ED, 190 (10.4%) had mild ED, and 73 (4.0%) had no ED (ITT population). In total, 1,005 patients (48.5%) had a mixed organic and psychogenic ED etiology, 1,672 patients (80.7%) had ED for at least 6 months, 59.7% had not previously received any treatment for ED, and fewer than 1% had previously taken vardenafil (Table 1). The IDF criteria were used to diagnose MetS for 1,123 patients (54.2%) in the safety population; other definitions were the World Health Organization (715 patients, 34.5%), the European Group for the Study of Insulin Resistance (17 patients, 0.8%),

Table 2. Patient characteristics related to metabolic syndrome (safety population, n = 2,072)

Characteristic	n	Mean (SD)	Range
Waist circumference, cm			
Asian	702	98.02 (11.17)	78.7–180.0
Non-Asian	1,214	106.93 (11.89)	79.0–180.0
Unknown ethnicity	107	104.31 (10.70)	90.0–133.0
Total cholesterol, mg/dL	1,051	221.44 (50.67)	89.00–479.51
LDL cholesterol, mg/dL	958	136.45 (42.90)	10.82–299.00
HDL cholesterol, mg/dL	1,058	46.38 (28.98)	10.44–371.23
Triglycerides, mg/dL	1,125	216.33 (113.93)	44.27–1,416.64
HbA_{1c}, %	603	7.48 (1.59)	3.57–13.00
Testosterone, nmol/L	923	13.38 (8.56)	0.13–61.37

HbA_{1c} = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

the NCEP ATP III (22 patients, 1.1%), and a consensus of the IDF and NCEP ATP III (225 patients, 10.9%). In the safety population, 31.3% had triglyceride levels of at least 150 mg/dL or were receiving treatment for dyslipidemia, 26.7% had high-density lipoprotein cholesterol levels lower than 40 mg/dL or were receiving treatment for dyslipidemia, 47.2% had systolic BP of at least 130 mmHg or diastolic BP of at least 85 mmHg or were receiving antihypertensive treatment, and 33.8% had fasting blood glucose levels of at least 100 mg/dL or were diagnosed with or treated for type 2 diabetes (Table 2).

Most patients reported a concomitant disease; 519 patients (25.0%) reported one, 456 (22.0%) reported two, 255 (12.3%) reported three, and 539 (26.0%) reported none (Table 1, Supplementary Table 1). Concomitant medications were reported by 1,431 patients (69.1%), with drugs acting on the cardiovascular system (930 patients, 44.9%) and drugs used in diabetes (632 patients, 30.5%) being the most common (Table 1, Supplementary Table 1).

Efficacy

The primary objective of a clinically relevant improvement in IIEF-EF score of at least four points was achieved by 82.4% of the ITT population and 85.5% of the PP population. Another 7.8% of patients recorded a one- to three-point increase; 4.4% and 5.5% reported no change and a decrease in score, respectively (ITT). The median IIEF-EF score increased from 15.0 at the initial visit to 25.0 at the final visit ($P < .0001$; Figure 2A). There were no differences in domain scores between the ITT and PP populations.

The secondary outcome, improvement of IIEF-EF score by at least five points, was achieved by 78.9% of the ITT population. At the end of the study, 45.4% and 29.4% of the ITT population had normal EF (IIEF-EF score $\geq$ 26) and mild ED (IIEF-EF = 22–25), respectively (Figure 2B). The percentage of patients (44.4%) with an improvement in IIEF-EF score from lower than 26 to at least 26 was significantly larger ($P = .0102$) than the

