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Innovative Approaches to Managing CKM Syndrome and HFmrEF/HFpEF

Announcer:
Welcome to CME on PACE-CME. This activity, titled “Innovative Approaches to Managing CKM Syndrome and HFmrEF/HFpEF” is provided by MEDCON International.
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Dr. Inciardi:
Hello, everyone. This is CME on PACE-CME. I'm Riccardo Inciardi, and I'm delighted to present the data that we recently showed at the ESC Preventive Cardiology meeting about novel therapies in managing patients with cardio-kidney-metabolic syndrome and heart failure with mildly reduced or preserved ejection fraction. I presented there, along with my esteemed colleagues, Cristina Gavina from Portugal and Giuseppe Galati from Italy.

So let's move at the beginning, understanding the burden of the cardio-kidney-metabolic syndrome and HFmrEF and HFpEF. Heart failure represents a major public health issue affecting more than 55 million people worldwide, and HFmrEF and HFpEF account for more than half of the estimated proportion of heart failure population worldwide.

This condition is also associated with a very high burden of mortality and morbidity, and this is mainly due to an increased risk of hospitalization for heart failure, which in turn is associated with an increase in risk of mortality.

As you can see on the left and on the right panel, the risk of mortality between ejection fraction categories, so between HFrEF, HFmrEF, and HFpEF, is very similar, while HFmrEF and HFpEF are more characterized by non-cardiovascular mortality as compared to HFrEF.

HFpEF is also characterized by a complex pathophysiology involving an overlapping of clinical conditions such as cardiometabolic conditions, arterial stiffness, pulmonary vascular stiffness, and left arterial myopathy. And this is particularly relevant across the cardio-kidney-metabolic spectrum, such as patients presenting more conditions are subjected to an increased risk of cardiovascular events.

These are data from the recent DELIVER trial showing an important overlap between type 2 diabetes, CKD, and atherosclerotic cardiovascular disease among patients with HFmrEF and HFpEF. Indeed, there is a continuum across the cardio- kidney-metabolic condition, moving from those at risk of developing CKM to those with overt cardiovascular disease and heart failure.

Let's try now to understand what is the management of this condition and what are the recent data from dedicated clinical trials across the CKM syndrome and HFmrEF and HFpEF.

In the last few years, there has been actually an increasing evidence of benefit of different medical treatments, in particular SGLT2 inhibitors, GLP-1 receptor agonists, and the nonsteroidal mineralocorticoid receptor antagonist finerenone, across the CKM syndrome and in patients with HFmrEF and HFpEF.

Let's start from SGLT2. SGLT2 inhibitors have been tested in many dedicated, randomized, international clinical trials among patients with heart failure, with type 2 diabetes, with chronic kidney disease. And across this condition, SGLT2 inhibitors showed a consistent reduction of cardiovascular outcomes, in particular hospitalization for heart failure, cardiovascular mortality, renal endpoint, and MACE.

Along with SGLT2 inhibitors, robust and consistent evidences have been showing the clinical benefit of GLP-1 receptor agonists across the cardio-kidney-metabolic spectrum and in patients with HFmrEF and HFpEF. This is the updated meta-analysis, including the data from SOUL and FLOW, showing a very important reduction of major adverse cardiovascular events by 14%, all-cause mortality, hospitalization for heart failure, and the composite kidney outcomes. This is regardless of the administration route, subcutaneous versus oral.

And more recently, finerenone, a nonsteroidal mineralocorticoid receptor antagonist, has also been shown to reduce the risk of cardiovascular and kidney events among patients with type 2 diabetes and CKD. This has been tested in 2 dedicated randomized clinical trials, FIDELIO-DKD and FIGARO-DKD, under the umbrella of the FIDELITY programs, where were included more than 10,000 participants with type 2 diabetes and CKD. In this program, finerenone showed a reduction, a 14% reduction of cardiovascular events, including time to CV death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure, but also showed a consistent reduction of hospitalization for heart failure, a 23% risk reduction of kidney events, and a 20% reduction of dialysis.

And recently, finerenone has also been tested in a dedicated clinical trial in patients with HFmrEF and HFpEF, under the name of the FINEARTS-HF trial, where finerenone, as compared to placebo, showed a reduction of total worsening heart failure events and death from cardiovascular causes with a rate ratio 0.84, an absolute rate reduction of 2.8 per 100 patient-years, and the time to first hospitalization for heart failure or CV death, both with a hazard ratio of 0.84.

