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Identifying Cardiovascular Risk Factors for HIV Patients

Dr. Cheeley:
You're listening to *Heart Matters* on ReachMD. I'm Dr. Mary Katherine Cheeley, and joining me today to discuss cardiovascular risks for people living with HIV is Dr. Steven Grinspoon. He is a Professor of Medicine at Harvard Medical School and Chief of the Metabolism Unit at Massachusetts General Hospital.

Dr. Grinspoon, welcome to the program.

Dr. Grinspoon:
Oh, thank you so much, Mary. I really appreciate it.

Dr. Cheeley:
Let's jump right in. Can you tell us why the HIV population may be at a higher risk for cardiovascular disease?

Dr. Grinspoon:
Sure. Many studies over the last few years have shown that the risks of cardiovascular disease are between 50 to 100 percent increased among patients with HIV, and that's pretty consistent, including in a global meta-analysis that was published in about 2017, and this risk is most likely due to chronic residual immune activation and inflammation in this population. A number of years ago, we used to think that the primary driver of this excess risk was metabolic derangements among patients with HIV, and that's still true to a certain degree. For example, we published a paper in *The Journal of Clinical Endocrinology and Metabolism* showing that the rates of heart disease were significantly increased in HIV patients, but that traditional cardiovascular risk only accounted for approximately 25 percent of that risk in people with HIV, and by that I mean hypertension, diabetes, and dyslipidemia, so they are very important, including smoking rates, which are increased, and they should be addressed and do likely contribute. But there's something else that's going on, and I think that the something else is likely some degree of residual immune activation in these patients, and that's likely because the antiretroviral therapy is itself enough to keep the virus generally in check and to prevent major infectious complications, but it doesn't bring the residual immune activation down to zero, and it does still persist. Also, a number of years ago, some of the antiretroviral therapies themselves were more toxic, including NRTIs and things, but largely, those drugs are not used so much anymore, and the newer classes of medications are generally better tolerated. And I might add that this excess disease can occur in young patients who have normal lipid levels and patients who may not have excess risk detected on traditional risk prediction algorithms that are used today, including the pooled cohort equation. We found that relatively young patients have significant excess of coronary plaque, and that was a paper we published in *JAMA Network Open* a few years ago.

Dr. Cheeley:
Are there specific cardiovascular diseases that patients living with HIV are at higher risk for?

Dr. Grinspoon:

I would say that acute myocardial infarction is one that is important. The risk of sudden cardiovascular death has been increased and shown by Priscilla Hsue in papers that she's published, so this can happen among patients who don't have a prodrome of angina or anything like that, likely because of high-risk plaque that they have that could be vulnerable to disruption and acute myocardial infarction. We've also seen a lot of strokes and other neuro cardiovascular complications, and those are the two that I think are the most common.

It's also interesting to note that some of the myocardial infarctions are not more typical type 1 due to a slow steady buildup of plaque occluding a vessel, but it can be type 2 myocardial infarction, which is more of a demand situation and more atypical, so we're waiting for further data to sort that out. But I think the message is that these may be atypical occurring in young people and may lead to sudden cardiac death, and we really desperately need ways to identify those who are at increased risk before it happens and potentially treat those patients to prevent this disease.

Dr. Cheeley:
Are there other ways that you recommend or that you have seen be beneficial to help us risk stratify these folks?

Dr. Grinspoon:
Yeah. We have begun the REPRIEVE trial, which is enrolling patients for primary prevention in the pooled cohort risk equation, and that study will tell us, I think, more definitively the accuracy of the pooled cohort risk equation. There have been some retrospective studies that show that it may underestimate risk in this population. I think people are wondering whether a new algorithm can be developed that may include some measures of immune activation, residual immune function, or immune activation that may help us to predict this—for example, perhaps nadir CD4, other factors—but those equations have yet to be developed formally.

A lot of studies have shown that coronary CT angiography has identified subclinical coronary plaque in such patients. More often it's noncalcified than calcified, so I'm not sure that traditional CAC scoring would be that useful, particularly, in young patients with HIV, but it's possible, and we'll look to ongoing studies to see if we could potentially use that as may be recommended in the general population when it's equivocal what the risk is.

Other than that, it's always important because there is increased risk and because traditional risk factors do account for some of this risk—to obviously minimize those traditional risks as much as possible, getting lipids under control, hypertension, smoking, diet, etc.

Dr. Cheeley:
So let's round out this picture in terms of total cardiometabolic risk. What do we need to know about the metabolic side of the cardiovascular metabolic risk for this patient population?

Dr. Grinspoon:
Well, patients living with HIV have been known to have some metabolic derangements. Insulin resistance is common in this population. It's not clear exactly the mechanism. It was initially thought to be perhaps due to some antiretroviral strategies. I think that's less the case today. It also may be due to a relative change in body composition, such that patients with HIV may have relatively more abdominal fat accumulation and relatively less fat in the extremities, so higher waist-hip ratio, if you will, or on more fancy CT scans, the excess visceral adiposity and less subcutaneous adiposity. This can also be associated with hypertriglyceridemia, which can accompany insulin resistance and dysmetabolism, if you will, or a formes frustes of the metabolic syndrome. Typically, LDL levels are not that elevated, and we show that in the baseline data of REPRIEVE that the baseline LDL level of a large, multinational, primary prevention cohort in the modern era of ART was only 108 milligrams per deciliters, so relatively modest elevations in general. So I think checking for diabetes and insulin resistance, hypertriglyceridemic levels, looking at the waist-hip ratio as a harbinger of potential excess cardiovascular risk will be really important.

