ACC/AHA Expert Consensus Document

Use of Sildenafil (Viagra) in Patients With Cardiovascular Disease

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Executive Summary

The pharmaceutical preparation sildenafil citrate (Viagra) is being widely prescribed as a treatment for male erectile dysfunction, a common problem that in the United States affects between 10 and 30 million men. The introduction of sildenafil has been a valuable contribution to the treatment of erectile dysfunction, which is a relatively common occurrence in patients with cardiovascular disease. This article is written to appropriately caution and not to unduly alarm physicians in their use of sildenafil in patients with heart disease.

Reported cardiovascular side effects in the normal healthy population are typically minor and associated with vasodilatation (ie, headache, flushing, and small decreases in systolic and diastolic blood pressures). However, although their incidence is small, serious cardiovascular events, including significant hypotension, can occur in certain populations at risk. Most at risk are individuals who are concurrently taking organic nitrates. Organic nitrate preparations are commonly prescribed to manage the symptoms of angina pectoris. The coadministration of nitrates and Viagra significantly increases the risk of potentially life-threatening hypotension. Therefore, Viagra should not be prescribed to patients receiving any form of nitrate therapy.

Although definitive evidence is currently lacking, it is possible that a precipitous reduction in blood pressure with nitrate use may occur over the initial 24 hours after a dose of Viagra. Thus, for patients who experience an acute cardiac ischemic event and who have taken Viagra within the past 24 h, administration of nitrates should be avoided. In the event that nitrates are given, especially within this critical time interval, it is essential to have the capability to support the patient with fluid resuscitation and α-adrenergic agonists if needed. In patients with recurring angina after Viagra use, other nonnitrate antianginal agents, such as β-blockers, should be considered.

Other patients in whom the use of Viagra is potentially hazardous include those with active coronary ischemia; those with congestive heart failure and borderline low blood volume and low blood pressure status; those with complicated, multidrug, antihypertensive therapy regimens; and those taking medications that may affect the metabolic clearance of Viagra. With respect to patients following complicated multidrug, antihypertensive programs, the randomized studies included a large number of hypertensive patients. However, most patients were controlled with 1 antihypertensive agent, and only a small number were controlled with 3 antihypertensive agents. Until adequate studies are done in these subgroups of patients, sildenafil should be prescribed with caution.

Viagra acts as a selective inhibitor of cyclic GMP (cGMP)–specific phosphodiesterase type 5, resulting in smooth muscle relaxation, vasodilatation, and enhanced penile erection. Although the cardiovascular effects of sildenafil

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*Those authors designated with an asterisk have indicated a potential conflict of interest with respect to the topic of this document. They have excused themselves from discussions or the preparation of the text whence this potential conflict would apply.

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reported in available randomized, controlled clinical trials were relatively minor, heart disease patients represented only a small fraction of studied patients and patients with heart failure, patients with myocardial infarction or stroke within 6 months or patients with uncontrolled hypertension were not included in these studies. Thus, there are possible problems in the use of Viagra in these patients that have not been adequately studied.

Given the increasing reports of deaths in which the use of Viagra may be implicated, clinicians need to exercise caution when advising their patients with heart disease about taking this medication. Specific recommendations regarding sildenafil (Viagra) and the cardiac patient are summarized in the following Table.

Summary Table of Clinical Recommendations

A. Use of Viagra clearly contraindicated
   1. Concurrent use of nitrates (see Appendix A)
B. Cardiovascular effects of Viagra may be potentially hazardous (use dependent on individual clinical assessment)
   1. Patients with active coronary ischemia who are not taking nitrates (eg, positive exercise test for ischemia)
   2. Patients with congestive heart failure and borderline low blood pressure and borderline low volume status
   3. Patients on a complicated, multidrug, antihypertensive program
   4. Patients taking drugs that can prolong the half-life of Viagra (see Appendix B)

I. Preamble

The present document is an expert consensus. This type of document is intended to inform practitioners, payers and other interested parties of the opinion of the American College of Cardiology (ACC) concerning evolving areas of clinical practice and/or technologies that are widely available or are new to the practice community. Topics chosen for coverage by Expert Consensus Documents are so designated because the evidence base and experience with the technology or clinical practice are not sufficiently well developed to be evaluated by the formal ACC/American Heart Association (AHA) Practice Guidelines process. Thus, the reader should view the Expert Consensus Documents as the best attempt of the ACC to inform and guide clinical practice in areas in which rigorous evidence is not yet available. Where feasible, Expert Consensus Documents will include indications and contraindications. Some topics covered by Expert Consensus Documents will be addressed subsequently by the ACC/AHA Practice Guideline process.

