



HEALTHY HEART

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Interventional Cardiologist



Greetings..

Things are changing very rapidly in the face of this corona pandemic. As the world grapples with the COVID-19 disease. It is equally important for us as clinicians to not forget or ignore Non-COVID ailments. It has been seen that due to the fear of the pandemic a number of cardiac, cancer and other patients are avoiding coming to hospitals with often fatal outcomes. In this newsletter, I have highlighted two pathbreaking trials presented at the just concluded ESC 2020 conference.

Hope you enjoy reading them.

LODOCO2:

ADDED STEAM FOR COLCHICINE AS SECONDARY PREVENTION

The anti-inflammatory drug colchicine picked up new support as secondary prevention in chronic coronary disease, cutting the risk of cardiovascular events by one third when added to standard prevention therapies in the double-blind LoDoCo2 study.

Across a median follow up of 29 months in more than 5000 patients, almost 1 in 10 patients assigned to placebo experienced the primary endpoint of cardiovascular (CV) death, myocardial infarction (MI), ischemic stroke, or ischemia-driven coronary revascularization. That risk was 31% lower and resulted in 77 fewer events in those assigned to colchicine (hazard ratio [HR], 0.69; 95% CI, 0.57 - 0.83).

The beneficial effect of low-dose colchicine 0.5 mg daily was seen early on and accrued over time, extending to 5 of the 8 secondary end points, including a near 30% reduction in the composite of major

adverse cardiac events, as well as reductions in the individual endpoints of MI and ischemia-driven revascularization.

"It did that with broadly consistent effects across a range of clinical subgroups, which together speak to the strength of the effect of colchicine on cardiovascular outcomes in the sort of patients we routinely see in our clinics," primary investigator Mark Nidorf, MD, MBBS, GenesisCare Western Australia, Perth, said at the digital European College of Cardiology (ESC) Congress 2020.

The results were published simultaneously in the New England Journal of Medicine.

"The totality of evidence from the big three double-blind placebo controlled trials — CANTOS, COLCOT, and LoDoCo2 — are highly consistent and should be practice changing," Paul Ridker, MD, MPH, director of the Center for Cardiovascular Disease

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Prevention at Brigham and Women's Hospital in Boston, Massachusetts said.

Massimo Imazio, MD, the formal discussant for the study and professor of cardiology at the University of Turin, Italy, also called for repurposing the inexpensive gout medication for cardiovascular patients.

This large randomized trial shows that colchicine is safe and efficacious for secondary prevention in chronic coronary syndrome, of course if tolerated," he said.

Imazio noted that colchicine demonstrated similar benefits in the smaller, open-label LoDoCo trial but that 1 in 10 patients couldn't tolerate the drug, largely due to gastrointestinal issues. The LoCoDo2 investigators very wisely opted for a 30-day run-in period for tolerance without a loading dose, and 90% of patients in each arm continued study medication while 3.4% stopped due to perceived effects.

Clinicians should bear in mind the potential for side effects and interactions with other medications, particularly statins, observed Imazio. "So monitoring of repeat blood tests is indicated, especially blood cell count, transaminase, and [creatinine kinase] CK."

Colchicine can be problematic in patients with chronic kidney disease, as it is renally excreted, particularly if patients also take some common antibiotics such as clarithromycin, said Ridker, who led the landmark CANTOS trial. "So while these

data are exciting and confirm the importance of inflammation inhibition in stable coronary disease, colchicine is not for all patients."

During the discussion of the results, Nidorf said: "We were very concerned at the outset that there would be an interaction because there is certainly literature there, particularly in renal patients. But as the data showed, the incidence of myotoxicity was decidedly rare."

Further, myotoxic episodes were independently assessed by a blinded reviewer and, although there was one case of mild rhabdomyolysis in the treatment group, it was considered not primarily due



to colchicine, he said. "So we're fairly comfortable that you can use colchicine at low dose quite comfortably with full-dose statins."

Notably, 94% of patients in both groups were taking statins, and two thirds were on moderate or high-dose statins. About one quarter were on dual-antiplatelet therapy and 12% on an anticoagulant.

In all, 5522 patients aged 35 to 82 years (mean 66 years) were randomly assigned to colchicine 0.5 mg once daily or placebo on top of proven secondary prevention therapies, and all but one was available for analysis.