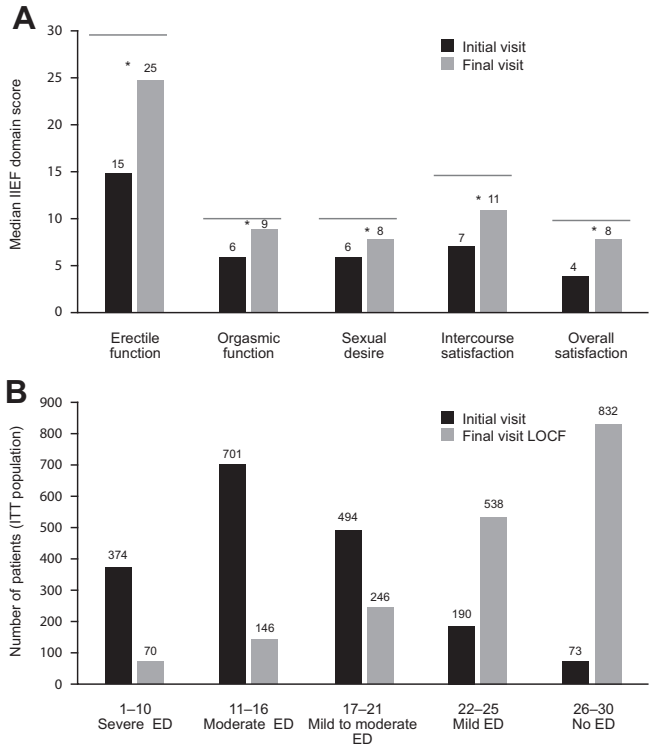

Figure 2. Analysis of IIEF domain scores. Panel A shows median IIEF domain scores for the ITT population at the initial and final visits. Panel B shows categorized IIEF-EF domain scores for the ITT population at the initial and final visits. *$P < .0001$. Lines indicate the maximum possible score achievable for each domain. ED = erectile dysfunction; IIEF = International Index of Erectile Function; IIEF-EF = International Index of Erectile Function—erectile function domain; ITT = intent-to-treat; LOCF = last observation carried forward.

percentage of patients (30.1%) reporting a decrease in IIEF-EF score of at least 26 to lower than 26.

Subgroup analyses demonstrated that fewer patients of Asian origin (66.3%) reported an IIEF-EF score improvement of at least five points compared with the complete ITT population (78.9%). This finding was particularly evident in patients from the Republic of Korea (57.6%) and Singapore (54.5%). Fewer Asian patients with a lower BMI (50.0% with BMI < 23 kg/m^2 and 58.7% with BMI = 23–25 kg/m^2) reported an IIEF-EF score improvement of at least five points compared with Asian patients with a higher BMI (76.5% with BMI > 30 kg/m^2).

Stratification of patients according to age showed that fewer patients older than 70 years had at least a five-point improvement in IIEF-EF score compared with the complete ITT population (65.1% vs 78.9%, respectively). Heavy alcohol consumption also had a negative effect on ED improvement, with 65.6% of patients in this group reporting at least a five-point improvement in IIEF-EF score.

For all IIEF domains, a mean improvement of at least two points was achieved (Figure 2A). After treatment, the percentage of patients rating their confidence of getting and maintaining an

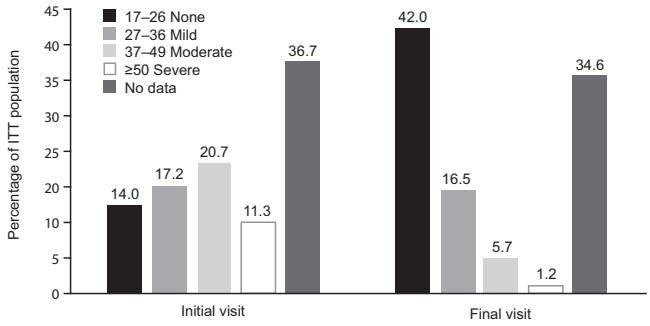

Figure 3. Percentage of ITT population (n = 1,832) achieving Aging Males' Symptoms total score in each category. The total score for all 17 questions was categorized according to the degree of symptom severity. ITT = intent-to-treat.

erection as high or very high increased from 5.3% to 44.9% and 1.1% to 17.4%, respectively. Furthermore, the percentage of patients reporting satisfactory sexual intercourse most times or almost always or always increased from 12.1% or 5.8% at the initial visit to 37.4% or 39.0%, respectively. Within the orgasmic function domain, at the initial visit, 35.3% of patients reported having the sensation of orgasm most times or almost always or always when they had sexual stimulation or intercourse; at the final visit, this increased to 78.7%. Contributing to the overall satisfaction domain, 30.9% of patients were very satisfied and 42.6% were moderately satisfied with their sex life at the final visit compared with 2.2% ($P = .0388$) and 13.5% ($P < .001$), respectively, at the initial visit.

The optional AMS questionnaire was completed by 1,159 patients at their initial visit and 1,198 patients at their final visit. The median total AMS score improved from 37.0 (moderate symptoms) to 24.0 (mild symptoms; Figure 3). After treatment, more than 40% of patients were classified as having no symptoms. Improvement was observed in all subscales, with decreases in the median from 13.0 to 8.0 on the sexual subscale, 10.0 to 6.0 on the psychological subscale, and 14.0 to 10.0 on the somatic subscale ($P < .0001$ for all comparisons).

Safety

In total, 185 TEAEs were reported, with 149 (7.19%) patients reporting at least one TEAE (Table 3). Drug-related AEs were reported by 107 patients (5.16%); the most common were headache (51 patients, 2.46%) and flushing and facial flushing (1−2%). Two patients had serious AEs; one died of leukemia and one had a non-fatal myocardial infarction, neither of which was related to vardenafil.

