Becky Campbell: Hi, my name is Becky Campbell, and I'm the senior manager of medical content here at PCF. I'm so excited to be joined today by Dr. Ashwin Sachdeva and Dr. Noel Clarke to discuss their recent publication on the risk of heart disease-related side effects among patients treated with the newer types of hormone therapies for prostate cancer. Dr. Sachdeva, Dr. Clarke, congratulations on the publication and thank you so much for joining me today.

Dr. Noel Clarke: Thanks for having me.

Dr. Ashwin Sachdeva: Thank you.

Becky Campbell: So, I'd like you to each introduce yourself and then we'll get into the study. Dr. Sachdeva?

Dr. Ashwin Sachdeva: Yeah so I'm Ashwin Sachdeva. I'm a urologist and a PCF Young Investigator in the University of Manchester in the Christie Hospital and I'm the senior author of this study that we're going to talk about today.

Becky Campbell: Wonderful. Dr. Clarke?

Dr. Noel Clarke: I'm Noel Clarke. I'm a professor of urologic oncology at the Christie in Manchester, and I'm closely involved with the study. I'm co-author and joint PI of the STAMPEDE study on which further work from this will be based.

Becky Campbell: Wonderful. So, to get into kind of setting the stage, what was unknown about this issue prior to the study? So, what questions did you aim to answer by embarking on this work? Dr. Sachdeva?

Dr. Ashwin Sachdeva: Yeah. So, over the last 10 to 15 years, in a number of trials, such as the STAMPEDE trials, have given us really good quality evidence to show that some of the newer treatments, particularly those based on novel ways of inhibiting the action of testosterone on prostate cancer cells, such as these androgen receptor signaling inhibitors—that's what we talk about in this paper—drugs such as this have dramatically improved survival. And this is really good news, actually, and patients are living longer. They're able to do things which previously would be—they'd be very limited from the adverse effects of the cancer progressing itself.

So, this is all really good news, actually, that we're able to help our patients more with these new therapies. On the flip side, since prostate cancer is, particularly in the more advanced or metastatic setting, relies on the use of hormone therapies which suppress testosterone levels, patients are now living longer with suppressed testosterone levels. So, they're therefore at greater risk of developing toxicities or developing adverse effects associated with these treatments, and that's what our program of work at the moment is looking to establish.

So, this was one aspect of our work where we're looking at cardiovascular effects, and the reason for this was that it was sort of emerging data

suggesting that rather than patients succumbing to their cancer, there are other causes that might contribute to their eventual death, such as cardiovascular-related events. And that's what we're hoping to get a better handle of by this body of work.

Becky Campbell: Understood, and thanks for that. And Dr. Clarke, what are the drugs that you studied in this paper? Just so patients are very clear. What are the names of the medicines?

Dr. Noel Clarke: Well, we were looking at this in the broad context of androgen deprivation, as Ashwin has mentioned. And we've known for many years that ADT—androgen deprivation—is associated with an enhanced cardiovascular toxicity profile. And the drugs that we were looking at were those androgen receptor-targeting agents, the blockers such as enzalutamide, apalutamide, darolutamide, and the enzyme inhibitor which blocks ADT very successfully—abiraterone. And this class of drugs has been given in association with standard ADT. The commonest way of utilizing ADT prior to the ARSIs was with GnRH analogs, drugs like Decapeptyl, goserelin (which is Zoladex) and so on. And this is a front-line therapy which everybody uses, and one always bases it on—in the knowledge that it's necessary to use the ADT to suppress the cancer but in relation to the addition of—if I might call it "super added" androgen deprivation with a drug like enzalutamide or abiraterone, then does that add to the toxicity?

And equally, can we sub-stratify patients in otherwise—in other words, identify men who are at greater risk of cardiovascular toxicity and work out ways of treating them in a slightly different way if we can, either by dose reductions, avoiding specific drugs in certain circumstances, or actually reducing the duration to which these men are exposed to a combination of androgen deprivation with GnRH and an ARSI.

Becky Campbell: Perfect. So that's helpful background to know just what are the treatments that we're talking about. And, you know, probably some patients that are watching this have heard of these or maybe are even taking them now, and it's good to know that there are some potential solutions that I'd like to get to in a moment. Dr. Sachdeva, please tell us about this actual study that was recently published in *JAMA Oncology*, if I'm not mistaken. What was the study that you performed and what were the results?

