

## Cardiovascular Risk Factors and Erectile Dysfunction

*Based on a presentation by Robert A. Kloner, MD, PhD*

### **Presentation Summary**

Vascular disease plays an important role in erectile dysfunction (ED) and is reported to result in a significant increase in impotence in later life. The introduction of the drug sildenafil has led many men to seek prescriptions, which in turn has resulted in their evaluation by physicians who have found a variety of serious, untreated medical conditions. The use of cardiac drugs increases the occurrence of ED,

with thiazide diuretic usage correlating most closely. Most of the deaths reported since sildenafil went on the market in late March 1998 have been cardiac related. Careful cardiac evaluation, which may include exercise stress testing, should be considered before sildenafil is prescribed, especially for older, physically and/or sexually inactive men with known coronary artery disease or multiple risk factors for it.

**R**obert A. Kloner, MD, PhD, examined the nature of erectile dysfunction (ED), raising the question: Is ED a vascular problem?

Dr. Kloner cited one of the first studies to address that question, which was published in 1985 by Virag and associates and focused on the distribution of four main arterial risk factors: diabetes, smoking, hyperlipidemia, and hypertension.<sup>1</sup> In it, 440 impotent men with an average age of 48 years were compared with the general male population.

### **Arterial Factors in ED**

"When Virag and associates<sup>1</sup> looked at the issue of smoking in the general

male population and in these impotent men, they found it was more common in the impotent men. Diabetes and hyperlipidemia were also more common in impotent men compared with the general population," Dr. Kloner said, noting that hypertension was not a risk factor for ED in this particular study, but that it has been in other studies.

The same investigators also looked at the penile blood pressure index (PBPI), which indicates the ratio between blood pressure in the penis versus the brachial artery. "Normally," Dr. Kloner explained, "the PBPI runs close to 0.9, and patients who had diabetes alone were found to have a depressed PBPI. The

PBPI fell as the number of risk factors accumulated."

The study found that smoking, diabetes, and hyperlipidemia were all significantly more common in impotent men than in the general male population. When two or more arterial risk factors were present, the mean PBPI was also significantly lower.

"That study was one of the first to suggest that some of the same kinds of risk factors seen in cardiovascular disease were common to ED as well," Dr. Kloner noted.

### Massachusetts Male Aging Study

The Massachusetts Male Aging Study<sup>2</sup> looked at risk factors for the development of ED. In it, data on ED were categorized as none, minimal, moderate, or complete. There was a correlation between age and the development of ED.

"In the moderate category," Dr. Kloner observed, "there was an increase in patients with untreated heart disease. Among treated patients who were nonsmokers there was a substantial increase in both the complete and the moderate category," he continued, noting that it may represent the fact that once patients are sick enough to need medication, their heart disease has progressed and is more severe, or it may also reflect the medications.

"One of the most striking things," Dr. Kloner observed, "is that when you look at treated patients who are smokers, there is a marked increase in ED, especially in the complete erectile dysfunction category."<sup>2</sup>

"Whereas smoking is plainly a very severe risk factor, there are also some interesting data in the literature on cholesterol,<sup>2</sup> both the 'good' and the 'bad' type," Dr. Kloner said, explaining that the former is high-density lipoprotein cholesterol (HDL-C), which tends to correlate inversely with coronary disease. In the Massachusetts Male Aging Study, patients who had HDL-C levels of <30

mg/dL were more likely to have erectile dysfunction than those who had HDL-C levels of 60 to 90 mg/dL.

"Simply having cardiac drugs present increases ED," Dr. Kloner said, "but as soon as you're a smoker everything gets a lot worse."

"Those with heart disease, hypertension, or diabetes were four times more likely to become completely impotent in later life,"<sup>2</sup> Dr. Kloner said, citing smoking as substantially increasing the likelihood of complete ED in men with heart disease, among whom the rates were 56% for current smokers and 21% for nonsmokers, according to the Massachusetts Male Aging Study.

"Diabetes can accelerate vascular disease, which was associated with ED in several studies,"<sup>1-3</sup> Dr. Kloner said, adding that diabetic men older than age 60 had about a 75% prevalence of ED, which increased with the duration of the disease.<sup>3</sup> "Diabetes can lead to ED, both by causing vascular disease as well as neuropathy," Dr. Kloner noted.

### ED as a Symptom

The NIH Consensus Conference<sup>4</sup> stated that most of the medical problems associated with erectile disorders appear to affect the arterial system. Erectile dysfunction is a symptom of many conditions, and several risk factors have been identified, some of which Dr. Kloner said may be amenable to prevention strategies.