A. Sildenafil (Viagra) Use for Erectile Dysfunction

Male erectile dysfunction defined as "the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance (1)" is a common problem in the United States affecting between 10 and 30 million men (2,3). Sexual dysfunction in men after the diagnosis of coronary artery disease or a myocardial infarction is common. Most is due to fear that the exertion of sexual activity will precipitate another myocardial infarction; [illegible] men take nitrates on a regular basis for angina pectoris (5), and another half a million will experience a heart attack annually and are potential candidates for nitrate therapy (6). Sildenafil is potentially contraindicated in as many as 6 million patients.

The introduction of sildenafil citrate (Viagra), a drug that acts as a selective inhibitor of cGMP–specific phosphodiesterase type 5 (PDE5), which results in smooth muscle relaxation, vasodilatation, and enhanced penile erection, has been a major advancement in the treatment of erectile dysfunction (7). The vasodilating action of sildenafil affects both the arteries and the veins, so the most frequent side effects of sildenafil are headache and facial flushing (8). Sildenafil causes small decreases in systolic and diastolic blood pressures, but clinically significant hypotension is rare. Studies of sildenafil and nitrates taken together show much greater drops in blood pressure. For that reason, it is contraindicated to use sildenafil in patients who take long-acting nitrates or who use short-acting, nitrate-containing medications.

In the phase II/III studies completed before Food and Drug Administration (FDA) approval, >3700 patients received sildenafil and almost 2000 received placebo in double-blind and open-label studies. None were taking long-acting nitrates, although patients with coronary artery disease were not excluded. Approximately 25% of the patients had hypertension and were taking antihypertensive medications, and 17% were diabetic. In these studies, the incidence of serious cardiovascular adverse effects was similar in the double-blind sildenafil group, the double-blind placebo group, and the open-label group. There were 28 patients who had a myocardial infarction. When adjusted for patient-years of exposure, there were no differences in myocardial infarction rate between the sildenafil group and the placebo group, and no deaths were attributed to treatment. The incidence of myocardial infarction was 1.7/100 patient-years (95% CI, 0.8 to 2.6) in the sildenafil group and 1.4/100 patient-years (95% CI, 0.2 to 2.6) in the placebo group (9). In the subsequent analysis done in May 1998, sildenafil exposure had increased to 4913 patient-years (693 double-blind sildenafil; 4220 open-label extensions), and 26 deaths had been reported, for an incidence rate of 0.53/100 patient-years. The incidence for placebo remained the same (ie, 2 deaths or 0.57/100 patient-years) (5).

There have now been >3.6 million prescriptions (10) written for sildenafil, and 4500 patients taking sildenafil have been followed up without any change in the above conclusions. A total of 69 deaths have been reported to the FDA as of August 26, 1998, in patients who have used Viagra (10,11). Twenty-one were due to unknown causes, 2 due to stroke, and 46 related to probable cardiac events (10,11). Twelve deaths involved a possible interaction between Viagra and nitrates (10,11).

Patients with erectile dysfunction are mostly over age 45 and are in general more likely to have risk factors predisposing them to cardiovascular disease, including myocardial infarction and stroke. The vast majority of patients in the clinical development program did not have known coronary [illegible]

medical regimens included in the program. Furthermore, 62% of the patients taking Viagra were within the 45- to 64-year-old age category, and only 23% were aged ≥65 years (Pfizer Inc, unpublished data). Although sildenafil is not presently indicated in women, the cautions referred to in this document should probably apply to both men and women, pending studies performed specifically in women.

