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### Treating Erectile Dysfunction: Key Cardiovascular Considerations

Dr. Brown:

You're listening to ReachMD and this is Lipid Luminations sponsored by the National Lipid Association. I am your host, Dr. Alan Brown, and with me today is Dr. Robert Kloner. He is Vice President of Translation at Huntington Medical Research Institutes and Professor of Medicine in the Cardiovascular Division at the Keck School of Medicine which is at the University of Southern California in Los Angeles.

Dr. Kloner, thank you very much for joining us.

Dr. Kloner:

Thanks for having me.

Dr. Brown:

So we are going to talk about a topic which I think most of us feel is very important but, for some reason, there has not been a lot of discussion about it, which is focusing on erectile dysfunction, cardiovascular risk, and also the debate about testosterone and testosterone replacement. It's one of those things that I think all of us in practice or in cardiology deal with because, for whatever reason, these patients are told by their urologists that if they have any kind of cardiovascular disease, you need to go get cleared by the cardiologist to use drugs for erectile dysfunction. Also, patients come to us and say is it okay to do testosterone replacement. Many times the average cardiologist has no idea what the right answer is. I think you are going to help us and you are going to help all the primary care physicians that listen to our program. If we could start, maybe we will talk about your research and the safety of drugs for erectile dysfunction. Or, maybe even better, talk about what one should think about when a patient presents with ED in terms of cardiovascular risk. Let us start there.

Dr. Kloner:

That is a great place to start. An erection is a vascular phenomenon; it's a vascular event. And so, the same things that affect cardiovascular risk affect your ability to have an erection. Risk factors such as smoking, hypertension, diabetes, dyslipidemia, being overweight, lack of physical activity; those are all risk factors not only for cardiovascular disease but also risk factors for erectile dysfunction. You need to have a functioning endothelium and anything that causes endothelial dysfunction can impede the ability of the arteries, arterial sinusoids, within the penis to dilate normally and that is what you need for an erection. The vast majority of erectile dysfunction is due to this vascular problem. There is an intersection between cardiovascular risk factors and risk factors for ED. When someone comes into your office complaining of ED, the physician should think Ah-ha! ED, there could be cardiovascular risk factors, we should really work this patient up for the known cardiovascular risk factors. Is the patient hypertensive? Does he smoke? Does he have dyslipidemia, diabetes, etc.?

Dr. Brown:

That's very interesting. What is the prevalence of coronary disease in a patient with erectile dysfunction? Once you identify such a patient, what is the likelihood that that patient actually has potentially clinically significant atherosclerosis?

Dr. Kloner:

The chances are reasonably high that that patient is going to have risk factors for cardiovascular disease. And if you look at the question of, if you take patients with known coronary disease, what percent have ED? It is very high. In one study that we did, the patients who had documented multi-vessel coronary artery disease, about 75% of those men had some element of erectile dysfunction. In a high percentage it was severe ED. Once you have coronary artery disease, you have a very good chance of having ED.

Dr. Brown:

Well that leads me to getting down to what do you in your office? So, if a patient comes in with ED and let's say that they are hypertensive, maybe a former smoker, middle-aged guy, how do you make a decision of whether further cardiovascular workup should be done? Do you ever decide we better do a stress test on you because you have ED? Does that add to your risk assessment as well as all of the other risk factors?

Dr. Kloner:

Well, it does. You want to obviously workup the patient for cardiovascular risk factors. You want to do a cardiovascular exam. You also want to make sure there is no anatomic cause for ED because there are other urologic causes such as Peyronie's disease and other diseases that are primarily urologic and those need to be ruled out. Once you've done that, if you have got a patient who presents with ED and you're pretty sure that it's vascular in origin, you want to make sure that, first of all, the patient can achieve the normal degree of exercise required for sexual activity which runs three to five METs, basically. In some of those cases, if the patient has absolutely no angina, no symptoms, the patient is active physically, walks long distances or bicycles long distances, and you're not concerned that they are having ischemia, then that's very, very low risk and that patient can probably go on to get a PDE5 inhibitor, phosphodiesterase 5 inhibitors such as sildenafil, vardenafil, tadalafil and others. If the patient cannot achieve three to five METs from just talking to the patient, you might want to then consider going on and doing an exercise stress test to see if there is ischemia. If the patient has unstable symptoms; unstable angina, severe heart failure, lethal arrhythmias, this sort of thing, then you really want to clear up the cardiac problem first; get the cardiac condition straightened out before you go on to recommend that that patient have sexual activity or receive the PDE5 inhibitors. There are a couple of guidelines on that. One is guidelines that were released from a group called the Princeton Consensus Guidelines. Another is guidelines from the American Heart Association by Levine and co-workers published in circulation a few years ago, so I would recommend your readers take a look at those.