"A number of cardiac drugs have been associated with the development of ED, many of which fall in the hypertensive category," Dr. Kloner explained.<sup>4,5</sup> "Many cardiologists are under the misconception that beta-blockers are the prime offenders, but that is a myth that has been perpetuated through the years.

"Studies that have made head-to-head comparisons of some of the diuretics compared with beta-blockers suggest that although beta-blockers have been associated with

the development of ED, it is actually the thiazide diuretics that seem to correlate more closely with the development of ED," Dr. Kloner noted.<sup>5</sup>

"Agents such as alpha blockers, the angiotensin converting-enzyme (ACE) inhibitors, or the calcium blockers are rarely the cause of ED," Dr. Kloner said. "Another category of cardiac drugs, the lipid-lowering agents—including clofibrate and gemfibrozil—have also been associated with ED. There are also reports of a link between digoxin and ED,"<sup>5</sup> he added.

"One of the things that is very important about the introduction of sildenafil is that patients are going to come to physicians' offices who previously might not have sought medical attention," Dr. Kloner said. "Many of these men who come in with ED are going to have risk factors for cardiovascular disease, so it is a good opportunity to ask such patients about their cardiovascular health, diagnose cholesterol abnormalities, hypertension and diabetes, and get them to stop smoking.

"These risk factors may increase the workup to some extent," Dr. Kloner observed, "but in the long run they may reduce costs because, for example, they might prevent a myocardial infarction (MI) if a patient with hypercholesterolemia can be found and treated. I tend to look at the availability of prescriptions for sildenafil as an opportunity to treat patients who might not otherwise have visited a physician.

"On the other hand," Dr. Kloner continued, "It is important to ask patients with cardiovascular disease about their sexual health and erectile function, which is something that most cardiologists don't do. Maybe now they will."

### **Sexual Activity and Mortality**

On the issue of whether sexual activity triggers MI and ischemic events, Dr. Kloner noted it has clearly

been of concern, especially since the release of sildenafil. Deaths have been reported, some of which have been the result of MI.

Dr. Kloner cited a classic article that appeared in *The Journal of the American Medical Association* by Muller and colleagues<sup>6</sup> that dealt with the risk of nonfatal MI triggered by

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the sexual activity of individuals with or without coronary disease. Eight hundred fifty-eight MI patients reported they had been sexually active during the previous year; 273 of them, or 32%, had coronary artery disease before their MIs, and 79, or 9%, reported sexual activity in the 24 hours preceding their MIs; another 27, or 3%, reported sexual activity within 2 hours prior to symptom onset.

"There is an increase in the relative risk of having an MI if you engage in sexual activity, according to this study," Dr. Kloner said, noting that the relative risk is about 2.5 and is greatest within the first 2 hours after sexual activity, after which it declines.<sup>6</sup> "If you have sex and are alive 3 hours later," he observed, "the chances of having an MI are pretty low."

### **Benefits of Exercise and Physical Activity**

According to the Muller study,<sup>6</sup> patients who actively engaged in reg-

ular physical activity or an exercise program were less likely to have an MI as a result of sexual activity. Patients who did not work out at all or those who worked out once a week had a somewhat higher risk than those who worked out three times a week.

Other researchers have looked at arrhythmias and put Holter monitors on patients, which revealed that arrhythmias occurred with sexual activity.<sup>7</sup> In general, these arrhythmias were similar to those that occurred with nonsustained exercise.

"There is a physiological expenditure with sexual intercourse," Dr. Kloner explained. "The heart rate typically increases to about 120 to 130 beats per minute, the systolic pressure goes up to about 150 to 180 mm Hg, and about five or six metabolic equivalents are expended.<sup>8</sup> Patients with coronary artery disease who get ischemic on an exercise test may also show ischemia with sexual activity if they are wearing a Holter monitor."

In terms of cardiac drug interactions, Dr. Kloner said the key information is the data on nitroglycerin as it relates to sildenafil enhances cyclic guanosine monophosphate (cGMP) levels by preventing their breakdown by interfering with phosphodiesterase type 5. Nitric oxide (NO) also enhances cGMP levels. "Nitroglycerin and organic nitrates donate NO," he explained, "and when you have sildenafil plus an NO donor, you get a marked decrease in blood pressure."

#### **Nitrate Use Contraindicated With Sildenafil**

Consistent with its known effects on the NO-cGMP pathway, Dr. Kloner stated that sildenafil has been shown to potentiate the hypotensive effect of nitrates. As a result, its administration to patients who are concurrently using organic nitrates in any form is absolutely contraindicated.<sup>9</sup>

According to a recent Food and Drug Administration (FDA) report, 46 of the 69 deaths attributed to sildenafil use were cardiac in nature; 12 of them were the result of the concurrent use of nitrates. (Data from FDA Website. August 24, 1998.)