Vardenafil Treatment

Throughout the course of the study, most patients were prescribed vardenafil 20 mg (Table 4). The optional dose-adjustment visit was attended by 988 patients (47.7%); of these, 635 patients (64.3%) were prescribed vardenafil 20 mg. The number of tablets taken during the course of the study ranged from 1 to 133.

After the final study visit, more than 80% of patients planned to continue treatment. The main reasons for discontinuation were insufficient efficacy (115 of 392 patients), price (108 of 392 patients), and ED cured or improved (79 of 392 patients).

DISCUSSION

This large, observational study demonstrates that in a clinical setting, vardenafil improves EF in patients with ED and MetS. After a treatment period of approximately 12 weeks, based on IIEF results, more than 80% of patients reported an improvement in EF and 45% of patients had normal EF. Patients receiving vardenafil had an improvement in all domains of the IIEF questionnaire, highlighting the beneficial effects of vardenafil not only on EF but also on intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction. These results support the findings of previous clinical trials that have reported the efficacy of vardenafil in patients with ED and cardiovascular or metabolic conditions.[18-23]

A strength of this study is that a large number of patients was recruited from a wide demographic base for age (range = 22−85 years), race (34.5% Asian and 50.2% white), and BMI (range = 19.5−70.8 kg/m^2). This demographic base enabled efficacy to be compared between subgroups. Vardenafil was less effective in patients of Asian ethnicity, particularly those with a lower BMI (18.5−23 kg/m^2). There is conflicting evidence regarding the effectiveness of PDE5 inhibitors in Caucasians and Asians. In agreement with this study, a recent meta-analysis found that, in a pooled analysis of PDE5 inhibitors, treatment was more effective in Caucasians compared with Asians.[36] However, a smaller (N = 334 patients; 264 vardenafil, 70 placebo) study investigating vardenafil efficacy in Asian men reported a significant increase in IIEF-EF score, which was similar to that seen in previous studies in Caucasians.[37] Direct comparisons between studies are difficult to make owing to differences in protocols; thus, further investigation is warranted to explore these potential ethnic differences and their causes. The lower effectiveness of vardenafil in Asian patients with a lower BMI also requires further investigation; this finding might need to be considered when physicians prescribe treatment for this specific subgroup of patients.

The subgroup analyses also demonstrated that vardenafil was less effective in improving EF in men older than 70 years. This is an important issue because the prevalence and severity of ED increase with age[38] owing to multiple pathophysiologic changes in erectile mechanisms, such as a decrease in endogenous nitric oxide production.[39] It has been proposed that combining testosterone supplementation with a PDE5 inhibitor might improve its efficacy by increasing nitric oxide bioavailability and helping to maintain the health of erectile tissue and surrounding nerves.[39,40] Further studies to determine the benefit of using a combination treatment strategy in elderly men are warranted.

Table 3. Treatment-emergent adverse events (safety population, n = 2,072)

MedDRA SOC	Preferred term	Patients reporting event, n (%)
Any body system	Patients with AEs	149 (7.19)
	Patients without AEs	1,885 (90.97)
	Missing	38 (1.83)
Cardiac disorders	All	5 (0.24)
	Heart pounding	1 (0.05)
	Myocardial infarction	1 (0.05)
	Palpitation	2 (0.10)
	Tachycardia	1 (0.05)
Eye disorders	All	4 (0.19)
	Ocular hyperemia	2 (0.10)
	Red eye	1 (0.05)
	Visual disturbance	1 (0.05)
Gastrointestinal disorders	All	9 (0.43)
	Abdominal discomfort	1 (0.05)
	Dyspepsia	1 (0.05)
	Gastritis	1 (0.05)
	Nausea	6 (0.29)
General disorders and administration site conditions	All	1 (0.05)
	Lack of drug effect	1 (0.05)
Infections and infestations	All	1 (0.05)
	Rhinitis	1 (0.05)
Investigations	All	1 (0.05)
	Heart rate high	1 (0.05)
Musculoskeletal and connective tissue disorders	All	8 (0.39)
	Back pain	2 (0.10)
	Bone pain	2 (0.10)
	Low back pain	1 (0.05)
	Muscle pain	1 (0.05)
	Musculoskeletal pain	1 (0.05)
	Myalgia	1 (0.05)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	All	1 (0.05)
	Leukemia	1 (0.05)
Nervous system disorders	All	81 (3.91)
	Dizziness	3 (0.14)
	Drowsiness	1 (0.05)
	Fainting	1 (0.05)
	Headache	75 (3.62)
	Sleepiness	3 (0.14)
	Tremor	1 (0.05)
Psychiatric disorders	All	3 (0.14)
	Anxiety	2 (0.10)
	Insomnia	1 (0.05)
Respiratory, thoracic, and mediastinal disorders	All	12 (0.58)
	Gasping	1 (0.05)
	Nasal congestion	10 (0.48)
	Nasal obstruction	1 (0.05)
Skin and subcutaneous tissue disorders	All	7 (0.34)
	Itching	1 (0.05)
	Rash	2 (0.10)
	Redness of face	1 (0.05)
	Skin hyperemia	2 (0.10)
	Skin warm	1 (0.05)
Vascular disorders	All	36 (1.74)
	Facial flushing	3 (0.14)
	Flushing	25 (1.21)
	Flushing of face	2 (0.10)
	Hot facial flushes	1 (0.05)
	Hypertensive crisis	4 (0.19)
	Hypotension	1 (0.05)
No coding available		8 (0.39)