Dr. Ashwin Sachdeva: So, in this particular study, we looked to compile information from a number of previous randomized controlled trials which were—which was primarily aimed at studying how effective these new treatments are in controlling cancer and controlling prostate cancer in particular. And from those studies, we extracted information about what was the incidence of adverse effects, particularly those pertaining to cardiovascular adverse effects. And this meant events occurring such as heart attacks and myocardial infarction or acute coronary syndrome, cardiac dysrhythmias.

So, this means things like atrial fibrillation or irregular heartbeats, which can—which—greater risk of strokes, strokes themselves, risk of getting blood clots in your legs or lungs.

So DVTs and PEs, which are deep venous thrombosis or pulmonary emboli, and also cardiovascular-related death. A more frequent event that was, already well established to occur with some of these agents was hypertension, and that really stood out in our results. And just briefly going through our results themselves, we found that cardiovascular-related events nearly double when patients are given these novel hormone-targeted agents in addition to their standard traditional hormone therapy. And this is quite important because with an aging population and the—there is an increased risk of prostate cancer.

And we are often faced with this dilemma, with regards to the patients' comorbidities, to help decide whether our treatments are more likely to do them—give them some benefit, or are they more likely to do them some harm.

So, our study really helped us understand a bit better than in trial populations, so relatively fit patients, the addition of these treatments seems to increase the risk of these cardiovascular events.

Becky Campbell: Understood. Thanks for laying that out. And, Dr. Clarke, which patients are most at risk for these side effects if they're taking an ARSI? And how would a patient know that he's maybe at particular risk?

Dr. Noel Clarke: Well, there are a couple of categories of men presenting with prostate cancer, that's those who got what we call "high risk localized disease," where they would have treatment with a combination ADT / ARSI for a relatively limited period of time—typically a couple of years.

And there are those who would have lifelong treatment, and these are patients who present with metastatic disease at first presentation or subsequently develop metastases. Now in amongst these, there will be a stratification of different population types and individuals with different disease characteristics. And the ones which we are most concerned about, I think, are those who are older, and we know that men with prostate cancer, particularly primary-presenting prostate cancer, a high rate of men presenting with an age of 75 or 80 plus. And what we know is that they tend to have an increased cardiovascular comorbidity.

So, we're looking at patients who've got established risk of cardiac failure, who have a risk—who have a history of angina, let's say, who are already taking, 1 or 2 or more cardiac medications. And these might be for blood pressure, as Ashwin has already mentioned, for cardiac dysrhythmias, for angina, and so on, and who may have had a history of stroke. And in order to get a risk profile, it's necessary to look really at what the patient's history is in terms of what's happened already and what their general fitness is. How far can they walk? Do they get upstairs? Do they go out on a cold day? And so on.

That then enables us to ask the question, well, what's the risk to this man, that he may get a further cardiovascular problem within the first 6 to 12 months of starting that antiandrogenic treatment. So, should we scale that back and just use one therapy? Should we use a different

therapy? Should we risk the use of a doublet therapy? In other words, an ADT GnRH analog therapy with an ARSI in the knowledge that the cancer is much more aggressive. And so, it's a balance between the risks of intervention—intervening with a maximal therapy, and actually scaling that back in certain circumstances in the knowledge that we might be doing more harm than good.

Dr. Ashwin Sachdeva: And—but perhaps just to put that into further context amongst a US-based population with prostate cancer, we know that two-thirds of men presenting with prostate cancer are at increased cardiovascular risk at presentation, and about half of all men presenting with prostate cancer have at least two or more cardiovascular risk factors which are poorly controlled. So, there's one aspect, which is to consider, who should we be giving these additional treatments to? And another to consider: how can we optimize these cardiovascular risk factors to be—to make patients eligible for these treatments? And help them live longer and better lives free of the side effects associated with these treatments.

Becky Campbell: Thank you both for that. It sounds like a sizable portion of men who may be listening to this or considering these therapies, they may be at risk for cardiovascular events, you know, adverse effects with—related to these medications. What are the preventive strategies that if they do decide to go on these medications and are mindful of the risks? Dr. Sachdeva, just lay out a couple of strategies that they can employ with their doctors in order to more safely be treated with ARSIs.

Dr. Ashwin Sachdeva: So, our paper really highlights that the onus is both on the patients and on the clinicians. So, hopefully, through this video today, we highlight this as something for patients to bring to the physicians who may or may not have considered these additional adverse effects and see where they can get additional input from the physicians on to be able to address. From a physician's point of view, I think we need a multidisciplinary approach.

