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CARDIOVASCULAR SAFETY OF SILDENAFIL CITRATE (VIAGRA®): AN UPDATED PERSPECTIVE

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ABSTRACT

Sildenafil citrate (Viagra®; Pfizer Inc, New York, NY) relaxes vascular smooth muscle, resulting in modest reductions in blood pressure that are insufficient to stimulate a reflex increase in heart rate. These blood pressure reductions are similar for healthy men and men with coronary artery disease (CAD) or who use antihypertensive drugs. Sildenafil does not affect the force of cardiac contraction, and cardiac performance is unaffected. Sildenafil is mildly vasodilating in the coronary circulation and does not increase the risk of ventricular arrhythmia. During exercise and recovery, sildenafil does not cause clinically significant alterations in hemodynamic parameters in men with CAD, and it has no negative effects on coronary oxygen consumption, ischemia, or exercise capacity. Clinical trial data from >13,000 patients, 7 years of international postmarketing data, and observational studies of >28,000 men in the United Kingdom and 3813 men in the European Union reveal that (1) there are no special cardiovascular concerns when sildenafil is used in accordance with product labeling and (2) the risk for serious events such as myocardial infarction or death is not increased. However, because safety has not been established in patients with recent serious cardiovascular events, hypotension or uncontrolled hypertension, or retinitis pigmentosa, physicians should consult their current local prescribing information before prescribing sildenafil for these patients. Among men with erectile dysfunction treated with sildenafil, the adverse event profile is similar overall to that in men with comorbid cardiovascular disease (CVD), it is similar between those with and without CAD, and it is similar between those who take and those who do not take antihypertensive drugs (regardless of the number or class). In a controlled interaction study of sildenafil and amlodipine, the mean additional reduction in supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic. Sildenafil should be used with caution in patients who take α-blockers because coadministration may lead to symptomatic hypotension in some individuals. When sildenafil is coadministered with an α-blocker, patients should be stable on α-blocker therapy before initiating sildenafil treatment and sildenafil should be initiated at the lowest dose. Also, in the absence of information specific to mixed α/β blockers, such as carvedilol and labetalol, similar care should be taken as for α-blockers. Sildenafil potentiates the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates in any form, either regularly or intermittently, is contraindicated. Before prescribing sildenafil, physicians should carefully consider whether their patients with underlying CVD could be affected adversely by resuming sexual activity. Management recommendations based on cardiovascular risk, from the Second Princeton Consensus Conference, are presented. UROLOGY **68** (Suppl 3A): 47–60, 2006. © 2006 Elsevier Inc.

Sildenafil citrate (Viagra®; Pfizer Inc, New York, NY), a phosphodiesterase-5 (PDE5) inhibitor, is an effective and generally well-tolerated treatment for erectile dysfunction (ED) in most patients. As of December 31, 2004, >27 million men worldwide had been prescribed sildenafil for the treatment of ED, including an estimated 16 million men in the United States.[1] As a clinical therapeutic agent, sildenafil has established a strong overall safety record.[2] Furthermore, extensive experience and numerous controlled clinical investigations have allowed the cardiovascular safety profile of sildenafil to be clearly defined. An expert consensus report on the use of sildenafil in patients with cardiovascular disease (CVD) has been published

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by the American College of Cardiology/American Heart Association (ACC/AHA),[3] and reports regarding the management of ED or sexual dysfunction in patients with CVD have been published by the Princeton Consensus Panel[4] and others.[5,6] The recommendations of the Princeton Consensus Panel were recently updated.[7]

This report examines the general cardiovascular effects of sildenafil in healthy men and in men with CVD, as well as the cardiovascular safety of sildenafil in 2 different populations of men: (1) otherwise healthy men with ED and (2) men with comorbid CVD and ED. To identify pertinent published data, the PubMed database was searched, using the terms *angina pectoris*, *arrhythmia*, *cardiovascular diseases*, *coronary arteriosclerosis*, *cerebrovascular accident*, *hypertension*, and *myocardial infarction*.

GENERAL CARDIOVASCULAR EFFECTS OF SILDENAFIL

The cardiovascular effects of sildenafil are mediated primarily by means of its relaxant effect on vascular smooth muscle, which causes vasodilation. Sildenafil was originally developed as an antianginal therapy but proved to be no more effective than nitrates.[8] PDE5, which is plentiful in vascular smooth muscle,[9] is inhibited by sildenafil, thereby increasing levels of cyclic guanosine monophosphate (cGMP).[10,11] Intracellular levels of cGMP affect numerous cellular functions, with protein kinase being a principal mediator of cGMP signals.[12] cGMP relaxes vascular smooth muscle by reducing intracellular Ca^{2+} and desensitizing the contractile apparatus to intracellular Ca^{2+}.[13,14]

The vascular endothelium releases substances that coordinate the ". . .vasomotion, smooth muscle proliferation, thrombosis, inflammation, coagulation, fibrinolysis, and oxidation. . ."[15] functions that are compromised when the endothelium is dysfunctional, resulting in atherosclerosis, plaque instability and rupture, and paradoxical vasoconstriction.[15] Because blood vessels throughout the body, including the penis, are vulnerable to endothelial dysfunction, it is not surprising that ED and CVD are associated epidemiologically.[16]

The vasodilatory effects of sildenafil on healthy and dysfunctional vascular endothelium vary. In a study of healthy men with normal endothelial function, sildenafil had no statistically significant effect on the maximal vasodilatory response of the hand and forearm vasculature to acetylcholine, which is an endothelium-dependent vasodilator, or on the flow-mediated vasodilatory response to brachial arterial occlusion and release.[17]

Because of the dissimilar effect of sildenafil on healthy versus dysfunctional endothelium, its cardiovascular effects are differentiated between healthy men and men with CVD in the single-dose studies reported below. However, because sildenafil is indicated for the treatment of patients with ED, data on the cardiovascular effects of sildenafil in men without ED, whether they are healthy or have concomitant CVD, should not be extrapolated to men with ED. The cardiovascular safety of sildenafil in the treatment of men with ED is discussed in the section, "Cardiovascular Safety of Sildenafil During Treatment of Erectile Dysfunction."