How significant are the 69 deaths, most of which were cardiovascular, that occurred among 2.5 million men who had been using sildenafil over the first 4-months<sup>10</sup> of its availability?

Citing data from the American Heart Association,<sup>10</sup> Dr. Kloner said there are about 185 to 275 cardiovascular deaths per 1 million men per month in the United States. "If you look at the figures for sildenafil, 69 deaths among 2.5 million men in 4 months, they don't seem that dramatic," Dr. Kloner observed, adding that of those 69 deaths, 12 were related to nitrates.

In terms of the causes of death, there were 21 MIs, 17 cardiac arrests, two strokes, and one case of severe hypotension; the others were suspected to be the result of coronary artery disease. "A few of these men had no history of coronary disease," Dr. Kloner said, but he observed that at autopsy they were found to have severe coronary disease. In some cases, the cause of death was unknown.

"Although sildenafil seems safe, when you look at the overall statistics," Dr. Kloner said, "there is still a concern that in older men, especially those who are physically inactive and have coronary disease, the newly acquired ability to engage in sexual activity can potentially trigger a cardiovascular event."

#### **Consensus Statement Available**

"The American College of Cardiology and the American Heart Association (ACC/AHA) have looked at this issue and put together a consensus statement that is expected to be published around December in the

*Journal of the American College of Cardiology*," said Dr. Kloner. "In the meantime, they have issued an interim statement, which is on the Internet.<sup>11</sup>

"In this interim report the authors reiterate that nitrates are absolutely contraindicated," Dr. Kloner said. He suggested that "if you have a patient who only occasionally uses nitroglycerin but has angina, you should not give him sildenafil, because he may get chest pain with sexual activity, reach for nitroglycerin, take it, and become hypotensive."

The authors of the interim report also suggested that physicians use caution in prescribing sildenafil to patients who have coronary disease and active myocardial ischemia, whether or not they are on nitrates, Dr. Kloner said, adding that they also recommended caution with patients who have heart failure with borderline low blood pressure or low blood volume and with those who have hypertension and are on multiple antihypertensive medications. Dr. Kloner said the suggestion regarding multiple antihypertensives was a consensus statement that was not really supported by hard data.

For patients on sildenafil who have stable and unstable angina, Dr. Kloner said the ACC/AHA suggest that non-nitrate antianginal agents such as beta-blockers, calcium blockers, and aspirin be used when indicated. For patients who developed an MI when using sildenafil, they recommended the usual therapy be used, including thrombolytic therapy and angioplasty, and that nitrates be contraindicated.

Dr. Kloner also suggested exercise tests might be considered for men who have coronary disease or multiple risk factors for coronary disease, especially those who are older and are physically and sexually inactive, before a decision is made to prescribe sildenafil.

#### Addendum

Since the submission of this manuscript, additional information was

released by the FDA reporting 130 deaths in the United States among sildenafil users from late March through mid-November 1998, among about 3 million men (6 million prescriptions). Seventy-seven men had cardiovascular events and cause of death was not known in 48. The average age was 64. Forty-one had definite or suspected myocardial infarction, 27 had cardiac arrests, 6 had other cardiac symptoms, and 3 had coronary disease at autopsy but no prior cardiac history. Forty-four patients died or had onset of symptoms leading to death within 4 to 5 hours of sildenafil (27 during or immediately following sexual intercourse), and 6 died later the same day. It is important to note that 90 patients had risk factors for atherosclerotic disease, including cigarette smoking, hypertension, hypercholesterolemia, dia-

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betes, obesity, and previous cardiac history.

The number of deaths in sildenafil users was 5.78 per million per month. According to the American Heart Association, there are about 185 to 275 cardiac deaths per million men per month in the United States.

In consultation with the FDA, Pfizer has revised the product labeling expanding on the issue of cardiovascular risk, as well as describing the infrequent side effect of priapism. The warning section stated that "sildenafil should not be generally

used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status." Transient vasodilator properties are described. The warning suggested cautious use with patients who have had myocardial infarction, stroke, life-threatening arrhythmia within 6 months, hypotension (BP<90/50), hypertension (BP>170/110), cardiac failure, unstable angina, or retinitis pigmentosa in which there was no controlled clinical data.

The contraindication with organic nitrates was reemphasized. See package insert for full details.

...DISCUSSION HIGHLIGHTS...

**Dr. Carson:** Dr. Kloner, what kinds of questions would you ask an older man to see if he is reasonably fit for sexual activity and taking drugs such as sildenafil?

