

# Heart Patients Don't Link Weight to CVD Risk

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WASHINGTON — Obese patients with coronary disease don't always see their excess weight as being part of the problem, Francisco Lopez-Jimenez, M.D., and his associates reported in a conference on cardiovascular disease epidemiology and prevention, sponsored by the American Heart Association.

A prospective survey of 229 patients

who had recently been hospitalized for a coronary syndrome or revascularization revealed that, despite being aware of their excess weight, few actually perceived that it was related to their heart problems.

"Don't assume your patients understand this. You must make them aware of the implications of obesity with regard to heart disease, because how people perceive themselves drives their behavior," Dr. Lopez-Jimenez told FAMILY PRACTICE NEWS.

The patients had a mean age of 66 years and a mean body mass index of 30.5 kg/m<sup>2</sup>. Most were either overweight (45%) or obese (33%); 77% were male. On average, the patients perceived themselves as being 22 pounds overweight, which was fairly accurate. "It was interesting . . . people were more or less realistic in estimating how overweight they were," Dr. Lopez-Jimenez, of the Mayo Clinic and Mayo Foundation, Rochester, Minn., said. The investigators looked for factors that

were correlated with self-perception of risk for heart disease. After adjustment for sex, comorbidities, socioeconomic status, and other potential confounders, only four factors—age, history of diabetes, and levels of readiness to change for weight loss and exercise—were significantly correlated with the patient's perceived risk for heart disease.

There was no such correlation with self-perception of obesity, despite 67% of patients endorsing the general concept that obesity is a risk factor for MI.

"It is complicated. . . . In general, we tend to recognize risky habits, but fail to recognize ourselves at risk," he said, adding that studies in patients who smoke, have AIDS, and engage in other risky behaviors have shown similar tendencies.

At the 6-month follow-up, the belief that obesity is a risk factor for heart disease was the strongest predictor of weight loss.

History of diabetes and self-perceived excess weight were also significantly cor-

References: 1. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA, for the Sildenafil Study Group. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med*. 1998;338:1397-1404. 2. Data on file. Pfizer Inc, New York, NY. 3. McMurray JG, Feldman RA, Auerbach SM, deFestral H, Wilson N. Long-term effectiveness and tolerability of Viagra® (sildenafil citrate) in men with erectile dysfunction. Poster presented at: International Society for Sexual and Impotence Research; September 22-26, 2002; Montreal, Canada.

## Brief summary of prescribing information

### VIAGRA<sup>®</sup> (sildenafil citrate) tablets

#### INDICATION AND USAGE

VIAGRA is indicated for the treatment of erectile dysfunction.

#### CONTRAINDICATIONS

Consistent with its known effects on the nitric oxide/cGMP pathway (see CLINICAL PHARMACOLOGY), VIAGRA was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

After patients have taken VIAGRA, it is unknown when nitrates, if necessary, can be safely administered. Based on the pharmacokinetic profile of a single 100 mg oral dose given to healthy normal volunteers, the plasma levels of sildenafil at 24 hours post dose are approximately 2 ng/mL (compared to peak plasma levels of approximately 440 ng/mL) (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism). In the following patients: age >65, hepatic impairment (e.g., cirrhosis), severe renal impairment (e.g., creatinine clearance <30 mL/min), and concomitant use of potent cytochrome P450 3A4 inhibitors (erythromycin), plasma levels of sildenafil at 24 hours post dose have been found to be 3 to 8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely administered at this time point.

VIAGRA is contraindicated in patients with a known hypersensitivity to any component of the tablet.

#### WARNINGS

There is a potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction, including VIAGRA, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

VIAGRA has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.4/5.5 mmHg), (see CLINICAL PHARMACOLOGY: Pharmacodynamics). While this normally would be expected to be of little consequence in most patients, prior to prescribing VIAGRA, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

Patients with the following underlying conditions can be particularly sensitive to the actions of vasodilators including VIAGRA — those with left ventricular outflow obstruction (e.g., aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure.

There is no controlled clinical data on the safety or efficacy of VIAGRA in the following groups; if prescribed, this should be done with caution.

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with resting hypotension (BP <90/50) or hypertension (BP >170/110);
- Patients with cardiac failure or coronary artery disease causing unstable angina;
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

The concomitant administration of the protease inhibitor ritonavir substantially increases serum concentrations of sildenafil (11-fold increase in AUC). If VIAGRA is prescribed to patients taking ritonavir, caution should be used. Data from subjects exposed to high systemic levels of sildenafil are limited. Visual disturbances occurred more commonly at higher levels of sildenafil exposure. Decreased blood pressure, syncope, and prolonged erection were reported in some healthy volunteers exposed to high doses of sildenafil (200-800 mg). To decrease the chance of adverse events in patients taking ritonavir, a decrease in sildenafil dosage is recommended (see Drug Interactions, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

#### PRECAUTIONS

##### General

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.