Systemic Hemodynamic Effects

The hemodynamic effects of sildenafil in healthy men were assessed in controlled, dose-response crossover studies. The vasodilatory action of sildenafil resulted in modest hemodynamic effects that were independent of dose in 8 healthy young men[18] and 16 middle-aged men.[19] After administration of sildenafil 100 mg, the mean maximum decrease in supine systolic/diastolic blood pressure, which occurred 1 to 3 hours after dosing, was approximately −10/−7 mm Hg; it returned to baseline levels within 6 to 8 hours in most men. No statistically significant difference in blood pressure reduction was noted between doses of 50 mg and 200 mg, which is twice the US Food and Drug Administration (FDA)–approved therapeutic maximum. Within this dose range, the mean difference between standing and supine blood pressure showed no evidence of an orthostatic effect.

Study reports show that sildenafil did not interact with common antihypertensive medications that lower blood pressure through cGMP-independent mechanisms.[19–21] In men with essential hypertension who were treated with antihypertensive medication, the magnitude of the hemodynamic changes that occurred after sildenafil administration was similar compared with that seen in healthy men. For example, in a randomized, double-blind, 2-way crossover study in 16 men aged 26 to 68 years (mean, 53.5 years) whose blood pressure was well controlled by the calcium channel blocker amlodipine besylate (Norvasc; Pfizer Inc) at 5 mg/day or 10 mg/day, mean maximal decrease from baseline in blood pressure after administration of sildenafil 100 mg was greater than that after administration of placebo; the differences between treatment periods were −8/−7 mm Hg supine ($P \leq 0.002$) and −10/−8 mm Hg standing ($P < 0.02$).[22] Greater blood pressure reduction tended to occur in patients with the highest baseline values. Similar results were reported in a case series of 22 men with hypertension (mean age, 58 years) who, along with 27 normotensive men (mean age, 42 years), underwent ambulatory blood pressure monitoring with readings taken every 15 or 30 minutes for 6 hours (3 hours awake and then 3

hours asleep) on 2 separate nights (untreated and after administration of sildenafil 100 mg, respectively).[23] Compared with results on the untreated night, mean blood pressure in the men with hypertension was lower over the 6-hour monitoring period after sildenafil administration (mean difference, −8.5/−5.7 mm Hg); the degree of blood pressure difference did not vary in terms of the number of antihypertensive drugs included in the regimen and was not statistically different from that in normotensive men (−3.7/−3.6 mm Hg). However, mean systolic blood pressure during the 3-hour awake period differed more between the untreated night and the sildenafil administration night in men with hypertension than in their normotensive counterparts (mean, −9.5 vs −2.6 mm Hg), which was statistically ($P = 0.04$) but not clinically significant. Only 2 men with hypertension (9.1%) and 1 normotensive man (3.7%) experienced a >30 mm Hg decrease in systolic blood pressure and a >20 mm Hg decrease in diastolic blood pressure between the 2 periods. These decreases were not accompanied by any hypotensive symptoms.

The hemodynamic effects of sildenafil were also modest in men with coronary artery disease (CAD). In a small pilot trial of 8 men with ischemic heart disease (IHD), intravenous sildenafil 40 mg was associated with small decreases from untreated control values in blood pressure at rest (−9/−8 mm Hg) and after a 4-minute exercise test (−12/−5 mm Hg).[18] This was true despite plasma sildenafil concentrations that were approximately 2 to 5 times higher than the mean maximum plasma concentrations following administration of a single oral dose of 100 mg in healthy male volunteers.[1] In a randomized, double-blind, crossover trial in 105 men with known or suspected CAD, mean blood pressure changed by −7/−2 mm Hg from baseline to 128/76 mm Hg after administration of sildenafil 50 mg or 100 mg; blood pressure after placebo administration (133/79 mm Hg) reflected a smaller decrease from baseline.[24] In 12 men (mean age, 53 ± 7 years) with stable IHD who underwent coronary angiography, sildenafil 50 mg had no statistically significant effect relative to baseline on blood pressure measured internally in the aorta (−2.7/−0.5 mm Hg) or on other hemodynamic variables.[25] In 14 men with severe CAD (stenosis of >70% of ≥1 coronary artery) who were scheduled to undergo percutaneous coronary revascularization, sildenafil 100 mg resulted in a small reduction from baseline in mean arterial blood pressure (−9.5/−4.4 mm Hg; $P = 0.01$).[26] In crossover studies, values of hemodynamic parameters during exercise or recovery did not differ significantly when men were given sildenafil compared with placebo[24] or in comparison with no treatment (untreated controls).[27]

Cardiac Effects

In most of the studies discussed above in healthy men, men with hypertension, and men with CAD, heart rate was not altered to a clinically significant extent by sildenafil administration. The minimal effect of sildenafil on heart rate indicated that blood pressure reductions were insufficient to stimulate a reflex increase in heart rate. Furthermore, sildenafil did not affect the force of cardiac contraction in isolated atrial tissue.[28] These results suggest a neutral effect on cardiac performance. In 8 healthy men, no significant changes in cardiac index were observed from 1 to 12 hours after administration of sildenafil 100 mg, 150 mg, or 200 mg compared with mean cardiac index at 1 hour after administration of placebo.[18] In 8 men with stable IHD, infusion of sildenafil 40 mg resulted in only a small decrease in cardiac output at rest (−0.4 L/min) and after a 4-minute exercise test (−1.3 L/min).[18] Sildenafil 50 mg or 100 mg administered orally was not associated with clinically significant changes in cardiac output or cardiac index in men with CAD,[25,27] CAD and ED,[29] or severe CAD who underwent revascularization.[26] In men with CAD, sildenafil had little effect on right atrial pressure or on pulmonary artery wedge pressure.[18,25,26,29,30]

