**Title: ESC 22: ACT: Anti-Coronavirus Therapies to Prevent Progression of COVID-19**

**Participants: Dr Sanjit Jolly**

**Date: 29th August 2022**

**Dr Sanjit Jolly**

"- My name is Sanjit Jolly. I'm an Interventional Cardiologist and Professor of Medicine at McMaster University in Hamilton, Canada.

**Study Design and Accommodations for Uncertainties in Protocol**

I'm going to take you back to the spring of 2020. And we were a group of cardiology researchers who were hearing stories from Italy and the catastrophe that was happening, patients were getting crash into intubation ventilation. They're running out of ventilators and patients were dying of COVID-19. All our cardiology trials had stopped and we pivoted to do a COVID-19 treatment trial. And we actually did a series of trials, an outpatient trial trying to reduce the load of hospitals, try to prevent hospital admission and death, and an inpatient trial to try to reduce mechanical ventilation, death, high-flow oxygen because we knew that those things were actually very, very important. And we understood from what we knew then that the pathophysiology, there were two important mechanisms of COVID-19. One was the inflammation. The inflammation was very, very important. And second, thrombosis, most patients who were dying were having microvascular thrombosis in many of their organs. So we designed a trial to target those specific mechanisms.

**Data**

So the outpatient trial, we tested two therapies. It was a randomised trial where there were two randomizations, about 4,000 patients, aspirin versus control to treat thrombosis and colchicine versus control to treat inflammation. And what we found for the primary outcome for colchicine which was hospitalisation or death there was absolutely no effect for colchicine compared to control. And for aspirin, when we looked at thrombosis as well as hospitalisation or death, there was no significant effect with aspirin and so it's really clear, you know, that both these therapies should not be used for the treatment of COVID-19 in outpatients. In the inpatient arm, I think it's important to note that most of these patients were hospitalised but not in the intensive care. 80% were on oxygen. Again, we targeted the same two mechanisms. For inflammation, we used a higher dose of colchicine, a loading dose that had been previously known to reduce IL6 acutely as well as maintenance dose for 28 days. And then the second randomization was different. It was a combination of Rivaroxaban 2.5 milligrammes twice daily, as well as low dose aspirin versus control. We randomised 2,500 patients. And what we found was for the primary outcome of need for high-flow oxygen, mechanical ventilation or death there was no difference between the colchicine arm and the no colchicine arm. And when you looked at mortality about 1/5 of patients died in the trial so mortality is still very high, but colchicine did reduce it. We looked at aspirin and Rivaroxaban, in fact, again the primary outcome of major thrombosis, death, mechanical ventilation or high-flow oxygen was not different and mortality was not different. And so, again, despite a lot of the hyper on anticoagulation, we did not find a benefit from aspirin and Rivaroxaban together. To put this research into context, we actually did a updated meta-analysis and you look at all the available trials of colchicine and there was some trials suggesting potential benefit, it's completely neutral for mortality. The story is a little bit different with anticoagulation. When you intensify anticoagulation, you do reduce venous thromboembolism by about 40%, but that reduction in venous thromboembolism doesn't translate into a reduction in mortality, but it also increases bleeding. So it's really this interplay. I think the conclusion is is that we should not be using colchicine in hospitalised patients with COVID-19 and Aspirin and Rivaroxaban were not beneficial and really need to think about the risk versus balance with regards to intensifying anticoagulation.

**Comparison to Existing Evidence on Colchicine in the Treatment of COVID-19**

Yeah, and I think the meta-analysis really puts into context. We had hoped, I mean, there were signals of benefit in the cold COVID trial and the cold Corona trial and outpatients that maybe colchicine was a inexpensive way and widely available way to improve outcomes, but that wasn't the case. And the meta-analysis now clearly shows that it doesn't work.

**Impact on Clinical Research and Care**

I think it's really important for, we've really seen the event rates drop over time. So certainly these variants have less morbidity and mortality associated with them. But when patients get hospitalised, they're still very sick. So we really need to focus on therapies that reduce mortality and that are really widely available to the entire world not just Western high income country. So I think we still need to search for therapies. Steroids is probably one of the most important innovations in the treatment of COVID-19. And we need to find further therapies that can reduce mortality and the need for mechanical ventilation in COVID-19.