Dr. Brown:

Obviously when these drugs first came out, the PDE5 inhibitors in general, there was some concern about cardiovascular safety with the drugs themselves. In just a couple of minutes I want you to follow up on that issue and give us some wisdom.

If you are just tuning in, you are listening to ReachMD. I am Dr. Alan Brown and I am speaking with Dr. Robert Kloner, Vice President of Translation at Huntington Medical Research Institutes and Professor of Medicine in the Cardiovascular Division at the Keck School of Medicine which is at the University of Southern California.

So there was this initial fear that if you took these drugs they might cause cardiovascular events and you've already alluded to the bigger issue probably being that you have to be fit enough to actually engage in sexual activity. Do we have to worry about any direct toxicity of the medications or is it just the cardiovascular health of the patient?

Dr. Kloner:

Mainly the cardiovascular health of the patient. The large studies that have been done and published looking at the incidence of cardiovascular events in patients getting PDE5 inhibitors versus a placebo have not really shown a signal. There are occasional case reports in the literature of men having cardiac events associated with taking a PDE5 inhibitor but usually then associated with sexual

activity. So the PDE5 inhibitors enable the person to achieve the 3 to 5 METs needed for sexual activity but there really is not data that suggest that the PDE5 inhibitors themselves have negative cardiovascular events. There are some contraindications. The major one is organic nitrates. That includes the short-acting sublingual nitroglycerin pills and sprays as well as the long-acting nitrates such as isosorbide dinitrate and isosorbide mononitrate. And there, what happens when you take a nitrate is you get an increase in NO and then an increase in cyclic GMP which causes vasodilatation. When you take the PDE5 inhibitor, that prevents the breakdown of cyclic GMP. So, NO increases cyclic GMP production, the PDE5 inhibitor prevents the breakdown of cyclic GMP, you get a build-up of cyclic GMP and a lot of vasodilatation and in some patients you will get symptomatic hypotension. Not everyone, and not all the time because there are differences in volume status of the patient, sympathetic tone of the patient which may alter it, but unpredictably, some patients that get the nitrate plus the PDE5 inhibitor will have hypotension and, therefore, that remains an absolute contraindication.

Dr. Brown:

I document in the chart when I prescribe these drugs to patients that I explain to them that if they have chest pain for any reason, not that the medicine will cause chest pain, but if they get chest pain, someone will likely hand them a nitroglycerin and I know that is improving in terms of the emergency room's awareness.

Dr. Kloner:

I think the emergency wards are becoming more aware of it. The other interaction that people should be aware of is alpha blockade can sometimes be associated with orthostatic hypotension and there is a newer drug out for pulmonary hypertension which can also interact with the PDE5 inhibitors.

Dr. Brown:

There has been less discussion about alpha blockers than there was initially. There was a lot of concern about alpha blockers. How has that changed? It seems like that has not been as big of a concern.

Dr. Kloner:

Well, it is a warning. Some patients do get orthostatic hypotension when the two are put together but it is not a contraindication, it is a warning. If you start with the lowest doses of both of the alpha blocker and PDE5 inhibitors, you can often avoid a problem.

Dr. Brown:

I suppose that you do not get nearly as dangerous hypotension as you do with the nitrates. Is that it or is that not predictable either?

Dr. Kloner:

Usually it is not as severe. It tends to be more orthostatic in nature.

Dr. Brown:

So, on that topic, there has been obviously an indication for low-dose tadalafil for BPH or obstructive uropathy. What do you think about that? Obviously some of those people are already on alpha blockers, I know you are not a urologist but, would that tendency be to switch from one to the other if they have ED and they have obstructive uropathy or BPH?

Dr. Kloner:

Tadalafil has been shown to be effective for both BPH and ED and there are some patients who are on the chronic low-dose of it for that. Some of those patients may or may not also need to be on an alpha blocker. I think it is again a question of titrating the dose

especially if you are on an alpha blocker; they tend to start with the lowest doses and sort of monitor the patients.