Most were male (85%), one half had hypertension, 18% had diabetes, and 84% had a history of acute coronary syndrome, with an equal number having undergone revascularization. Patients with advanced renal disease, severe heart failure, or severe valvular heart disease were excluded.

Colchicine, when compared with placebo, was associated with significant lower incidence rates of the top five ranked secondary endpoints:

- CV death, MI, or ischemic stroke (4.2% vs 5.7%; HR, 0.72)
- MI or ischemia-driven revascularization (5.6% vs 8.1%; HR, 0.67)
- CV death or MI (3.6% vs 5.0%; HR, 0.71)
- Ischemia-driven revascularization (4.9% vs 6.4%; HR, 0.75)
- MI (3.0 vs 4.2%; HR, 0.70)

The incidence rates were similar for the remaining three secondary outcomes: ischemic stroke (0.6% vs 0.9%), all-cause death (2.6% vs 2.2%), and CV death (0.7% vs 0.9%), Nidorf reported.

The effect of colchicine was consistent in 13 subgroups, including those with and without hypertension, diabetes, or prior acute coronary syndrome.

"Importantly, the effect when we looked at the predictors of outcome of our patients in this trial, they related to factors such as age and diabetes, which were included in both populations. So we believe the effect of therapy to be universal," he added.



Session moderator Stephan Achenbach, MD, chair of cardiology at the University of Erlangen, Germany, however, noted that event rates were about 3% per year and many patients had undergone coronary revascularizations for acute coronary syndromes, suggesting this may be a preselected, somewhat higher-risk cohort. "Do you think we can transfer these findings to the just average patient who comes in with chest pain and gets an elective PCI?" he asked.

Nidorf replied that unlike the patients in COLCOT, who were randomized to colchicine within 30 days of an MI, acute events occurred more than 24 months before randomization in most (68.2%) patients. As such, patients were quite stable, and major adverse cardiac event and CV death rates were also exceedingly low.

"We did not see them as a particularly high-risk group, which I think is one of the beauties of this study," Nidorf said. "It looks at people that are very similar to those who come and meet us in our clinics for regular review and follow-up."

"And in that regard, I think the next time we're faced with patients in our rooms, we have to ask the question: are we doing enough for this patient beyond aspirin and statins? Should we be considering treating the inflammatory axis? And now we have an opportunity to do that," he said.

Serious adverse effects were similar in the colchicine and placebo groups, including hospitalizations for infection (5.0% vs 5.2%), pneumonia (1.7% vs 2.0%) or

gastrointestinal reasons (1.9% vs 1.8%). Myotoxicity occurred in 4 and 3 patients, respectively.

Although the signal for increased risk of infection observed in CANTOS and COLCOT was not borne out, Nidorf observed that chest infections can occur frequently in these patients and echoed caution about a potential unfavorable interaction between clarithromycin and colchicine.

"If we are to use this drug widely, clinicians will need to learn how to use this drug and what drugs to avoid, and that's an important teaching point," he said.

Limitations of the study are the small number of women and lack of routine measurement of C-reactive protein or other inflammatory markers at baseline.

SGLT2 Inhibitors in HFrEF: Putting EMPEROR-Reduced in Context EMPEROR-Reduced Trial

This is a trial of 3730 patients with heart failure and a reduced ejection fraction (HFrEF), with or without diabetes. Most of the patients had ejection fractions of 30% or less. We specifically enriched the trial for patients with more severe disease, and that distinguishes EMPEROR-Reduced from an earlier trial, also with an SGLT2 inhibitor, called DAPA-HF. Both DAPA-HF and EMPEROR-Reduced studied HFrEF in patients with and without diabetes, but DAPA-HF included patients with milder HF and we studied more severe patients. That also is evidenced by the fact that 20% of our patients were taking a neprilysin inhibitor (sacubitril/valsartan) at baseline vs only 10% of DAPA-HF patients. Otherwise the trials are very complementary.