Several studies have examined the effects of sildenafil in men who underwent exercise testing. Rate-pressure product during exercise testing of men with known or probable CAD,[24] symptomatic CAD,[27,30] or severe CAD who underwent revascularization[26] indicated no increase in myocardial oxygen consumption relative to control values. In a 2-way crossover trial of 105 men with known or suspected CAD, echocardiography indicated that administration of sildenafil (50 mg [n = 97] or 100 mg [n = 8]) and of placebo was associated with a similar incidence (24% vs 26% of men) and degree (19% vs 20% of segments, $P = 0.51$) of myocardial ischemia.[24] During each period, new wall motion abnormalities began at a mean heart rate of 96 beats per minute ($P = 0.76$). In a double-blind, placebo-controlled, parallel trial that evaluated 108 men with ED and chronic stable angina, sildenafil 100 mg was statistically noninferior to placebo for the time to onset of angina, time to limiting angina, total exercise time, and time to 1-mm ST-segment depression.[31] Sildenafil was not associated with any decrease in exercise capacity relative to placebo in men with known or suspected CAD,[24] relative to baseline in men with stable IHD,[18] or relative to placebo in men with chronic stable IHD who were taking β-blocker therapy with atenolol.[32] In the latter study, 14 men showed

improvement in time to 1-mm ST-segment depression and in exercise time after administration of atenolol 100 mg once daily; these improvements were not negated when subsequent exercise testing was preceded by sildenafil 50 mg or placebo, administered in random order in a 2-way crossover study.[32]

The human ether-a-go-go-related gene (HERG) channel is important for repolarization in human myocardium and is a common target for drugs that prolong the QT interval; the concentration of sildenafil required to evoke 50% inhibition of the HERG channel in vitro (33 mol/L) was 39 times higher than maximum therapeutic plasma concentrations.[33] In healthy male volunteers, no consistent or clinically significant dose-related changes were seen in electrocardiographic intervals, including the QT interval, at 1 hour or 24 hours after administration of oral sildenafil in doses ranging from 1.25 mg to 200 mg.[19] Sildenafil did not increase the risk for ventricular arrhythmia in men, including those with CAD.[24,27,34–36]

Comparison of the Cardiovascular Effects of Sildenafil and Nitrates

The hemodynamic effects of sildenafil mimic those of a weak nitrate. In a randomized, double-blind, 3-way crossover study, 12 healthy men and 24 men with IHD received sildenafil 100 mg, isosorbide dinitrate 10 mg, and placebo on 3 separate days.[30] In healthy men, the difference from placebo in blood pressure was similar between sildenafil and the nitrate at rest (−1/−5 mm Hg vs −6/−5 mm Hg). In men with IHD, the difference from placebo was less with sildenafil than with the nitrate at rest (−12/−9 mm Hg vs −21/−11 mm Hg) but was similar between sildenafil and the nitrate during exercise (−5/−5 mm Hg vs +1/−7 mm Hg). The difference in the incidence of angina was not statistically significant between the sildenafil (29%), nitrate (25%), and placebo (50%) periods. As reported in a double-blind, placebo-controlled, parallel study in 31 men (mean age, 60 years) with CAD and ED, the effects of sildenafil 100 mg on most hemodynamic parameters were in the same direction and more modest than those of isosorbide mononitrate 40 mg.[29] For example, for sildenafil 100 mg versus placebo, the mean maximum difference in the decrease in blood pressure from baseline occurred 2 hours after administration and was −13.5/−5.2 mm Hg, compared with a difference between the nitrate and sildenafil of −20/−3 mm Hg at the same time point.[29]

CARDIOVASCULAR SAFETY OF SILDENAFIL DURING TREATMENT OF PATIENTS WITH ERECTILE DYSFUNCTION

The cardiovascular safety of sildenafil in the treatment of patients with ED has been assessed in tens of thousands of individuals worldwide. Data were pooled from up to 37 phase 2, 3, and 4 clinical trials of men with ED who received sildenafil (N = 4405) or placebo (N = 3945). These data enabled calculation of the adverse event profile, including cardiovascular adverse events, in the sildenafil clinical trial population of men with ED[1,37] and in subpopulations with concomitant CVD[1] or CAD,[38] or those receiving antihypertensive therapy.[1,20,39] The most recent pooled data analysis, which included 120 phase 2, 3, and 4 clinical trials involving 7462 men with ED who received sildenafil and 5753 men with ED who were given placebo, determined the incidence of cardiovascular serious adverse events and deaths in the sildenafil clinical trial population of men with ED (Table I).[40,41] Two other recent studies, a postmarketing prescription event monitoring study in >28,000 men in the United Kingdom[42,43] and a prospective postmarketing observational cohort study in 3813 men in the European Union,[1,44] examined the incidence of serious cardiovascular adverse events and deaths in the general ED population. Other recent data include prospective clinical trials that reported the adverse event profile of sildenafil in populations of men with ED selected for the presence of concomitant CVD,[45] concomitant stable CAD,[46] or the use of antihypertensive therapy.[21,47] Because safety has not been established in patients with recent serious cardiovascular events, hypotension or uncontrolled hypertension, or retinitis pigmentosa, physicians should consult their current local prescribing information before prescribing sildenafil for these patients.

Men with ED

Sildenafil has a strong overall safety profile. Pooled data from 37 phase 2, 3, and 4 double-blind, placebo-controlled trials revealed low levels of treatment-related adverse events, most commonly headache (12%), facial flushing (11%), dyspepsia (3%), abnormal vision (2%), dizziness (3%), and rhinitis (2%).[1] A subset of these data, pooled from 18 placebo-controlled trials, showed a lower incidence of cardiovascular adverse events in 2722 men receiving sildenafil (3.0%) than in 1552 men given placebo (3.5%), with most events in the sildenafil group described as mild (79%) or moderate (16%) in severity, and an associated rate of treatment discontinuation that was identical to that for placebo (0.9%).[37] The use of sildenafil was not associated with increased risk for serious car-

TABLE I. ***Recent studies examining cardiovascular safety of sildenafil in men with erectile dysfunction (ED)***