We need the oncologists, the urologists working together with primary care physicians, with cardiologists to help best optimize cardiovascular risk factors. And this could involve simple things like getting diabetes under better control, getting your hypertension under better control. And also considering whether patients might have higher lipid levels. So—and considering the use of statins in that setting, perhaps. On monitoring patients for these risk factors over time. From a patient's perspective, one of the key things that—two key things that would help: one, to ensure that there's a well—there's a well-balanced diet, and that might reduce some of the cardiovascular risk factors irrespective of what condition they might have.

And secondly, there is emerging evidence, also suggests that the use of exercise might help reduce these cardiovascular adverse effects of these treatments.

So, I think this is something that both physicians and patients need to work together on to try and best optimize the use of these treatments and minimize side effects of these treatments.

Becky Campbell: Absolutely. Thank you for laying that out so clearly. So there's things that patients can do on their own with respect to nutrition and exercise. And we'll have some links in the show notes, obviously, speaking with your doctor or a nutritionist before you change your diet or start an exercise program.

And then, many things they can also do with their doctor to get other conditions under control. Dr. Clarke, I wanted to ask you a little bit about the context of this work in the overall…the STAMPEDE trial and some of the other work that you are embarking on, other types of adverse events and how we can better manage those with patients.

Dr. Noel Clarke: Yes, and as I mentioned, one of the important things with this kind of pathfinder paper is to uncover some of the areas which we want to get a bit more information on.

One key thing is how to predict this and can we use some of the tests which we're doing routinely in virtually all of these patients, can we get some information from those tests and identify and substratify patients who are at risk?

One way of doing that potentially is to look at the imaging. So, we have a very large imaging bank, which we pulled in from the STAMPEDE patients, to look at things such as vascular calcification and other risk factors which might be associated with the development, or increased risk of development, of an acute serious cardiac problem such as coronary syndrome, stroke, fatal MI, arrhythmia, and so on.

The other thing which we are looking at, and we've been successful in making big strides to do this, is to link the data from a large-scale trial, with the data from populations. And we're able to do that through a big healthcare system like the National Health Service in England, for example, where we can look at this at population scale.

So that's probably looking at, somewhere between 40 and 50,000 cases annually, newly diagnosed. And that equates pro-rata with a US population in relation to the size of the populations. We can get the information from hospital episode statistics so we can actually look right down at patient level as to how many people have presented to hospitals with acute coronary problems.

So we have the—on the one hand, the data from STAMPEDE, which might enable us to look at predictive risk factors, and we can cross correlate that with what happens in the trial. And then we can look at that in relation to what happens out in the general population, looking at co-morbidities even right down to weight, height, waist measurement, diabetic characteristics, lipid levels and so on. It really is very detailed. So we're very excited about this, and we think we might be able to get that to the pitch where the patient attending a doctor's clinic can just be in a position where the risk factors can be demonstrated to an individual and demonstrated to the doctor so that the patient is empowered in a way to say, "Well, I'm going to do something about my lifestyle, and I'd like a bit of help to do it. And equally, the

physician, whether that's a urologist, a medical oncologist or a primary care physician, can then give the patient advice, modulate their treatment strategy, and personalize it in a way which is to the benefit of an individual.

Becky Campbell: That's fantastic. I know, personalized medicine is kind of the present and future of cancer care, and it would be wonderful to apply it to this setting as well, when we're talking about the adverse effects of hormone treatments. Dr. Sachdeva, any last words or final thoughts for our audience today? What they can do for their next appointment, for example, or educational resources that you might suggest?

Dr. Ashwin Sachdeva: So I think the key takeaway from this is that we are getting better at managing prostate cancer. Patients are living longer. We're just trying to see what can we do to help them live better, more fulfilling lives, with a better quality of life in that period of time. And in terms of resources, the Prostate Cancer Foundation has some tremendous resources, as do a number of other charities as well.

And in particular, I appreciate that cardiovascular risk has been on the radar for Prostate Cancer Foundation for a number of years, and I would speak to your physician to get some appropriate advice in your particular circumstances to see what's best for you.

Becky Campbell: Wonderful. Well, thank you both so much. Congratulations on this publication, and we appreciate you discussing with us today.

Dr. Noel Clarke: Thank you. Becky. Bye bye.

Dr. Ashwin Sachdeva: Thank you.