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**Dr. Kloner:** Well, the rule of thumb used to be that if a patient could walk up two flights of stairs then he was fit for sexual activity. I'm not sure that's such a great test. One thing you want to know is whether he has any risk factors, such as angina, diabetes, smoking, hyperlipidemia, or hypertension, as well as any cardiovascular symptoms. If he does, then that is the kind of patient I would probably want to do an exercise treadmill on. If he can get his heart rate up to 120 or 130 beats per minute and get a systolic

pressure of 150 to 180 mm Hg and not develop chest pain or any ST segment changes with 5-6 METS [metabolic equivalents], the likelihood that he is going to have an event with sexual activity is very low.

**Sildenafil and Mortality**

**Dr. Sadovsky:** There are several issues here, one of which is discussing the data available to us. However, there are also data about those 69 people who were using sildenafil at the time of their deaths. It is not clear whether all of them had used it in the previous 24 hours or whether they had used it 4 hours or 6 hours before intercourse.

**Dr. Kloner:** Twenty-five patients died or had onset of fatal symptoms within 4 to 5 hours of sildenafil; three within the same day; seven the following day; four 2 days later; and two 3 to 4 days later. In 28 cases, the timing was unknown.

**Dr. Jarow:** What are reasonable guidelines for a cardiology or internal medicine consultation prior to prescribing sildenafil?

**Dr. Kloner:** Primary care physicians and internists are used to routinely assessing cardiovascular risks. One guideline is whether we have symptoms or enough risk factors for cardiovascular disease followed by consideration for a stress test. A negative stress test will then convert to a low probability of cardiovascular disease, whereas a positive stress test will convert to a high probability. Patients who are at high risk could then be referred to a cardiologist.

**ACC/AHA Guideline**

**Dr. Rajfer:** Dr. Kloner, how do you treat a patient who takes sildenafil and becomes hypotensive after nitroglycerin?

**Dr. Kloner:** That scenario is addressed in the ACC/AHA guideline,

which suggests that if, after you check the blood pressure, the patient is hypotensive, you put him in the Trendelenburg position and give him fluids. You could even give the patient alpha agonists. Beta agonists can be considered; however, the problem is that in some of these patients beta agonists could conceivably worsen the ischemia if they have coronary disease. Intra-aortic balloon counterpulsation could be considered in very sick patients.

**Dr. Rajfer:** Do cardiologists always intervene in patients who have a positive stress test?

**Dr. Kloner:** Not necessarily. Let's say a patient exercises for 9 to 11 minutes and has just a little ST segment depression in one ECG lead. Some of those patients can do just fine on agents such as beta-blockers and calcium channel blockers. They don't necessarily need to see a cardiologist. But if the patient has a drop in blood pressure within the first couple of minutes of an exercise test and he has severe ST segment depression across several leads, he is more likely to be at higher risk of having severe multi-vessel coronary disease. That is the kind of patient who should be seen by a cardiologist and considered for cardiac catheterization.

**Dr. Rajfer:** The first type of patient you mentioned, would you prescribe sildenafil for him?

**Dr. Kloner:** It really depends on how many minutes the patient went on the exercise stress test and whether he got chest pains and had an ST segment change. If the patient really had chest pain due to angina on an exercise treadmill, especially at a low level of exercise. I probably would not prescribe sildenafil, because such a patient is likely to wind up needing sublingual nitroglycerin at some point in time for chest pain. If the patient achieved 5 to 6 METS on an exercise

test, did not have chest pain, and had no history of angina or need for nitrates, then sildenafil probably would be okay.

**Dr. Rajfer:** Are we doing all these tests to determine whether that patient can have sildenafil? If we are going to do a test, there ought to be some objective criteria that we can use to decide whether to put him on sildenafil or not. It seems a little wishy-washy to intervene and then not give the patient sildenafil.

**Dr. Kloner:** There is no hard-and-fast rule. A lot of it comes down to common sense. The objective criteria is no ischemia on an exercise test and ability to achieve 5 to 6 METS on an exercise test. There is a good correlation between developing ischemia during sexual activity [Holter monitoring] and developing ischemia with exercise testing.

**Dr. Rajfer:** But again, you do not know whether that patient will get chest pain when taking sildenafil during sexual activity. Logic would dictate he would.

**Dr. Kloner:** A study by Drory et al<sup>12</sup> used Holter monitoring during coitus and showed that patients with ischemia during sexual activity also had ischemia during exercise testing. So I think that the exercise test is a pretty good screen for now. However, there is no way of being 100% sure if a patient will have chest pain with sexual activity.

**Dr. Basskin:** Is the FDA saying we don't even need a clear correlation with coronary artery disease for sildenafil to be contraindicated?