B. Development of an ACC Expert Consensus Document

In July 1998, responding to inquiries from both concerned physicians and the press, ACC president Spencer King asked the ACC Technology and Practice Executive Committee (TPEC) to supervise the writing of a press release, summary statement and Expert Consensus Document on sildenafil (Viagra). This article was written to appropriately caution and not to unduly alarm physicians in their use of sildenafil in patients with heart disease.

Dr. King and TPEC chair Dr James Forrester selected a group of physicians with specific expertise to prepare the document. Drs. Melvin Cheitlin and Adolph Hutter, Jr, were chosen as cochairs of the Writing Group, on the basis of their status as well-recognized senior clinical cardiologists and their experience in producing clinical practice guidelines. Other members were selected for specific expertise: Dr Brindis (managed care), Dr Ganz (vascular reactivity), Dr Kaul (nitric oxide donors), and Dr Zusman (pharmacology of antihypertensive agents). Dr King also invited the AHA to jointly author the document. Dr Richard Russell (critical care cardiology) was appointed to the Writing Group by AHA president Dr Valentin Fuster. All members of the Writing Group were asked to carefully review any potential conflicts of interest they might have regarding their industry relationships. Those writers who indicated conflicts are identified in the byline.

The Writing Group reviewed both the limited published data on Viagra and unpublished data provided by the manufacturer of Viagra, Pfizer Inc. With respect to the unpublished data, all members of the Writing Group who had access to these documents signed statements that they would not distribute this information outside of the Writing Group until such time as it became public information. Members of the Writing Group were instructed to channel all communications with Pfizer through ACC professional staff to eliminate the appearance of bias.

After completion of the document, 10 external referees reviewed the text. A copy of the draft was also provided to Pfizer and to the FDA for comment. The comments from external review, which were kept anonymous, were provided to the Writing Group, which made revisions as they deemed appropriate. The Expert Consensus Document was approved by vote of the TPEC for presentation to the ACC Board of Trustees, which voted to approve its publication in the *Journal of the American College of Cardiology*. The AHA Scientific Advisory Committee also reviewed and approved

II. Background

A. Physiology of Erection

Penile erection is accomplished by engorgement of cavernous spaces within the corpora cavernosa under near-arterial pressures and involves dilation of arterial inflow, relaxation of corpora cavernosa smooth muscle, and constriction of venous outflow (12). The blood flow to the penis is supplied by the cavernosal arteries and their branches, the helicine arteries, which empty directly into the cavernous spaces (12). Erection is initiated by dilation of helicine arteries, resulting in marked augmentation of blood inflow and transmission of arterial pressures to the cavernosal spaces. Relaxation of smooth muscle trabeculae surrounding cavernosal spaces facilitates blood pooling and engorgement. Restriction of venous outflow is also essential to entrapment of blood in the corpora cavernosa and is caused by compression of venules by the expanding smooth muscle trabeculae against the thick tunica albuginea (12).

B. Role of Nitric Oxide and cGMP

The relaxation of the penile arterial smooth muscle, the corporal smooth muscle, and therefore erection is under the control of the autonomic nervous system (13). The principal neural mediator of penile smooth muscle relaxation is nitric oxide (NO) (13,14). NO and its derivatives have received much attention because they also account for the biological activity of the endothelium-derived relaxation factor and of organic and inorganic nitrate vasodilators. Three isoforms of NO synthase (NOS) that convert L-arginine to NO have been identified: neuronal (nNOS; type I NOS), inducible (iNOS; type II NOS), and endothelial (eNOS; type III NOS). Terminals containing nNOS densely innervate the corpus cavernosum and its arterial supply (13,14). NO derived from the endothelium lining penile arteries and cavernosal sinuses also participates in the erectile response. The arterial dilator actions of NO and its relaxant effect on the smooth muscle of the corpus cavernosum are mediated by the activation of soluble guanylate cyclase and production of cGMP, which acts as a second messenger (13,14). Accumulation of cGMP leads to a reduction in intracellular calcium and smooth muscle relaxation. The degradation of cGMP into its inactive form, GMP, is catalyzed by cyclic nucleotide phosphodiesterase enzymes (15,16). The predominant isoform of this enzyme in the corpus cavernosum is PDE5 (12,15). Inhibitors of the activity of this enzyme prevent the breakdown of cGMP, resulting in enhanced penile erection.