Dr. Brown:

You have helped us in terms of realizing that cardiovascular safety of those drugs is actually pretty good and you have published some nice papers on showing treadmill testing and other things do not seem to be effected by being on those drugs. The main issue is to make sure they are healthy enough for sexual activity and also to do what doctors are supposed to do; examine the patient when you see it and make sure you are not missing anything else, so that has all been really great. Also, some of the contraindications.

I wanted you to weigh in on something that cardiologists frequently are asked to do which is to clear a patient for these drugs so that the patient who has known coronary disease is either told by their primary care doctor or somebody else that you better check with your cardiologist before we put you on it. What should the average cardiologist know because I think many of them just tell people you should not take these medications and how do you deal with someone with established coronary disease who really could benefit from being on a PDE5 inhibitor?

Dr. Kloner:

I think the first question is, is it safe for the patient to have sexual activity? Are they low risk, moderate risk or high risk? If they are low risk, it is fine for them to be on it. If it is moderate risk, consider an exercise stress test or other test to look at stress. If they are high risk, they are unstable from a cardiovascular standpoint, I would get the cardiac problem fixed first. The cardiologist then has to discuss with the patient if they are on a nitrate, then they cannot be on a PDE5 inhibitor. This brings up another point, and that is there are a lot of patients walking around out there on nitrates who may not need to be on nitrates. Very often patients will undergo percutaneous coronary intervention or coronary bypass surgery and they continue to have a nitrate prescription even though they do not need it. If the patient does not really need to be on a nitrate then there should be consideration of discontinuing that particular drug or consider substituting other anti-anginal agents which are out there that do not have a contraindication with PDE5 inhibitors. We've seen that many times where the patient can actually be taken off the nitrate and does not need it because the patient's been fully revascularized and does fine on a PDE5 inhibitor.

Dr. Brown:

I think that is such an important point. Some of our colleagues tell people if you had a bypass surgery you should not use these drugs, but if you have had a bypass surgery, have great exercise capacity, and have been through rehab, you are otherwise fine. Early on, even the company that sold these drugs had made some joking commentary, they had little sales aids that were somewhat sophomoric and joking; this has been a topic that has been the brunt of a lot of jokes. In reality, one of the things that I noticed after 30 years in practice is once there was a treatment for ED, patients I had taken care of for years brought it up to me. It turned out that it actually was affecting their relationship significantly. Their wife did not think they were attractive to them or the husband felt like less than a man and it added that closeness to the relationship that was missing, the intimacy. Far from being a joke, it seems like this is something we should attend to. It is important to people and their relationships. I just wonder if that has been your experience.

Dr. Kloner:

Absolutely, I think, now that there is a therapy it is something that people can talk about. People are more open about it now and I think physicians are more open about it. Before, you never talked about it. You should talk about it with your patients; it is an important part of life.

Dr. Brown:

One of the issues that frequently comes up, and it is sort of confusion even for us lipid geeks, is whether it is safe to supplement testosterone. I have noticed more and more patients are getting their testosterone tested when they are fatigued and they have a number of nebulous symptoms which is sometimes just getting older. What is the risk? There has been a lot of debate about the risk of

replacing testosterone?

Dr. Kloner:

I would have to say that at this time it is an unresolved issue. If one looks at the literature, it is extremely confusing. There are studies suggesting that exogenous testosterone increases cardiac events. There are studies suggesting that exogenous testosterone reduces cardiovascular events. I think that if the patient is truly symptomatic and is documented to have hypogonadism and is cardiovascularly fit, reasonably fit, it is probably safe. The question comes up in the elderly, frail individual whether it is safe. I think that there still needs to be additional research to determine that. There is really a need for a large multi-center, placebo-controlled outcome trial where exogenous testosterone compared to placebo and the primary outcome is major adverse cardiovascular events. That study probably will be done at some time in the future, but it will be a while before it is done.

Dr. Brown:

The studies where it was a secondary analysis, it looked like it was people primarily with established coronary disease who might get some risk.

Dr. Kloner:

I think you are referring to the TOM trial from the New England Journal of Medicine.

Dr. Brown:

Not perfect science and there have been a lot of debates about it.

Dr. Kloner:

There have been tremendous amount of debate about it.

Dr. Brown:

We should suggest to our audience to keep their eyes on the literature because more and more people are receiving it. Of course, from a lipid standpoint, we worry a little bit about the testosterone replacement. We will just have to see how it goes.

Thank you very much. I cannot thank you enough for your insights and I think our audience, from all specialities, will gain a lot from your commentary today. So, Dr. Kloner, thank you for being with us.

Dr Kloner:

Thank you.

Dr. Brown:

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