For those just tuning in, you're listening to CME on PACE CME. I'm Riccardo Inciardi from the University Hospital Brescia in Italy, and today I'm highlighting the key messages and clinical data presented at a satellite symposium at ESC Preventive Cardiology 2025, focused on the burden and the potential management option for CKM syndrome in patients with HFmrEF and HFpEF.

So the totality of evidence regarding finerenone has been finally evaluated in the FINE-HEART pooled analysis of FIDELIO-DKD, FIGARO-DKD, and the FINEARTS, including more than 18,000 participants, where finerenone showed a marginal nonstatistical significance of CV death, although the analysis was actually significant while including the determinate cause of death, also showed a reduction of hospitalization for heart failure by 17%, a 10% risk reduction of the composite of kidney endpoint, and a 9% risk reduction of all-cause death.

There is no dedicated clinical trial testing whether taking 3 drugs is better than 2 is better than 1. But of course, we have to think about a combination of treatment in these population, and this has been tested in this interesting analysis from CANVAS, CREDENCE, FIDELIO, and FIGARO-DKD in 8 GLP-1 receptor agonist trials where the authors assess what would have been the estimated lifetime benefit of combination of treatment across the cardio-kidney-metabolic spectrum. And there was a consistent reduction of the analyzed endpoint, MACE, hospitalization for heart failure, cardiovascular mortality, CKD progression, and all-cause mortality, among patients taking the 3 drugs, or with the estimation of taking 3 drugs compared to 2, compared to 1. And this is where probably the future should move. So the management should be complete with an up-titration of the background medical therapy.

And this is what we are going to explore in the evidence, clinical practice, with a dedicated clinical case that has been shown in the last presentation, a 78-year-old man with different cardiovascular risk factors such as arterial hypertension, type 2 diabetes, hypercholesterolemia, and obesity and CKD stage 3. The patient started to complain of dyspnea in March 2023 and was admitted for acute heart failure and an exacerbation of COPD in September 2023. So the echocardiography showed preserved left ventricular ejection fraction. The coronary angiography didn't show any critical arterial coronary artery stenosis, and the patient was just discharged with furosemide, ARB, calcium antagonist, metformin, and insulin. So at admission, the BNP level was around 5000, at discharge was around 1800, so the patient went home just with the treatment of hypertension and the compensation thanks to the diuretic use.

But after a few months, in January 2024, the patient complained again of worsening of dyspnea. He was admitted again to the emergency department for heart failure determined by a hypertensive crisis. Again, there was a rise of NT-proBNP around 3000. The patient was treated for the hypertensive crisis and discharged with an up-titration of the antihypertensive medication.

But again, in March 2024, the patient was admitted again for hospitalization for heart failure, related in this case to paroxysmal AF. Again, there was a preserved, mildly reduced ejection fraction, 42%, pulmonary hypertension, and around 7000 NT-proBNP. So the patient was treated, first of all, with a rhythm control. He was also treated with an anticoagulant, but for the first time, was also treated with dedicated medical therapy for the underlying heart failure condition with SGLT2 inhibitors and an MRA and was discharged.

After this, the patient was evaluated at the outpatient clinic after a few months. The patient was pretty well in NYHA class II, preserved left ventricular ejection fraction, no pulmonary hypertension, but complains of gynecomastia. The creatinine was around 1.9, NT-proBNP 180. So was better in terms of the compensation. But due to the gynecomastia, the patient was treated in a specificated way with nonsteroidal MRA finerenone and with GLP-1 receptor agonist. This was possible thanks to the multidisciplinary team, including the

nephrologist and a diabetologist, and was discharged also with furosemide and, of course, the other medication.

So at the last visit, the patient was in NYHA class I. There was an optimal control of the blood pressure. There was an optimal control of the pulmonary pressure, with a preserved ejection fraction and an NT-proBNP of around 850, and again, the patient was continuing the treatment with SGLT2 inhibitor, with the nonsteroidal MRA finerenone, with the GLP-1, with the treatment for hypertension, ARB, and beta-blockers and, of course, with a diuretic and anticoagulant therapy.

So the take-home message is first to understand that there is an important clinical overlap of the cardio-kidney-metabolic condition with HFmrEF and HFpEF. So it's important to improve our diagnostic accuracy and to understand what type and what kind of phenotype we have in clinical practice, but also today, across the cardio-kidney-metabolic spectrum, hard endpoint, including hospitalization for heart failure, CKD progression, and cardiovascular mortality, represent, for the first time, modifiable events. And a combination treatment with SGLT2 inhibitors, GLP-1 receptor agonists, and the nonsteroidal MRA finerenone should represent the up-front treatment to reduce morbidity and mortality across the CKM spectrum.

Thank you for your attention.

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