III. Sildenafil

A. Introduction and Mechanism of Action

Sildenafil belongs to a class of compounds called PDE inhibitors. PDEs comprise a diverse family of enzymes that hydrolyze cyclic nucleotides (cAMP and cGMP) and therefore play a critical role in the modulation of second-messenger signaling pathways (15).

Sildenafil is a potent and selective inhibitor of cGMP-specific PDE5 (Pfizer, unpublished data), the predominant

principal mediator of smooth muscle relaxation and vasodilatation in the penis. By inhibiting the hydrolytic breakdown of cGMP, sildenafil prolongs the action of cGMP. This results in augmented smooth muscle relaxation and hence, prolongation of the erection. Prior production of cGMP by NO, released primarily from the nonadrenergic, noncholinergic (nitroxidergic) cavernosal nerves in response to sexual stimulation, is required for sildenafil to be effective (13,14).

Relatively high levels of PDE5 are found in the human corpus cavernosum; in vascular, visceral and tracheal smooth muscle; and in platelets (15). Sildenafil is a potent inhibitor of PDE5, with favorable selectivity (>1000-fold) for human PDE5 over human PDE2 (isozyme found predominantly in the adrenal cortex) (15), PDE3 (found predominantly in smooth muscles, platelets, and cardiac tissue) (15), and PDE4 (found predominantly in the brain and lung lymphocytes) (15) and moderate selectivity (>80-fold) over PDE1 (a cGMP-hydrolyzing isozyme found predominantly in the brain, kidney, and smooth muscle) (15). Sildenafil is only ≈10-fold as potent for PDE5 as for PDE6 (an enzyme found in the photoreceptors of the human retina); this lower selectivity is presumed to be the basis for abnormalities related to color vision observed with higher doses or plasma levels of sildenafil (Pfizer, unpublished data). The ≈4000-fold greater selectivity for PDE5 over PDE3 is important because inhibitors of PDE3 (the isozyme involved in regulation of cardiac contractility), such as milrinone, vesnarinone and enoximone, that have been used in patients with heart failure, are generally associated with increased incidence of cardiac arrhythmias and other serious side effects (17).

B. Pharmacokinetics and Metabolism

Sildenafil is rapidly absorbed after oral administration, with absolute bioavailability of ≈40%. Plasma concentrations peak within 30 to 120 minutes (median, 60 minutes) of oral dosing in the fasted state. Sildenafil is primarily metabolized by the cytochrome P450 3A4 (major route) and 2C9 (minor route) hepatic microsomal isoenzymes, which convert it to an active *N*-desmethyl metabolite that has been shown to possess 50% of the parent drug's potency for inhibiting PDE5. Plasma concentrations of this metabolite are ≈40% of those seen for sildenafil, so that the metabolite accounts for ≈20% of the pharmacological effects of sildenafil. Sildenafil and its active metabolite are both highly bound to plasma proteins (≈96%), and their terminal half-lives are ≈4 hours each. The mean steady-state volume of distribution for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil is excreted as metabolites predominantly in the feces (≈80% of administered oral dose) and to a lesser extent in the urine (≈13% of the administered oral dose). Less than 0.001% of the administered dose appears in the semen; this dose is very unlikely to have any effects in the partners of patients taking sildenafil. Plasma levels of sildenafil are increased in patients aged >65 years (40% increase) and in patients with hepatic impairment (eg, cirrhosis; 80% increase), severe renal impairment (creatinine clearance <30 mL/min; 100% increase), and concomitant use of potent cytochrome P450 3A4 inhibitors (eg, macrolide antibiotics such as erythromycin [300% increase] and clarithromycin, and azole antifungals such as ketoconazole and itraconazole) (18). Protease inhibitors such as indinavir, ritonavir, nelfinavir, and saquinavir have not been formally studied but, being potent 3A4 inhibitors, are anticipated to have similar effects on sildenafil metabolism (Pfizer, unpublished data).