Before prescribing VIAGRA, it is important to note the following:

Patients on multiple antihypertensive medications were included in the pivotal clinical trials for VIAGRA. In a separate drug interaction study, when amlodipine, 5 mg or 10 mg, and VIAGRA, 100 mg were orally administered concomitantly to hypertensive patients mean additional blood pressure reduction of 8 mmHg systolic and 7 mmHg diastolic were noted (see Drug Interactions).

When the alpha blocker doxazosin (4 mg) and VIAGRA (25 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH), mean additional reductions of supine blood pressure of 7 mmHg systolic and 7 mmHg diastolic were observed. When higher doses of VIAGRA and doxazosin (4 mg) were administered simultaneously, there were infrequent reports of patients who experienced symptomatic postural hypotension within 1 to 4 hours of dosing. Simultaneous administration of VIAGRA to patients taking alpha-blocker therapy may lead to symptomatic hypotension in some patients. Therefore, VIAGRA doses above 25 mg should not be taken within 4 hours of taking an alpha-blocker.

The safety of VIAGRA is unknown in patients with bleeding disorders and patients with active peptic ulceration. VIAGRA should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia).

The safety and efficacy of combinations of VIAGRA with other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

In humans, VIAGRA has no effect on bleeding time when taken alone or with aspirin. *In vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and VIAGRA had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

##### Information for Patients

Physicians should discuss with patients the contraindication of VIAGRA with regular and/or intermittent use of organic nitrates. Physicians should discuss with patients the potential cardiac risk of sexual activity in patients with preexisting cardiovascular risk factors. Patients who experience symptoms (e.g., angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their physician.

Physicians should advise patients to stop use of all PDE5 inhibitors, including VIAGRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors (see POST-MARKETING EXPERIENCE/Special Senses).

Physicians should warn patients that prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

Physicians should advise patients that simultaneous administration of VIAGRA doses above 25 mg and an alpha-blocker may lead to symptomatic hypotension in some patients. Therefore, VIAGRA doses above 25 mg should not be taken within four hours of taking an alpha-blocker.

The use of VIAGRA offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), may be considered.

##### Drug Interactions

###### Effects of Other Drugs on VIAGRA

*In vitro* studies: Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance.

*In vivo* studies: Cimetidine (800 mg), a nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when coadministered with VIAGRA (50 mg) to healthy volunteers.

When a single 100 mg dose of VIAGRA was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg bid for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In addition, in a study performed in healthy male volunteers, coadministration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1200 mg tid) with VIAGRA (100 mg single dose) resulted in a 140% increase in sildenafil C<sub>max</sub> and a 210% increase in sildenafil AUC. VIAGRA had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole or itraconazole would be expected to have still greater effects, and population data from patients in clinical trials did indicate a reduction in sildenafil clearance when it was coadministered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, or cimetidine) (see DOSAGE AND ADMINISTRATION).

In another study in healthy male volunteers, coadministration with the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg bid) with VIAGRA (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C<sub>max</sub> and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. VIAGRA had no effect on ritonavir pharmacokinetics (see DOSAGE AND ADMINISTRATION).

Although the interaction between other protease inhibitors and sildenafil has not been studied, their concomitant use is expected to increase sildenafil levels.

It can be expected that concomitant administration of CYP3A4 inducers, such as rifampin, will decrease plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of VIAGRA. Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic

antidepressants), thiazide and related diuretics, ACE inhibitors, and calcium channel blockers. The AUC of the active metabolite, N-desmethyl sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by nonspecific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

#### Effects of VIAGRA on Other Drugs

*In vitro* studies: Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC<sub>50</sub> >150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

*In vivo* studies: When VIAGRA 100 mg oral was coadministered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic. No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

VIAGRA (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

VIAGRA (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

In a study of healthy male volunteers, sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**  
Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposure (AUCs) for unbound sildenafil and its major metabolite of 29- and 42-times, for male and female rats, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 100 mg. Sildenafil was not carcinogenic when administered to mice for 18-21 months at dosages up to the Maximum Tolerated Dose (MTD) of 10 mg/kg/day, approximately 0.6 times the MRHD on a mg/m<sup>2</sup> basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in rats given sildenafil up to 60 mg/kg/day for 36 days to females and 102 days to males, a dose producing an AUC value of more than 25 times the human male AUC.