Dr. Cheeley:
For those of you just joining us, you're listening to *Heart Matters* on ReachMD. I'm Dr. Mary Katherine Cheeley, and I'm speaking with Dr. Steven Grinspoon about cardiovascular disease risk for people living with HIV.

This has been such a great conversation so far. I can't wait to keep going. Can you tell me a little bit about the differences or the

disparities between men and women living with HIV?

Dr. Grinspoon:
Yeah, that's a really excellent question. Women, at least based on the pool cohort equation, as you know, have lower risk in general than men, particularly premenopausal. If you put the same characteristics in that equation and switch it from female to male, the risk will go up significantly, so there is built into that equation a protective effect of premenopausal status in women. Interestingly, despite the lower predicted risk among women with HIV based on traditional algorithms, women may have a relatively greater cardiovascular risk compared to men. And I don't mean women compared to men; I mean women with HIV compared to women without HIV. That differential is greater than in men with HIV versus men without HIV. So the relative differential is greater among women, so we say in that regard they may have relatively greater cardiovascular risk for a given relatively low predicted risk. That is something we'll be looking at quite carefully in REPRIEVE.

Now why that is the case is not entirely clear. It may be an interaction with the sex hormones and immune activation, perhaps with lipids. We're not entirely sure why that is the case, but it is a signal that's been seen in a number of papers, including the one we published in *Journal of Clinical Endocrinology and Metabolism,* that risk ratio was significantly higher among women.

Dr. Cheeley:
If you're saying that the LDL cholesterol is not really high, we certainly can work on some of our lifestyle modifications, but what can we do to reduce risks for these patients living with HIV?

Dr. Grinspoon:
Well, I think one thing, which is natural, and I think is already being done is that it's important to get patients with HIV on antiretroviral therapy as early as possible, and that's really accepted dogma in the field already, but it's important to emphasize that; early treatment, getting people on effective ART is really, really important.

Beyond that and the measures that we spoke about, lifestyle, I think there are some potential strategies, which are being tested. One of them that's being tested in the REPRIEVE trial is whether the use of specific statin therapy may prevent cardiovascular disease. Now you may be asking, "Why are you talking about this when you just told us that the LDL is relatively normal?" And I think that's because there's an increasing recognition of the pleiotropic effects of statins, which not only may lower LDL but may also reduce inflammation and even excess immune activation, and a hint of that was seen in the JUPITER trial by Paul Ridker in which non-HIV patients with heart disease but low LDL, but elevated CRP, a measure of inflammation, were randomized to rosuvastatin or not, and they had a significant reduction in major adverse cardiovascular events, or MACE.

So I can say that REPRIEVE was developed with the theory analogous in that perhaps statins, while lowering LDL to even better levels may have simultaneous effects to improve immune activation and residual inflammation, there are other strategies, which are being talked about; more specific anti-inflammatory strategies. But I think some of those strategies while potentially effective—for example, canakinumab—that may have effects to increase infections, and so one has to be very, very careful in the HIV population to not cause more harm than good. So in that regard, I think as we examine potential anti-inflammatory strategies, one has to keep in mind that they can't lead to infections. They need to be well-tolerated, have a good uptake. They need to be inexpensive, etc.

Dr. Cheeley:
Absolutely. Before we close, I would like to know from your vantage point, how can we keep working towards better care for these patients living with HIV?

Dr. Grinspoon:
I think a lot of the work we're doing now to simply identify that this population has excess risk is really important, and that will inform the field that we should pay attention to this population. I think more needs to be done about how we may identify early this population beyond the pooled cohort equation and other traditional risk algorithms. I think we need to understand the degree to which inflammation or residual immune activation actually contributes to the excess cardiovascular disease, if statins reduce or prevent that disease, and to what extent that reduction mitigates that risk and to really just know that HIV is probably a risk equivalent. So I think we're trying to raise

knowledge in that regard, and we look toward large clinical trials to guide us in the future, but it's a really important topic, and I think it actually has implications for other diseases—for example, other inflammatory diseases, such as lupus and psoriasis—they are associated with excess cardiovascular disease, and patients with those diseases are often not targeted for primary prevention because they're often young or whatever. And if the REPRIEVE study is successful, it might suggest other studies may need to be done in those populations, as well analogous to REPRIEVE to develop prevention therapies for them. So I think conclusions that could be drawn from other populations as well.

Dr. Cheeley:
I have loved this discussion. I think we've had such a great time not just talking about how to better risk stratify and think through our patients living with HIV and their cardiovascular disease but really just continuing to do a better job, like you just mentioned, for that young patient who seemingly you wouldn't think would have a high risk but they have these other risk equivalents of these other diseases. This has been so great. Thank you so much for joining me, Dr. Grinspoon. I really appreciate it.

Dr. Grinspoon:
Thank you so much.

Dr. Cheeley:
For ReachMD, I'm Dr. Mary Katherine Cheeley. To access this and other episodes in our series, visit ReachMD.com/HeartMatters where you can Be Part of the Knowledge. Thanks for listening.