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Clinical Implications of Heart Failure Trials Presented at the ACC.20/WCC Virtual Late-Breaker Session

Dr. Butler:
Greetings. The recently concluded annual American College of Cardiology meeting showcased many important clinical trials, including the VICTORIA trial, which assessed the efficacy of novel sGC stimulator, vericiguat, in patients with worsening heart failure. This trial comes on the heels of the DAPA-HF trial, which was another positive trial in patients with heart failure and reduced ejection fraction that studied SGLT2 inhibitor, dapagliflozin. Along with valsartan/sacubitril, these positive trials now increased both the medical options available and the complexity of heart failure management, which is why today we'll be examining the rational use of these various agents in patients with heart failure so we can improve their outcome and guard their safety. This is ReachMD. I am Dr. Javed Butler, Patrick H. Lehan Chair in Cardiovascular Research and Professor and Chairman of the Department of Medicine at University of Mississippi, and joining me today to explore the results and clinical implications of recent advances in the management of heart failure is Dr. John McMurray, Professor of Medical Cardiology and Consultant Cardiologist at the Institute of Cardiovascular and Medical Sciences from the University of Glasgow and Queen Elizabeth University Hospital. It is a real pleasure to have Dr. McMurray today, not only because of his expertise in heart failure, but the fact that he has actually led many of the trials that we will be discussing today. Welcome to you, John.

Dr. McMurray:
Thank you very much, Javed. Thanks for the kind introduction, and good evening from Glasgow.

Dr. Butler:
So, John, can you tell me the main results from the VICTORIA trial that was recently presented?

Dr. McMurray:
Of course. So, first of all, congratulations to Javed and your colleagues for running, uh, an incredible trial. Um, as you know very well, this was a large, more than five thousand patient trial. The patients had heart failure and reduced ejection fraction. They had been recently hospitalized – that's a very key thing that I think we'll come back to – and the primary composite endpoint was our usual composite of time to first occurrence of heart failure hospitalization or cardiovascular death, and overall that composite outcome was reduced by ten percent. That was a ten percent relative risk reduction – statistically significant. The absolute risk reduction was 4.2 people per 100 patient-years to follow-up, uh, acquiescing to a number needed to treat of only 24 patients to prevent one primary endpoint per 100 patients treated.

Dr. Butler:
So, that's, that's very good information. Now, you know, heart failure patients – we sort of used to segment them in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction…

Dr. McMurray:
Mm-hmm.

Dr. Butler:
What do you consider worsening heart failure?

Dr. McMurray:
Well, that's a very good question. So, worsening heart failure is, the term itself, explanatory, but what causes it, I think, is much less

clear. What is also clear is the consequences of heart failure worsening, and, and those are very detrimental for patients. So, I, I would say the things that we've learnt in recent years, Javed, is that, you know, there are various ways of classifying the causes of worsening heart failure. You can think of what you might call intrinsic causes, which is actually progression of the syndrome itself because it is a progressive disease. Then, there's sort of extrinsic causes that can be cardiovascular/non-cardiovascular, so, you know, pneumonia and acute coronary syndrome and non-adherence with effective therapy – taking the wrong treatments and non-steroidal anti-inflammatory – and then there are those things that I know you and I have talked about in the past that are difficult to know whether they're part of the condition itself, you know, the chicken or the egg. What we do know is – worsening is really bad – and what, and that's whether the worsening is treated in the ambulatory setting as an outpatient or whether the worsening leads to hospital admission, or I would say of all the recent things we've discovered about worsening, that's probably the most important thing. If you see a patient in your clinic or your office and they're a bit more breathless or they've got a bit more edema and you do something – you increase the dose of a drug, you add another drug – you have just identified a very high-risk patient.

Dr. Butler:
So, so just to be sure that I can summarize what you said correctly – if you get hospitalized with, uh, heart failure symptoms that's worsening heart failure…

Dr. MuMurray:
Uh-huh.