C. Pharmacodynamics

The pharmacodynamic end points that have been investigated with sildenafil reflect the distribution of PDE5 in different tissues, ie, human corpus cavernosum (penile tumescence), vascular smooth muscle (vasodilatation), and platelets (antiplatelet function).

1. Effects on Penile Tumescence

The efficacy of sildenafil in enabling patients with erectile dysfunction due to a broad spectrum of causes, including vasculogenic (diabetes), neuroreflexogenic (spinal cord injury), and psychogenic (nonorganic), to achieve and maintain erection sufficient for satisfactory sexual intercourse has been demonstrated in all 21 double-blind, randomized, placebo-controlled, multicenter studies (Pfizer, unpublished data).

2. Cardiovascular Effects

a. Effects on Cardiac Contractility

Unlike cAMP-specific PDE3 inhibitors (milrinone, vesnarinone, and enoximone) that increase long-term mortality in patients with heart failure (17,19), sildenafil is highly selective (>4000-fold) for human PDE5 over human PDE3 and has not been found to elevate cAMP (Pfizer, unpublished data). The cardiotoxic effects of PDE3 inhibitors are thought to be related to increases in intracellular cAMP in the myocardium (15,19,20). Furthermore, PDE5 is not present in cardiac myocytes, and sildenafil has been shown to have no direct inotropic effects on dog trabeculae muscle (Pfizer, unpublished data). However, sildenafil has not been investigated extensively in heart failure patients.

b. Effects on Blood Pressure and Heart Rate

Sildenafil produces a transient modest reduction in systolic (8 to 10 mm Hg) and diastolic (5 to 6 mm Hg) blood pressures, with peak effects evident at 1 hour after the dose (coincident with peak plasma concentrations) and returning to baseline values by 4 hours after the dose (Pfizer, unpublished data). No significant effects are observed on heart rate. The hypotensive effects of sildenafil are neither age dependent (similar reductions in blood pressure in patients aged <65 years compared with those >65 years) nor dose related (over the range of 25 to 100 mg) and rarely result in reports of orthostatic effects. Doses as high as 800 mg have been well tolerated in some healthy volunteers (13).

c. Effects on Central Hemodynamics and Peripheral Vasculature

In normal volunteers, no significant changes in cardiac index were evident up to 12 h after the dose for oral sildenafil (100 to 200 mg) or intravenous sildenafil (20 to 80 mg) (Pfizer, unpublished data). Significant decreases in systemic vascular resistance index were reported at the end of intravenous sildenafil infusion (30 to 80 mg) when plasma concentrations

arteriodilator and venodilator effects on the peripheral vasculature (Pfizer, unpublished data). In 8 patients with stable angina, intravenous sildenafil reduced systemic and pulmonary arterial pressures and cardiac output by 8%, 25%, and 7%, respectively, consistent with its mixed arterial (systemic and pulmonary hypotension) and venous (drop in stroke volume secondary to decreased preload) vasodilator effects (14).

In conclusion, consistent with the anticipated effects resulting from an increase in cGMP levels in vascular smooth muscle, sildenafil possesses vasodilatory properties, which result in mild, generally clinically insignificant decreases in blood pressure when taken alone.

d. Platelet Effects

Sildenafil has no direct effects on platelet function but will modestly potentiate the inhibitory effect of the NO donor sodium nitroprusside on ADP-induced platelet aggregation ex vivo, consistent with the requirement for an NO drive for sildenafil to produce its pharmacological effects (Pfizer, unpublished data). No effects on bleeding or prothrombin times were seen in healthy subjects receiving sildenafil alone or concurrently with aspirin or warfarin. In addition, no adverse bleeding episodes have been reported with the use of sildenafil (Pfizer, unpublished data). However, because the effects of sildenafil have not been evaluated in patients with bleeding disorders or in patients taking nonaspirin antiplatelet agents (eg, ticlopidine, clopidogrel or dipyridamole), caution should be exercised when the drug is administered in these clinical settings.