There was no effect on sperm motility or morphology after single 100 mg oral doses of VIAGRA in healthy volunteers.

**Pregnancy, Nursing Mothers and Pediatric Use**  
VIAGRA is not indicated for use in newborns, children, or women.

**Pregnancy Category B.** No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the MRHD on a mg/m<sup>2</sup> basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the nonpregnant rat the AUC at this dose was about 20 times human AUC. There were adequate and well-controlled studies of sildenafil in pregnant women.

**Geriatric Use:** Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil (see CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations). Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered (see DOSAGE AND ADMINISTRATION).

#### ADVERSE REACTIONS

##### PRE-MARKETING EXPERIENCE:

VIAGRA was administered to over 3700 patients (aged 19-87 years) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

In placebo-controlled clinical studies, the discontinuation rate due to adverse events for VIAGRA (2.5%) was not significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.

In trials of all designs, adverse events reported by patients receiving VIAGRA were generally similar. In fixed-dose studies, the incidence of some adverse events increased with dose. The nature of the adverse events in flexible-dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-dose studies. When VIAGRA was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials, the following adverse events were reported:

**TABLE 1. ADVERSE EVENTS REPORTED BY ≥2% OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES**

Adverse Event	VIAGRA N=734	Percentage of Patients Reporting Event	PLACEBO N=725
Headache	16%		4%
Flushing	10%		1%
Dyspepsia	7%		2%
Nasal Congestion	4%		2%
Urinary Tract Infection	3%		2%
Abnormal Vision*	3%		0%
Diarrhea	3%		1%
Dizziness	2%		1%
Rash	2%		1%

\*Abnormal vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

Other adverse reactions occurred at a rate of >2%, but equally common on placebo: respiratory tract infection, back pain, flu syndrome, and arthralgia.

In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

The following events occurred in <2% of patients in controlled clinical trials; a causal relationship to VIAGRA is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:

**Body as a whole:** face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, postural hypotension, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.

**Digestive:** vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal hemorrhage, gingivitis.

**Hemic and Lymphatic:** anemia and leukopenia.

**Metabolic and Nutritional:** thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hypernatremia.

**Musculoskeletal:** arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis, abnormal dreams, reflexes decreased, hypesthesia.

**Nervous:** ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypesthesia.

**Respiratory:** asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

**Skin and Appendages:** urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

**Special Senses:** mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, deafness, ear pain, eye hemorrhage, cataract, dry eyes.

**Urogenital:** cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

**POST-MARKETING EXPERIENCE:**  
**Cardiovascular and cerebrovascular**

Serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, subarachnoid and intracerebral hemorrhages, and pulmonary hemorrhage have been reported post-marketing in temporal association with the use of VIAGRA. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of VIAGRA without sexual activity. Others were reported to have occurred hours to days after the use of VIAGRA and sexual activity. It is not possible to determine whether these events are related directly to VIAGRA, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors (see WARNINGS for further important cardiovascular information).

**Other events**  
Other events reported post-marketing to have been observed in temporal association with VIAGRA and not listed in the pre-marketing adverse reactions section above include:

**Nervous:** seizure and anxiety.

**Urogenital:** prolonged erection, priapism (see WARNINGS) and hematuria.

**Special Senses:** diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction, paracardular edema and epistaxis.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors (see PRECAUTIONS/Information for Patients).

#### OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

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Few patients with coronary disease view their obesity as part of the problem.

related with weight loss, but self-perceived risk for heart disease was not, the investigators reported.

Although these data suggest some denial on the part of patients, a previous study by Dr. Lopez-Jimenez and his associates indicated that underappreciation of obesity as a cardiovascular disease risk factor extends to clinicians as well. In a randomly selected sample of 627 patients discharged after an MI during 2001-2002 from five U.S. teaching hospitals, BMI had been documented in the charts of only 14% and waist circumference in none, despite the fact that 83% were overweight, including 55% who were obese and 8% who were morbidly obese (Int. J. Obes. Relat. Metab. Disord. 2005;29:137-41).

In only 20% of patients with a BMI at or above 30 was the diagnosis of obesity documented as a current medical problem, part of the past medical history, or as a final diagnosis. The proportion that received dietary counseling (61%) was identical for those with a BMI at or above 25 and for those with a BMI below 25.

Weight loss was described as part of treatment or among goals at discharge for just 7% of overweight and 9% of obese patients.