The EMPEROR-Reduced trial randomized patients to empagliflozin 10 mg once daily or placebo for an average of 16 months. We specified only three major endpoints and they were ranked in a hierarchical manner. The first, which was our primary endpoint, was a composite of cardiovascular death and hospitalization for heart failure. Empagliflozin reduced that risk by 25%. Our second endpoint was total hospitalizations for heart failure — first and repeated events. Empagliflozin reduced that risk by 30%. The third endpoint was the slope in the rate of decline in glomerular filtration rate (GFR), and that was supported by a renal composite endpoint of hard renal events. Empagliflozin significantly slowed the rate of decline. And it reduced the risk for serious hard renal events by 50%.

We achieved success on all three endpoints. They were all clinically important and highly significant (all with $P < 0.001$). We also found an excellent safety profile — the drug was very well tolerated. Aside from an imbalance in genital tract infections, there were none of the traditional side effects of heart failure drugs — no excess in hypotension, no volume depletion, no potassium problems, no renal insufficiency issues. We were very excited about this. We think this trial together with the DAPA-HF trial are very reinforcing and complementary, and they both support the use of SGLT2 inhibitors as a new cornerstone for the treatment of patients with HFrEF.

Is This a Class Effect? How Do These Drugs Work?

The results of the trials are not just concordant with each other, but they are



also really concordant with the trials in diabetes. A 30% reduction in heart failure hospitalizations and a 50% reduction in renal events, which we saw in HFrEF, is what was seen in large-scale outcome trials in type 2 diabetes. And it's also being seen in trials of chronic kidney disease. There is an enormous concordance of data. We have more large-scale trials with SGLT2 inhibitors in different aspects of the cardiovascular disease spectrum than we have with almost any other class of drugs. I don't see any difference among members of the drug class. We studied empagliflozin and DAPA-HF studied dapagliflozin, so we do have specific data with those drugs.

A lot of questions have been raised as to how these drugs work. It's not just glucose in the urine doing this. Is it the improved renal function? Or do you believe the theory of the shifting metabolism in the myocardium?

I do not believe the theory of shifting metabolism. I don't think it's a natriuretic effect. I absolutely do not think it has anything to do with glucose lowering. I've written a whole host of papers about this in the past 6 months. What is really interesting about these drugs is that they fool the body into thinking that it is being starved. And when the body activates nutrient deprivation sensors, those exert a dramatic protective effect on both the heart and the kidneys with respect to cellular stress and cellular survival. This involves pathways such as autophagy, but it also involves autophagy-independent pathways. I really think that there is a direct, cytoprotective effect of these drugs on the heart and kidney.

Mortality Benefits

That is fascinating because we have not seen drugs like this before. Another tough question that came up with the DAPA-HF trial is about the mortality. As heart failure cardiologists, we keep believing that higher hospitalizations mean higher mortality. Now we're seeing in these trials that those two are split. Tell us about the mortality benefits in both of these trials.

In both DAPA-HF and EMPEROR-Reduced, the success on the primary endpoint was primarily driven by hospitalizations for heart failure. The effect on hospitalizations for heart failure was at least twofold greater than the effect on cardiovascular death. In VICTORIA, there was a similar pattern. At least for these classes of drugs [SGLT2 inhibitors], it may be related to the median duration of follow-up. In the VICTORIA trial the median duration of follow-up was 10 months; in EMPEROR-Reduced it was 16 months. Trials that we did in the past had longer durations of follow-up. And, of course, we expect patients who are suffering heart failure hospitalizations to in fact have an adverse lethal consequence. But from a trial design point of view, that takes time, and it's really hard to pick up that mortality benefit in trials of relatively short duration.

Are these patients going to be followed now for a longer term to take a look at what happens to mortality? I'm sure that when the blind was broken, the patients were going to be given the real drug.

I would be delighted to be able to follow these patients long term, and I think we will see a mortality difference if we were able to do that, even if patients were to

take open-label therapy. Because remember, the two groups are still different. One has gotten empagliflozin for a couple of years before the other, so I think a mortality difference would emerge. But because of worldwide privacy laws, our ability to follow mortality is limited.

NT-proBNP

I would be remiss if I didn't ask about NT-proBNP. What did you find?

There was a significant reduction in NT-proBNP at 52 weeks, but it was modest. And it was modest in the trial with dapagliflozin. I understand that some people think of these drugs as being natriuretics, but the effect on urinary sodium excretion with these drugs is modest and short lived. After about 5 or 6 days it's gone.