3. Effects on Visual Function

Transient visual abnormalities (mostly color-tinged [blue-green] vision, increased perception of light, and blurred vision) have been reported in patients taking sildenafil, especially at high oral doses (>100 mg) (Pfizer, unpublished data). These visual effects appear to be related to the weaker inhibiting action of sildenafil on PDE6, which regulates signal transduction pathways in the retinal photoreceptors. Sildenafil is 10-fold selective for PDE5 over PDE6 (Pfizer, unpublished data). In patients with inherited disorders of retinal PDE6, such as retinitis pigmentosa, sildenafil should be administered with extreme caution (Pfizer, unpublished data).

4. Adverse Effects

The adverse effects of sildenafil reflect its pharmacological activity of inhibition of PDE5 in various tissues and can be broadly classified into 4 major adverse reactions:

1. *Vasodilatory effects* resulting in headache (16%), flushing (10%), and rhinitis (4%) (the latter presumably as a result of hyperemia of nasal mucosa where PDE5 is present). Dizziness (2%), hypotension (<2%), and postural hypotension (<2%) have been reported rarely and occur at a similar rate in sildenafil- and placebo-treated patients (Pfizer, unpublished data).
2. *Gastrointestinal effects* resulting in dyspepsia and burn-
3. *Visual abnormalities* resulting in blue-green color-tinged vision, increased perception of light, and blurred vision (3%), especially at higher doses (Pfizer, unpublished data).
4. *Musculoskeletal effects* resulting in myalgias, especially with multiple daily doses. No treatment-related changes in serum creatine kinase or electromyogram have been observed, however (Pfizer, unpublished data). There is no obvious pharmacological explanation for this effect.

IV. Drug-Drug Interactions and Concomitant Disease States

A. Interaction With Nitrates

The vasodilator actions of nitrates are profoundly amplified with concomitant use of sildenafil, resulting in major hemodynamic compromise and potentially fatal events (Pfizer, unpublished data). This interaction likely applies to all nitrates and NO donors, irrespective of their predominant hemodynamic site of action (see Appendix A for a list of commonly used nitrates). Sildenafil may also potentiate the hypotensive effects of an inhaled form of nitrate, such as amyl nitrate or nitrite, also known as "poppers," and therefore is contraindicated. Poppers act by dilating blood vessels, and the concurrent recreational use of poppers and sildenafil could result in sudden and marked lowering of blood pressure, which can be potentially serious or even fatal. This interaction may be even more pronounced in patients taking protease inhibitors concurrently (eg, indinavir [Crixivan], ritonavir [Norvir], nelfinavir [Viracept], or saquinavir [Invirase]).

Dietary sources of nitrites, nitrates, and L-arginine (the substrate from which NO is synthesized) do not contribute to the circulating levels of NO in humans and therefore are unlikely to interact with sildenafil. The anesthetic agent nitrous oxide does not undergo any detectable biotransformation and is eliminated unchanged from the body, mostly via the lungs, usually within minutes of its administration. Because it does not form NO in the human body and does not itself activate guanylate cyclase, there is no contraindication to its use after administration of sildenafil.

It is not known how much time must elapse from the time at which a patient takes sildenafil before a nitrate-containing medication might be given without the marked hypotensive effect being produced. On the basis of the pharmacokinetic profile of sildenafil, it can be assumed that the coadministration of a nitrate within the first 24 hours is likely to produce an exaggerated hypotensive response and is therefore contraindicated unless the benefits are determined to far outweigh the risks. After 24 h, the administration of a nitrate may be considered, but once again, the response to initial dosages must be monitored carefully. In patients in whom the half-life of sildenafil may be prolonged (see below), a more extended period of time from sildenafil administration to nitrate administration may be required. The preferred form of nitrate therapy in this setting would be short-acting intravenous nitroglycerin infusion under close hemodynamic monitoring.

Similarly, all patients taking either sildenafil or nitrates

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