Study	Population	Study Design (Level of Evidence)*	No. of Patients	Outcome	Results
Mittleman *et al.*[40,41]	General ED population	Pooled analysis of >120 studies (3)	DBPC trials: Sildenafil 7462 Placebo 5753 Open-label: 11,540 person-yr of follow-up	Serious CV events/ death	Rate of MI or CV death/100 person-yr: DBPC trials: Sildenafil = 0.91 (95% CI, 0.52–1.48) Placebo = 0.84 (95% CI, 0.39–1.60) Open-label trials: 0.56 (95% CI, 0.44–0.72) RR for sildenafil vs placebo in DBPC trials: MI or CV death overall: 1.08 (95% CI, 0.45–2.77; $P = 0.88$) MI within 24 hr of intercourse: 0.80 (95% CI, 0.52–1.26) MI within 6 hr of intercourse: 0.79 (95% CI, 0.33–1.87)
PEM study[42]	General ED population	Postmarketing observational (4)	Sildenafil >22,000 (mortality ratio based on interim analysis of 8893)	Serious CV events/ death	Standardized mortality ratio vs overall male population of England = 31.4 (95% CI, 18.29–50.29)
IMHS[1,44]	General ED population	Postmarketing prospective (4)	Sildenafil 3813	Serious CV events/ death	Rate of CV end points/100 person-yr: Death: 0.4/100 person-yr Fatal MI: 0.1/100 person-yr Nonfatal MI: 0.5/100 person-yr Stroke: 0.1/100 person-yr Trend toward a numerical increase in the incidence of CV events with increasing age, ED severity, and number of CV risk factors Mean interval since last sildenafil use to the onset of symptoms in men who used any ED treatment in the month before their event: CV event: 6 ± 7 days (range, 0–14 days) Non-CV event: 13 ± 24 days (range, 0–119 days)
Israilov *et al.*[45]	CV disease	Open-label (2)	Sildenafil 417	AEs (eg, CV) in selected population	Facial flushing (n = 25 [6%]) Headache (n = 20 [5%]) Dizziness (n = 7 [2%], including 5 men with HTN and 2 men with HTN plus CAD) Tachycardia (n = 9 [2%], including 3 men with controlled HTN and 6 with arrhythmia and HTN) Abnormal vision (n = 5 [1%]) Dyspepsia (n = 3 [1%]) Chest pain (n = 4 [1%], including 3 men with stable angina and 1 after coronary artery bypass)
Aranda *et al.*[47]	HTN therapy	Open-label (2)	Sildenafil 291	AEs (eg, CV) in selected population	No statistically significant association between prevalence of AEs and the number of antihypertensive agents included in the treatment regimen

TABLE I. *Continued*

Study	Population	Study Design (Level of Evidence)*	Number of Patients	Outcome	Results
Pickering *et al.*[21]	HTN therapy	DBPC (1)	Sildenafil 281 Placebo 287	AEs (eg, CV) in selected population	Treatment-related AEs were most often transient and mild to moderate in severity; none were serious, and they occurred at a higher incidence with sildenafil vs placebo: Headache (8% vs 1%) Facial flushing (6% vs <1%) Dyspepsia (3% vs <1%) Dizziness (3% vs <1%) Nasal congestion (1% vs 0%) Abnormal vision (2% vs 0%) 5 treatment-related AEs resulted in discontinuation: Sildenafil—mild headache, moderately blurred vision, chromatopsia Placebo—moderate chest pain, moderate arthralgia During DBPC and open-label extension, the incidence of AEs was similar between men taking 2 classes and those taking ≥3 classes of antihypertensives
DeBusk *et al.*[46]	CAD	DBPC (1)	Sildenafil 74 Placebo 76	AEs (eg, CV) in selected population	Treatment-related AEs occurred at a higher incidence with sildenafil vs placebo: Headache (8% vs 1%) Flushing (7% vs 0%) Nasal congestion (3% vs 0%) Abnormal vision (1% vs 1%) Moderate chest pain (pressure) in a sildenafil recipient Angina status deteriorated in 3 sildenafil recipients and 2 placebo recipients but was unchanged in most patients (94% and 97%, respectively)

AE = adverse event; CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; DBPC = double-blind, placebo-controlled; HTN = hypertension; IMHS = International Men's Health Study; MI = myocardial infarction; PEM = Prescription Event Monitoring; person-yr = person-years; RR = relative risk.

**Levels of evidence included the following: 1 = randomized, placebo-controlled study consisting of ≥2 arms, with random assignment to groups; 2 = nonrandomized, controlled study consisting of 1 arm of patients who received the same drug dose for the same duration; 3 = cohort study consisting of ≥2 arms, with group assignment based on previous exposure to treatment, and with prospective following of subjects for outcomes; and 4 = uncontrolled, descriptive study.*

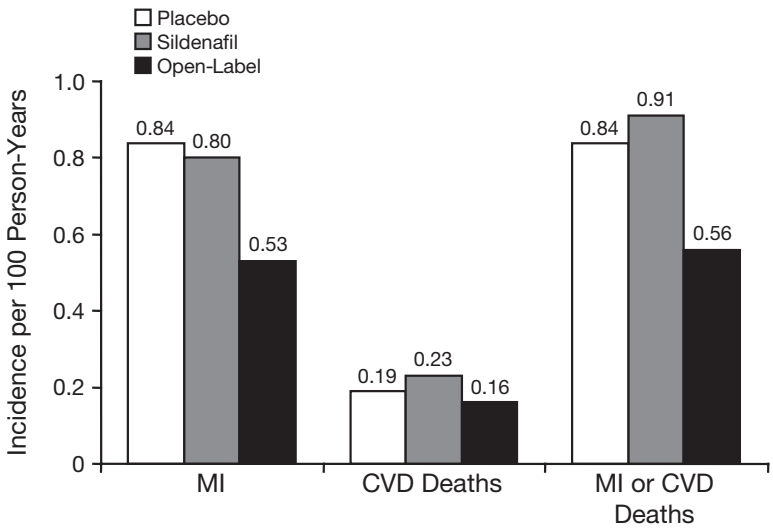

FIGURE 1. *Overall incidence of myocardial infarction (MI) and death in 120 clinical studies of sildenafil citrate for the treatment of patients with erectile dysfunction conducted between 1993 and 2002. MI includes fatal and nonfatal MI, cardiovascular disease (CVD) death includes fatal MIs and other CVD deaths. (Adapted from* Int J Clin Pract.[40]*)*

diovascular events, such as myocardial infarction (MI) or cardiovascular death, as documented by pooled clinical trial data and large postmarketing studies described below.