Dr. Butler:
But you don't need to be hospitalized even in the outpatient setting, if your stable medical therapy is now not enough and you're developing worsening symptoms that require some escalation, uh, that would be qualified as worsening heart failure?

Dr. McMurray:
You're absolutely right, Javed. I mean, there's no question. We've now shown this in, in several studies where we've begun to collect that information. In fact, in the PARADIGM-Heart Failure trial, an episode of a heart, heart patient worsening had the same extra risk of being admitted to hospital. Now, I don't think it's always like that, but there is a substantial elevation in risk if you have required a change in treatment for worsening signs or symptoms, and you and I probably do that in our clinics almost reflexively sometimes. You know, you increase the dose of diuretics, and there's a bit more breathless, bit more edematous – if you've done that, you've identified a patient who's in a much worse prognostic trajectory.

Dr. Butler:
So, that's very helpful. Now, when PARADIGM-HF came out about four/five years ago, there was sort of a lot of discussion whether valsartan/sacubitril, or Entresto, can be started as a first-line therapy because these were chronic heart failure patients, and they were sort of, were already on, ACE inhibitor or ARB, but now sort of, you know, more data has come out both in real life registries and in the PIONEER-HF. What is your approach? Do you consider valsartan/sacubitril only after you've given an ACE inhibitor/ARB trial? Can you use it upfront in de novo heart failure?

Dr. McMurray:
Well, we've always been able to use it upfront because, in fact, the global approval labeling in almost all jurisdictions is, in fact, that it is a treatment for HFrEF with no mention of having to use an ACE inhibitor first, although I know in, in various countries there have been various restrictions, uh, put in place about the use of sacubitril/valsartan that may limit its use, sort of, in a more restrictive way than the labeling, but we have been able to, and have been using, sacubitril/valsartan here since about 2015, I think it was, uh, quite routinely both in inpatients and in outpatients as first-line therapy. It, it, it's never really made sense to me why you would put somebody on an ACE inhibitor for a month, which would then make them eligible for the PARADIGM-Heart Failure trial, and then switch them and go through all of that inconvenience for the patients, and also recognizing, and, and I think we've now seen this both in PIONEER and PARADIGM, a very rapid onset of benefits of neprilysin inhibition. I mean, sacubitril/valsartan's two drugs. It's, it's a old favorite – a renin-angiotensin system blocker that we all know all about, but also a neprilysin inhibitor that's a completely new therapeutic approach – and, and why would you deny a patient that additional therapeutic approach that we know to be life-saving? So, that's always been my view about it.

Dr. Butler:
So, I am 100 percent on the same page with you. So, so then let me ask you a really straightforward question. We had ACE inhibitors, then ARBs and beta blockers and MRAs and hydralazine-nitrates and ivabradine and digoxin, and now we have valsartan/sacubitril and dapagliflozin and vericiguat – how do you recommend clinicians use these plethora of medications that we have?

Dr. McMurray:
So, very straightforward question, Javed.

Dr. Butler:
Ha.

Dr. McMurray:
I think, think so, heh. Well, I, I think, I think it's probably relatively easy to think about. So, we know that RAAS blockade is a core therapy, I'd say. Uh, uh, it's a pillar – one of our pillars of therapy. It's life-saving treatment. The same is true for beta-blockers; the same is true for mineralocorticoid receptor antagonists. I would say we've shown that convincingly for neprilysin inhibition. So, that's our four drugs, but fortunately three pills because, of course, sacubitril/valsartan is, is two treatments in, in one tablet, and, and then I would add to that dapagliflozin. So, those are the core life-saving therapies, and then we've got the other drugs that you mentioned that I think have a place for particular individuals. So, as you know, ivabradine we would use in patients who have a persistently high heart rate during sinus rhythm. Um, they benefit from the addition of ivabradine, so if you're on a dose of beta-blocker and your heart rate remains above 70 and you're in sinus rhythm, I think ivabradine is a very good, uh, treatment to add, and then vericiguat – I mean, I think the VICTORIA trial has shown us that for patients who have been recently hospitalized who are at a phenomenally high risk, and, and that was beautifully illustrated by the results of VICTORIA. So, I think we can probably in our minds come up with an algorithm with what you might call basic life-saving therapies for most people, and that is a combination of pills, and I know people will always ask questions about that, but we do it all the time, for example, in our acute coronary syndrome patients, you know, the statin, the beta-blocker, antiplatelet therapy, and ACE inhibitor. We have to do the same for heart failure, and then for selective subsets of patients, there are these additional treatments.