**Dr. Kloner:** The FDA is not saying that, but the ACC and the AHA are saying to use sildenafil with caution in patients with coronary disease who have active ischemia. I believe part of the reason they are saying that is that there is a finite chance of having a

cardiac event with the energy expenditure required for sexual activity.

You have a group of older patients who may be physically inactive and haven't made such an energy expenditure, either through physical activity or sexual activity, who are suddenly going out and having sexual activity and raising their heart rates and elevating their blood pressures. There certainly also could be an emotional component to sexual activity that increases oxygen demand, and as a result, some of them are having cardiac events.

**Dr. Sharlip:** Most of my patients who ask for sildenafil have been sexually active, despite a poor erection, so I have very few patients who are going from total inactivity to having a great erection and being very active sexually. I assume they almost all have had some tachycardia from sexual stimulation as well as from other forms of physical activity.

**Dr. Sadovsky:** I think it would be wonderful if the recommendations were evidence based, but the evidence isn't there, so what we are looking at are the physiological mechanisms, while we try to think about what the risks might be.

A lot of my patients who have this problem are not necessarily having that much sex right now, because I may have suggested ED as a symptom, which gave the patient the opportunity to talk about it and realize that it was a problem. However, your patients may be a little bit more selective, because they are coming to you because they have a problem.

#### Managed Care Concerns

**Dr. Leider:** Back to the managed care perspective. If the algorithm for some patients becomes a consultation and for a subset of these patients a stress test that is done either by the primary care physician or the referring cardiologist, it might progress from there to other diagnostic modal-

ities. Should managed care cover that? After all, if the patient had not had ED and wanted sildenafil to treat it, he might not have come in at all.

I am simply saying this ups the ante in terms of cost. Of course, the argument could be made that if the patient has hypertension or hyperlipidemia that was previously undiagnosed, intervention might avert years of debilitation resulting from a stroke or MI, so there might ultimately be some cost savings.

**Dr. Carson:** If you were going to do a stress test on a patient without that patient having requested sildenafil, you would use the same risk factors to determine whether that patient needed treatment for his cardiac disease, wouldn't you?

**Dr. Sharlip:** I think it makes sense to tell patients age 65 and older or who have cardiac disease that there is a greater risk of having a serious cardiac event if they take sildenafil. You need to warn the patient so he can bear part of the burden.

**Dr. Rajfer:** But do we know that? Intellectually and theoretically, that sounds like the right thing to do, but do the data support it?

#### Sexual Activity and Cardiac Events

**Dr. Kloner:** What you can say to the patient is that there is a small but significantly increased chance of his having a cardiac event if he engages in sexual activity, because that is what the data show, independent of sildenafil.

**Dr. Jarow:** We have been treating men for years with a variety of successful treatments for ED and have never seen any reports of death. In a study we did that looked at men who used injection therapy versus a penile implant over a 10-year period, we had about 20% of the men in the implant group die over that time period, but their deaths were not related to the implant.



**Dr. Kloner:** Has anyone actually got death rates for these other interventions? Or are death rates being reported just because 3.6 million prescriptions for sildenafil have suddenly been written?

**Dr. Rajfer:** What about patients who don't respond to sildenafil? There are a few of those, aren't there? So, what methods do they try? They go on the other modalities.

I have patients who are 80 or 90 years of age, and as for sexual activity per se, I can't recall that any adverse event such as death has occurred.

**Dr. Jarow:** If the patient is new to you and says that he has ED, is that going to lead to your doing tests such as lipids, blood pressure, glucose, and other tests looking for cardiac risk factors, when that is not something you would have done if you had known him for some time?

**Dr. Sadovsky:** Because I would normally do 80% of those tests, it might cause me to do one or two additional blood tests I might not have done before. So there may be some additional testing, but not much.

**Dr. Leider:** Well, the sticky wicket here for me is in primary care we would certainly never do a stress test on a patient with multiple risk factors who has no evidence of clinical ischemia and no chest pain.

**Dr. Parham:** That is definitely the issue.

**Dr. Kloner:** Some of those patients who died had no history of coronary disease, yet at autopsy they were found to have had severe coronaries.

**Dr. Rajfer:** What precautions should you take when using sildenafil with multiple drugs that are non-nitrates?

**Dr. Kloner:** There is not much published data on that issue. One study from Pfizer (unpublished data) in which patients were on two or three

antihypertensive medications did not show big drops in blood pressure when patients took sildenafil. Also, the drops in pressure with sildenafil that are in general mild are not dose-related. If a patient has low preload or is hypotensive to begin with you may want to avoid the drug.

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