Pooled data collected prospectively from >120 clinical trials conducted worldwide from 1993 to 2001 showed no increase in the relative risk of MI or cardiovascular death with the use of sildenafil overall[40] or within the first 6 or 24 hours after intercourse (Table I).[41] Overall, the rate per 100 patient-years of MI or cardiovascular death in men treated with sildenafil was similar to that in men treated with placebo (0.91 [95% confidence interval (CI), 0.52 to 1.48] vs 0.84 [95% CI, 0.39 to 1.60] per 100 person-years of follow-up) and was slightly lower in open-label and extension studies (0.56; 95% CI, 0.44 to 0.72) (Figure 1).[40] The overall relative risk of MI or cardiovascular death for patients receiving sildenafil compared with patients given placebo in double-blind, placebo-controlled trials was 1.08 (95% CI, 0.45 to 2.77; $P = 0.88$). To determine whether use of sildenafil might trigger an MI in the hours immediately following sexual intercourse, a self-matched case-crossover approach was used.[41] The relative risk of MI was 0.80 (95% CI, 0.52 to 1.26) within 24 hours (6 half-lives) of taking sildenafil and was 0.79 (95% CI, 0.33 to 1.87) within 6 hours (1.5 half-lives) of taking sildenafil, indicating that sildenafil was not associated with a short-term risk for MI.[41]

The Prescription Event Monitoring (PEM) study was an independently conducted postmarketing study based on British National Health Service data in >28,000 men with ED treated with sildenafil.[42,43] Risk analysis of 8893 of these men, who were treated for an average of approximately 16 months, has shown no evidence of an increased risk of death from MI or IHD associated with sildenafil use (Table I).[42] The standardized mortality ratio (31.4; 95% CI, 18.3 to 50.3) indicated that the estimated risk of mortality caused by IHD was 69% lower compared with that for the overall male population of England.[42] The estimated 30% lower risk of mortality from IHD in the cohort treated with sildenafil compared with that for the overall male population during the first 6 months that sildenafil was available in the United Kingdom[43] indicates that initial administration of sildenafil does not trigger a serious cardiovascular event.

The International Men's Health Study (IMHS), a prospective postmarketing observational cohort study conducted in 4 European Union countries (France, Germany, Spain, and Sweden), quantified the rates of serious cardiovascular events in men with ED who received sildenafil treatment (Table I).[1,44] Men with ED documented by a score of ≤21 on the Sexual Health Inventory for Men (SHIM)[48] were recruited through primary care physicians or urologists, with follow-up after 1 month and quarterly for approximately 1.5 years. The analyzable population, defined as men who completed the baseline questionnaire and ≥1 follow-up questionnaire, and for whom evaluable data existed, included 3813 men aged 18 to 100 years (mean, 57 ± 11 years) with ED for 0 to 36 years (mean, 3 ± 4 years) that was minimal (13%), moderate (66%), or complete (20%) at enrollment. The most common cardiovascular risk factors were diabetes mellitus (14% of patients), family history of MI (19%), current smoker (25%), elevated cholesterol level (26%), hypertension (36%), and frequent alcohol use (45%). In all, 95% of these men had ≥1 cardio-

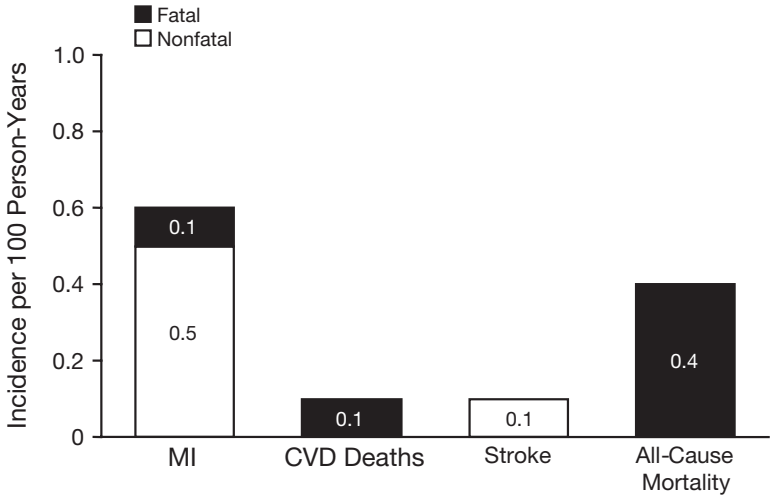

FIGURE 2. *Incidence of cardiovascular events and mortality in men with erectile dysfunction treated with sildenafil citrate in the International Men's Health Study (IMHS).*[1,44] *In comparison, all-cause mortality was 0.53 per 100 person-years and the overall incidence of myocardial infarctions (MIs) was 0.95 per 100 person-years among 5054 men treated with placebo in double-blind trials that were included in a pooled analysis of 124 double-blind and open-label clinical trials.*[2] *CVD = cardiovascular disease. (Adapted from* Pfizer Inc *data on file,*[1] Urology,[2] *and* Eur Urol.[44]*)*

vascular risk factor, and 40% had >2 risk factors. The incidence of cardiovascular end points was low overall, with 13 deaths reported during 2935 person-years of study participation, corresponding to an incidence of 0.4 deaths per 100 person-years (Figure 2). This compares with an all-cause mortality incidence of 0.53 per 100 person-years among 5054 double-blind placebo-treated men in a pooled data analysis of 124 double-blind and open-label clinical trials.[2] In all, 3 fatal MIs (0.1/100 person-years) and 15 nonfatal MIs were reported in 14 patients (0.5/100 person-years), compared with an overall MI incidence of 0.95 per 100 person-years among men who received placebo in a double-blind fashion in the pooled data analysis mentioned above.[2] A total of 4 strokes were reported in 4 patients (0.1/100 person-years). The incidence of cardiovascular events increased with the number of cardiovascular risk factors and with increasing age and severity of ED, but these increases were not statistically significant. For men who used any ED treatment in the month before their event, the mean interval between last sildenafil use and onset of symptoms was 6 ± 7 days (range, 0 to 14 days) in those who experienced a cardiovascular event compared with 13 ± 24 days (range, 0 to 119 days) in those who experienced a noncardiovascular event.