AEs = adverse events; MedDRA SOC = Medical Directory for Drug Regulatory Activities—System Organ Class.

In patients who completed the AMS scale, an improvement in HRQoL was reported. This improvement was not limited to the sexual subscale but also was seen for the psychological and somatic subscales, highlighting the importance of EF in overall HRQoL.

Vardenafil was well tolerated with no serious TEAEs reported. The low incidence and type of drug-related AEs were in line with the vardenafil product information[25] and previous studies.[11,12,16,18,24]

The main limitation of this study is that the follow-up period was only 12 weeks; a longer follow-up with more scheduled visits would have strengthened the data. Although completion of the AMS scale was optional, a total score for the initial and final visits were provided for 63% and 65% of the ITT population, respectively. AEs were recorded only at the follow-up visit and therefore might have been under-reported. However, the incidence of AEs reported here was similar to that observed in other studies,[11,12,16,18,24] suggesting that the reliability of the data has not been adversely affected. In addition, owing to the observational nature of this study and to the lack of a control group, we cannot rule out potential confounding; a further placebo-controlled study is warranted. Although this study was non-interventional, to date, it is the only study in which vardenafil

Table 4. Prescribed dose of vardenafil (safety population, n = 2,072)

Dose of vardenafil	Initial visit, n (%)	Dose adjustment visit, n (%)*	Final visit, n (%)
5 mg	94 (4.5)	71 (7.2)	109 (5.3)
10 mg	616 (29.7)	256 (25.9)	471 (22.7)
10 and 20 mg	4 (0.2)	0	0
20 mg	1,339 (64.6)	635 (64.3)	1,242 (59.9)
Missing data	19 (0.9)	26 (2.6)	250 (12.1)

*Attended by 988 patients.

initiation in men with ED and MetS was observed in routine clinical practice.

In summary, the REVITALISE study has demonstrated that, in clinical practice, vardenafil is effective and has an acceptable safety profile in men with ED and MetS.

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Supplementary Table 1. AMS Questionnaire

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none".

Symptoms:					extremely
	none	mild	moderate	Severe	severe
Score =	1	2	3	4	5
1. **Decline in your feeling of general well-being** (general state of health, subjective feeling)	☐	☐	☐	☐	☐
2. **Joint pain and muscular ache** (lower back pain, joint pain, pain in a limb, general back ache)	☐	☐	☐	☐	☐
3. **Excessive sweating** (unexpected/sudden episodes of sweating, hot flushes independent of strain)	☐	☐	☐	☐	☐
4. **Sleep problems** (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)	☐	☐	☐	☐	☐
5. **Increased need for sleep, often feeling tired**	☐	☐	☐	☐	☐
6. **Irritability** (feeling aggressive, easily upset about little things, moody)	☐	☐	☐	☐	☐
7. **Nervousness** (inner tension, restlessness, feeling fidgety)	☐	☐	☐	☐	☐
8. **Anxiety** (feeling panicky)	☐	☐	☐	☐	☐
9. **Physical exhaustion / lacking vitality** (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities)	☐	☐	☐	☐	☐
10. **Decrease in muscular strength** (feeling of weakness)	☐	☐	☐	☐	☐
11. **Depressive mood** (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use)	☐	☐	☐	☐	☐
12. **Feeling that you have passed your peak**	☐	☐	☐	☐	☐
13. **Feeling burnt out, having hit rock-bottom**	☐	☐	☐	☐	☐
14. **Decrease in beard growth**	☐	☐	☐	☐	☐
15. **Decrease in ability/frequency to perform sexually**	☐	☐	☐	☐	☐
16. **Decrease in the number of morning erections**	☐	☐	☐	☐	☐
17. **Decrease in sexual desire/libido** (lacking pleasure in sex, lacking desire for sexual intercourse)	☐	☐	☐	☐	☐
Have you got any other major symptoms?	**Yes**	☐	**No**	☐	
If Yes, please describe:————————————————————————————					
THANK YOU VERY MUCH FOR YOUR COOPERATION					