Dr. Butler:
So, this is very, very helpful and very, uh, well put. Uh, now, we also know that many of these drugs have, uh, overlapping physiologic, uh, actions, so, for instance, many of these drugs lower blood pressure. Do you choose one drug and just give them maximum doses and sort of ignore the other drugs? Do you think that we should try to use a little bit of all the medications? How – how would you approach a person with low blood pressure?

Dr. McMurray:
Well, I, I previously have really been a very strong advocate of always trying to get to the top dose, but actually as I've learned more about these drugs, and, in fact, when I look at the trials, I think what they tell me is that certainly some, for – for example, for RAAS blockers and beta-blockers, probably get most of the benefits, uh, with a moderate amount of the drug. You do get, I think, additional benefit if you go to target dose, but that's generally more for hospital admission than for mortality, and I think because these drugs work in complementary, uh, additive ways, then probably – and this is a judgment call rather than, than strongly evidence-based – but I think probably a patient is, is better off to get some of or many of these treatments working in all the different ways than, you know, just one treatment at a full dose. I don't think it makes any sense, for example, just to have a full dose of beta-blocker and not get anything else. So, I would try and get them on board, and again, as you know very well, Javed, because I know you look after a lot of these patients, actually the, the interesting thing is that often when you start to get these drugs on board, people start to improve. Actually, their blood pressure gets better, or their kidney function gets better, and that gives you then the opportunity to add more drugs and to increase the dose of drugs that they've already been given, and sometimes, you know, you can use drugs that are essentially hemodynamically neutral in their effect in very sick patients to then facilitate the introduction of other drugs that might previously have been – for example, digoxin, today it might be ivabradine. So, very occasionally, you maybe start with those drugs because you can start them, and once they start to work and the patient starts to improve, then you can start to add the, the other drugs, so life-saving drugs that you'd always like to have people on if you can get them on them.

Dr. Butler:
So, so you mentioned the word renal function, uh, as well. So, I…

Dr. McMurray:
Hahaha.

Dr. Butler:
…the same philosophy. If, uh, to choose between MRA or a RAAS inhibitor if somebody's, uh, borderline GFR – again, same philosophy – go with low doses of both rather than use one and not the other.

Dr. McMurray:
Definitely, and, uh, again, this is another example, um, where we actually have evidence and, and – and we almost forgot this, Javed – in, in the EMPHASIS-Heart Failure trial, in fact, we stratified people at baseline according to their renal function, and in people with impaired renal function, the target dose of eplerenone was only 25 rather than 50 milligrams per day, and, in fact, when we remembered this and we went back and we looked at those two strata so it's a very legitimate thing to do statistically, the patients with poor renal

function who got low dose eplerenone, in fact, got at least as large a treatment benefit as the patients with better renal function who, who had a higher target dose of eplerenone. So, that there is an example of how a tailored lower dose, with a very effective treatment, in particularly sick, sick and high-risk patients as, as patients with chronic kidney disease are, in fact had an awful lot to gain from judicious use of a drug that many doctors, in fact, would be afraid to use in, in patients like this. So – absolutely – I think I completely agree with what you said that it is careful use – sometimes it's a lower dose – but, uh, usually you can manage.

Dr. Butler:
Well, I'm afraid we are all out of time. This has been great, John – great stimulating, important discussion, and, and thank you so much, uh, uh, for being with us today.

Dr. McMurray:
Thank you very much, Javed. It was a pleasure to talk to you, as always.

Dr. Butler:
I'm Dr. Javed Butler. Thanks for listening.