Men with ED and Comorbid Cardiovascular Disease

Sildenafil also has a strong overall safety profile in men with ED and comorbid CVD. Pooled data from 37 double-blind, placebo-controlled phase 2, 3, and 4 trials (N = 8350) showed similar adverse event profiles for the subset of men with comorbid CVD and the overall ED population enrolled in these sildenafil clinical trials (Table II).[1] Except for facial flushing (vasodilatation), each type of treatment-related cardiovascular adverse event (eg, palpitations, tachycardia) occurred in <1% of men, regardless of treatment assignment or comorbid condition. In addition to these pooled data analyzed retrospectively, men with ED and stable comorbid cardiovascular conditions were selected prospectively in a randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study[49] and in a recent large open-label study.[45]

In the double-blind study, 224 men with ED and stable CVD who were treated for >6 months with β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or calcium channel blockers, were randomized to sildenafil 50 mg (adjustable to 25 mg or 100 mg according to efficacy and tolerability) or to placebo, taken 1 hour before sexual activity but not more than once daily for 12 weeks.[49] Excluded were men receiving concomitant nitrate treatment and men who had had a significant cardiovascular event within 6 months (ie, stroke, MI, cardiac failure, unstable angina, or life-threatening arrhythmia). The most common CVD diagnosis in the sildenafil and placebo groups was hypertension (80% and 89%, respectively); 40% and 37% of men, respectively, had ≥1 diagnosis indicating IHD (ie, chronic IHD, status post MI, angina pectoris, and/or post coronary bypass). Most (66%) of the men were being treated with ≥2 drugs for their CVD. The most frequent adverse events in the sil-

TABLE II. ***Most frequently reported adverse events by cause and comorbid condition, according to data pooled from 37 double-blind, placebo-controlled phase 2, 3, and 4 trials****

	Diabetes		Hypertension		IHD		All Patients†	
	Placebo (n = 1139)	Sildenafil (n = 1173)	Placebo (n = 1504)	Sildenafil (n = 1532)	Placebo (n = 460)	Sildenafil (n = 511)	Placebo (n = 3945)	Sildenafil (n = 4405)
All causality								
Headache	4.4	11.7	3.6	12.5	3.0	13.1	4.8	13.5
Facial flushing	1.2	8.0	1.5	10.4	0.2	11.5	1.5	11.4
Dyspepsia	1.8	5.5	1.2	5.4	1.3	4.9	1.3	4.7
Dizziness	1.5	1.7	1.1	2.6	0.7	2.2	1.5	3.0
Rhinitis	1.2	2.8	0.7	3.7	1.5	3.5	1.1	3.4
Abnormal vision	0.9	2.5	0.9	2.6	1.1	2.7	0.7	2.7
Treatment related								
Headache	2.6	9.2	2.3	10.6	2.0	12.1	3.1	11.8
Facial flushing	1.2	7.8	1.5	10.2	0.2	11.4	1.5	11.2
Dyspepsia	0.6	3.7	0.5	3.3	0	2.9	0.5	3.2
Dizziness	0.9	1.3	0.7	2.0	0	1.2	1.0	2.5
Rhinitis	0.2	1.4	0.1	2.4	0.2	1.6	0.3	2.2
Abnormal vision	0.4	1.5	0.5	2.0	0.7	2.0	0.4	2.3
Discontinuations because of adverse events	1.4	1.8	1.5	1.4	2.0	2.0	1.2	1.4

IHD = ischemic heart disease.
**Values are given as percentages.*
†*Includes patients with diabetes mellitus, hypertension, and IHD, as well as others without these comorbid conditions.*
Adapted from data on file, Pfizer Inc.[1]

denafil group were flushing (17% vs 2% in the placebo group), headache (15% vs 1%), and dyspepsia (5% vs 0%). Flushing was the only cardiovascular adverse event reported, and sildenafil did not change blood pressure compared with placebo or with baseline values. Only 1 patient, in the placebo group, was withdrawn because of an adverse event.

A recent open-label study included 453 men with a 6-month to 18-year history (mean, 2.5 ± 1.2 years) of ED and a 4-month to 20-year history (mean, 4.5 ± 1.5 years) of CAD (25%), congestive heart failure (7%), hypertension alone (28%) or with concomitant CAD (26%), arrhythmia (10%), valve disease (3%), or postcerebrovascular accident (1%) (Table I). The men were being treated with 2 to 8 drugs, including β-blockers, ACE inhibitors, calcium channel blockers and other antihypertensive agents, thiazides and other diuretics, lipid-lowering agents, aspirin, warfarin sodium, and nitrates.[45] Underlying conditions (ie, long-term nitrate therapy [n = 14], recent bypass surgery [n = 5], recent MI [n = 4], unstable angina [n = 6], unstable hypertension [n = 5], or valve replacement [n = 2]) excluded 36 of the men from sildenafil treatment in the study, and so intracavernosal injection rather than sildenafil (25 to 100 mg) was initiated for their ED. Physicians should consult their current local prescribing information before prescribing sildenafil for patients with recent serious cardiovascular events, hypotension or uncontrolled hypertension, or retinitis pigmentosa, because safety has not been established in these patients. Of the 417 men treated with sildenafil, adverse effects included facial flushing (n = 25 [6%]); headache (n = 20 [5%]); dizziness (n = 7 [2%], including 5 men with hypertension and 2 men with hypertension plus CAD); tachycardia (n = 9 [2%], including 3 men with controlled hypertension and 6 with arrhythmia and hypertension; it is not clear whether this was symptomatic or asymptomatic); abnormal vision (n = 5 [1%]); dyspepsia (n = 3 [1%]); and chest pain (n = 4 [1%], including 3 men with stable angina and 1 post coronary artery bypass).

Several studies of sildenafil for the treatment of ED, described below, specifically targeted patients who were being treated with antihypertensive therapy or who had CAD.

Men with ED Who Were Taking Antihypertensive Medication

To determine the cardiovascular safety of sildenafil for the treatment of men with ED who were being treated with antihypertensive therapy, several retrospective subanalyses have been conducted on data pooled from controlled clinical trials of sildenafil for the treatment of ED.[2,20,39] The earliest—a pool of 5 randomized, double-blind, placebo-controlled, fixed-dose or flexible-dose trials (N = 1685)—found that the overall incidence

TABLE III. *Most frequently reported adverse events by cause and antihypertensive therapy status, according to data pooled from 37 double-blind, placebo-controlled phase 2, 3, and 4 trials (percentages)*