The kidney readjusts very quickly.

The kidney is really smart. I think that the effect we are seeing, and what has been seen in other trials on natriuretic peptides, is not the driver of the benefit on heart failure. It is the result of the effect that these drugs have on the heart; the reduction in natriuretic peptide is a reflection of a favorable effect on remodeling.

All Hospitalizations as Outcome

Remodeling may take a little bit longer to really see, but we're seeing links between NT-proBNP dropping and reverse remodeling. We're seeing that in other trials, especially with the ARNI [angiotensin receptor/neprilysin inhibitor], which is very significant. The other interesting thing about this trial is picking up all the hospitalizations. A lot of



the statisticians around the world have been moving us toward that. Before, when you and I were doing beta-blocker trials, we used the first hospitalization. Now we're picking up the total burden of the hospitalizations, which can be very significant in these sick people.

We did it two ways. Not only did we look at first and repeated hospitalizations for heart failure (so all hospitalizations for heart failure), we looked at all hospitalizations for any reason — first and repeated events. I don't think many trials have done that before. We found a significant reduction in risk with empagliflozin on total hospitalization for any reason, first and repeated events, during the entire course of double-blind therapy.

A good message to our audience here is, "I bet this is going to be in the guidelines." The new guidelines for heart failure are

being written as we journey. I can tell you that the American Heart Association and Get With the Guidelines are very interested in looking at the SGLT2 inhibitors because you can start either drug regardless of what you are doing with the whole RAAS system, because it seems to be totally independent. It's another parallel path that can be chosen; you even may be able to adjust the diuretic depending upon how the patient looks. You should not have to wait until you get somebody well [controlled] on ACE inhibitors, ARBs, ARNIs, beta-blockers, or mineralocorticoid receptor antagonist to start these drugs. We're even hoping that the primary care [providers] are going to start to look at this earlier, because right now it seems to me like it's only been given to the patients with diabetes. But the data are so powerful in the nondiabetics, and that has been seen pretty much across the board.

I completely agree. In terms of adoption in

clinical practice, it's really worth noting that both dapagliflozin and empagliflozin are one dose given once daily, not requiring uptitration, and not replicating the adverse-effect profile of other drugs for heart failure. This fits very nicely into our current regimen.

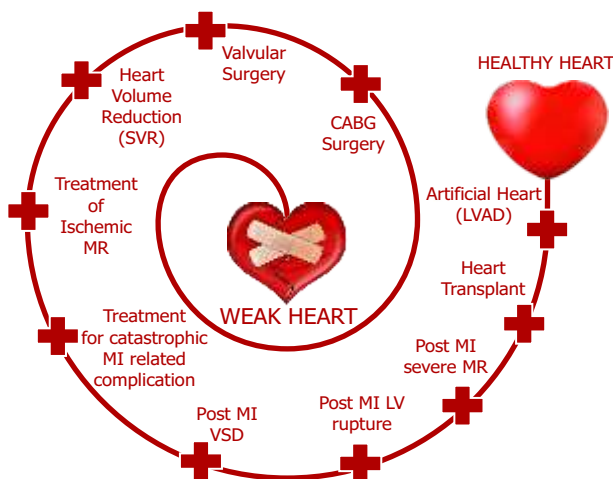
Renal function is so important. Everybody looks at the creatinine, and if it bumps up, they stop the drugs. This therapy may actually be beneficial to the kidney. Certainly, slowing down the decline in GFR is a big deal.

It's a big deal. This is the first heart failure trial that has ever seen a 50% reduction in major renal events. That is unprecedented.

Think about it: It may even then give you room to go ahead and uptitrate the RAAS inhibition that you still need to do anyway, because it almost feels like the kidney is more protected.

The future appears bright.

ARE YOU SUFFERING FROM HEART FAILURE ?



Heart Failure, also called Congestive Heart Failure (CHF), means your heart does not pump blood as well as it should. This does not mean your heart has stopped working, but it is not as strong as it used to be and fluid builds up in the lungs and other parts of your body. This can cause shortness of breath, swelling in the legs, feet, and stomach. Heart failure starts slowly and can get worse over time.

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