	Antihypertensive Regimen										All Patients	
	None		1 Class		2 Classes		≥3 Classes		Any Antihypertensive			
	Placebo (n = 2315)	Sildenafil (n = 2736)	Placebo (n = 709)	Sildenafil (n = 731)	Placebo (n = 569)	Sildenafil (n = 599)	Placebo (n = 352)	Sildenafil (n = 339)	Placebo (n = 1630)	Sildenafil (n = 1669)	Placebo (n = 3945)	Sildenafil (n = 4405)
All causality												
Headache	5.7	13.7	3.8	15.6	3.7	11.9	2.6	10.3	3.5	13.2	4.8	13.5
Facial flushing	1.8	12.0	1.6	12.4	1.2	9.8	0.6	5.9	1.2	10.2	1.5	11.4
Dyspepsia	1.4	4.1	1.1	5.6	1.1	6.5	1.7	3.5	1.2	5.5	1.3	4.7
Dizziness	1.5	3.0	2.1	3.4	0.9	2.8	0.9	2.1	1.4	2.9	1.5	3.0
Rhinitis	1.5	3.2	0.7	4.0	0.9	3.8	0.3	3.2	0.7	3.8	1.1	3.4
Abnormal vision	0.6	2.6	0.8	2.9	0.9	2.0	0.6	4.1	0.8	2.8	0.7	2.7
Treatment related												
Headache	3.8	12.2	2.8	13.1	1.8	10.4	1.7	8.3	2.2	11.1	3.1	11.8
Facial flushing	1.8	11.9	1.6	12.0	1.2	9.7	0.6	5.9	1.2	9.9	1.5	11.2
Dyspepsia	0.5	3.0	0.3	4.2	0.5	4.0	0.3	1.5	0.4	3.6	0.5	3.2
Dizziness	1.1	2.7	1.0	2.9	0.7	1.8	0.6	0.9	0.8	2.1	1.0	2.5
Rhinitis	0.3	2.2	0.3	2.5	0.2	2.2	0.0	2.1	0.2	2.3	0.3	2.2
Abnormal vision	0.5	2.3	0.3	2.6	0.5	1.5	0.3	2.7	0.4	2.2	0.4	2.3
Discontinuations due to adverse events	0.9	1.3	0.8	1.5	2.1	2.0	2.3	0.9	1.6	1.6	1.2	1.4

Adapted from Pfizer Inc data on file.[1]

of all-causality adverse events in men treated with sildenafil, including those related to changes in blood pressure (ie, dizziness, hypotension, syncope) were comparable for men taking and men not taking antihypertensive drugs.[20] A subsequent analysis included 13 additional double-blind, placebo-controlled, fixed-dose or flexible-dose trials, for a total of 18 trials (N = 3975). In this analysis of men treated with sildenafil, the incidence of treatment-related adverse events overall, the incidence of the most common adverse events (eg, headache, flushing, dyspepsia), and the incidence of adverse events potentially related to blood pressure decreases (eg, hypotension, dizziness, syncope) were similar for men taking and those not taking antihypertensive drugs, regardless of the antihypertensive class (ie, diuretic, β-blocker, α_1-blocker, ACE inhibitor, calcium channel blocker) or the number of agents taken (0 to $\geq$3). A total of 2.4% of patients who were and 2.4% of patients who were not taking antihypertensive drugs discontinued sildenafil prematurely.[39] The most recent analysis, which included a total of 37 double-blind, placebo-controlled phase 2, 3, and 4 trials (n = 4405 sildenafil, n = 3945 placebo), confirmed the earlier conclusion that the incidence of adverse events associated with sildenafil treatment in men taking antihypertensive drugs was similar to that in men who were not taking such medication, regardless of the number of agents used (Table III).[1]

In addition to retrospective subanalyses of pooled data, men who were taking antihypertensive medication were selected prospectively in 2 recently published trials. In an open-label trial of sildenafil 50 mg for the treatment of 291 men with ED who were taking antihypertensive drugs, no statistically significant association was observed between the prevalence of adverse events and the number of antihypertensive agents in the treatment regimen (Table I).[47] In a double-blind, parallel-group trial, 568 men (mean age, 59 years) with ED (mean duration, 4.5 years) and hypertension (mean, 12 years) who were taking $\geq$2 antihypertensive drugs were randomized to flexible-dose sildenafil (25 to 100 mg) or placebo for 6 weeks, followed by 6 weeks of open-label sildenafil (Table I).[21] The most common antihypertensive agents taken in the sildenafil and placebo group were diuretics (59% and 60%, respectively), calcium channel blockers (49% and 52%), ACE inhibitors (44% and 47%), β-blockers (41% and 37%), and α_1-blockers (19% and 17%). Treatment-related adverse events occurred at a higher rate among men who received sildenafil than among those given placebo, but most were transient and mild to moderate in severity, and none were serious. Only 5 resulted in discontinuation. These were mild headaches, moderately blurred vision, and chromatopsia in the sildenafil group and moderate chest pain and moderate arthralgia in the placebo group. The incidence of adverse events was similar for men taking 2 classes (n = 324) and men taking $\geq$3 classes (n = 235) of antihypertensive drugs during the double-blind phase and the subsequent open-label phase.

Sildenafil should be used with caution in patients who take α-blockers because coadministration may lead to symptomatic hypotension in some individuals.[50] When sildenafil is coadministered with an α-blocker, patients should be stable on α-blocker therapy before initiating sildenafil treatment and sildenafil should be initiated at the lowest dose. Also, in the absence of information specific to mixed α-/β-blockers, such as carvedilol and labetalol, similar care should be taken as for α-blockers.[7]

Men with ED and CAD

A retrospective subanalysis of data pooled from 11 double-blind, placebo-controlled trials of sildenafil treatment of patients with ED (N = 3672) demonstrated that the safety profile of sildenafil is similar in men with or without concomitant stable IHD. The incidence of the most commonly reported adverse events associated with sildenafil treatment was similar for the 237 men with IHD and the 2103 men without IHD for headache (25% vs 21%, respectively), flushing (14% vs 15%), and dyspepsia (12% vs 10%).[38] In men with concomitant IHD who received sildenafil for their ED, the incidence of cardiovascular events other than flushing was 5%, and the incidence of the most common serious cardiovascular events (eg, MI, unstable angina) was 5%, compared with 3% and <1%, respectively, in men without concomitant IHD who were given sildenafil, 8% and 5%, respectively, in men with concomitant IHD who received placebo, and 4% and <1%, respectively, in men without concomitant IHD who received placebo.

In a recent double-blind trial, 150 men aged 39 to 82 years (mean, 62 years) with stable CAD and a mean ED duration of 5 years (range, 0.05 to 33 years) were randomized to sildenafil 50 mg (adjustable to 25 mg or 100 mg) or placebo for 12 weeks and received $\geq$1 dose of study medication (Table I).[46] Other concomitant cardiovascular conditions or risk factors were similar between treatment groups and were common, including hypertension (78%), hyperlipidemia (68%), angina (17%), previous coronary artery bypass graft (52%), MI (58%), and percutaneous transluminal coronary angioplasty (50%). Concomitant medication use was also similar between the

TABLE IV. ***Risk from sexual activity in cardiovascular diseases: Second Princeton Consensus Conference***

Low Risk (Typically Implied by Ability to Perform Exercise of Modest Intensity Without Symptoms)	Intermediate or Indeterminate Risk (Evaluate to Reclassify as High or Low Risk)	High Risk (Defer Resumption of Sexual Activity Until Cardiologic Assessment and Treatment)
• Asymptomatic and <3 major risk factors (excluding sex) —Major CVD risk factors include age, male sex, hypertension, diabetes mellitus, cigarette smoking, dyslipidemia, sedentary lifestyle, and family history of premature CAD • Controlled hypertension —β-blockers and thiazide diuretics may predispose to ED • Mild, stable angina pectoris —Noninvasive evaluation recommended —Antianginal drug regimen may require modification • Post revascularization and without significant residual ischemia —ETT may be beneficial in risk assessment • Post MI (>6–8 wk), but asymptomatic and without ETT-induced ischemia, or post revascularization —If post revascularization or no ETT-induced ischemia, intercourse may be resumed 3–4 weeks post MI • Mild valvular disease —May include select patients with mild aortic stenosis • LVD (NYHA class I) —Most patients are at low risk	• Asymptomatic and ≥3 CAD risk factors (excluding sex) —Increased risk for acute MI and death —ETT may be appropriate, particularly in sedentary patients • Moderate, stable angina pectoris —ETT may clarify risk • MI >2 weeks but <6 weeks —Increased risk of ischemia, reinfarction, and malignant arrhythmias —ETT may clarify risk • LVD/CHF (NYHA class II) —Moderate risk of increased symptoms —Cardiovascular evaluation and rehabilitation may permit reclassification as low risk • Noncardiac atherosclerotic sequelae (peripheral arterial disease, history of stroke, or TIAs) —Increased risk of MI —Cardiologic evaluation should be considered	• Unstable or refractory angina —Increased risk of MI • Uncontrolled hypertension —Increased risk of acute cardiac and vascular events (eg, stroke) • CHF (NYHA class III–IV) —Increased risk of cardiac decompensation • Recent MI (<2 wk) —Increased risk of reinfarction, cardiac rupture, or arrhythmias, but impact of complete revascularization on risk is unknown • High-risk arrhythmias —Rarely, malignant arrhythmias during sexual activity may cause sudden death —Risk is decreased by an implanted defibrillator or pacemaker • Obstructive hypertrophic cardiomyopathies —Cardiovascular risks of sexual activity are poorly defined —Cardiologic evaluation (ie, exercise stress testing and echocardiography) may guide patient management • Moderate-to-severe valve disease —Use vasoactive drugs with caution

CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebrovascular accident; CVD = cardiovascular disease; ED = erectile dysfunction; ETT = exercise tolerance test; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association; TIA = transient ischemic attack.
Adapted from Am J Cardiol.[7]

treatment groups, with most men using anti-inflammatory analgesics, antihyperlipidemics, antihypertensives, and/or β-blockers. Adverse events were experienced by 47% of men receiving sildenafil and 32% of those given placebo, but treatment-related events were limited to headache (8% and 1%, respectively), flushing (7% and 0%), nasal congestion (3% and 0%), abnormal vision (1% and 1%), and a single reported case of moderate chest pain (pressure) in a sildenafil recipient. The angina status deteriorated in 3 sildenafil recipients and 2 placebo recipients but was unchanged in most patients (94% and 97%, respectively).

Sildenafil potentiates the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates in any form, regularly or intermittently, is therefore contraindicated.

CONCLUSIONS

Men with ED tend to be at increased risk for cardiovascular events because of shared risk factors with CVD. In the 2 hours after sexual activity, the relative risk of MI is increased 2.5-fold in men without a history of cardiac disease and 2.9-fold in those with a history of cardiac disease, although the absolute risk is low (0.9%).[51] However, no evidence suggests that the use of sildenafil is associated with an increased risk for cardiovascular events. The sildenafil adverse event

profile, including cardiovascular adverse events, is similar between the sildenafil clinical trial population of men with ED and subpopulations with concomitant CVD or CAD, or those receiving antihypertensive therapy. Sildenafil may be well tolerated when combined with most antihypertensive agents, including multidrug regimens. Regardless, before prescribing sildenafil, physicians should carefully consider whether their patients with underlying CVD could be affected adversely by the vasodilatory effects of sildenafil, especially in combination with sexual activity. Because safety has not been established in patients with recent serious cardiovascular events, hypotension or uncontrolled hypertension, or retinitis pigmentosa, physicians should consult their local prescribing information before prescribing sildenafil for these patients. For sildenafil, as for all vasodilators, caution is advised in patients with left ventricular outflow obstruction (eg, aortic stenosis, hypertrophic obstructive cardiomyopathy) and in those with severely impaired autonomic control of blood pressure.[7] Sildenafil should be used with caution in patients who take α-blockers because coadministration may lead to symptomatic hypotension in some patients. When sildenafil is coadministered with an α-blocker, patients should be stable on α-blocker therapy before initiating sildenafil treatment and sildenafil should be initiated at the lowest dose. Also, in the absence of information specific to mixed α-/β-blockers, such as carvedilol and labetalol, similar care should be taken as for α-blockers. Consistent with its known effects on the nitric oxide–cGMP pathway, sildenafil potentiates the hypotensive effects of organic nitrates, and its administration to patients who are using organic nitrates in any form, either regularly or intermittently, is therefore contraindicated.[50,52] The Second Princeton Consensus Conference provides management recommendations based on the degree of cardiovascular risk associated with sexual activity for men with various cardiovascular diseases (Table IV).[7] Low risk typically implies the ability to perform exercise of modest intensity without symptoms, intermediate or indeterminate risk indicates the need for further evaluation to reclassify risk as low or high, and high risk indicates deferral of the resumption of sexual activity until cardiologic assessment and treatment has been provided.

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