Title: COP-AF: Colchicine for Perioperative AF
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Dr David Conen

"My name is David Conen. I'm a cardiologist and scientist from the Population Health Research Institute in Hamilton, Canada, affiliated with McMaster University, where I'm also an associate professor.

Rationale Behind Trial

So most patients undergoing major noncardiac thoracic surgery have a high risk of cardiovascular complications. Two of the most common cardiovascular patients that you observe in these patients are perioperative atrial fibrillation and myocardial injury after non-cardiac surgery, which is defined as either a myocardial infarction or a troponin that is elevated due to an ischemic cause. These complications occur in about 10% of the population for atrial fibrillation and 20% for myocardial injury. So these are common complications. There's currently no approved treatment that can safely reduce those complications, and therefore finding new treatment approaches to try to prevent these complications is a major clinical need.

Why Colchicine?

So both complications that we just mentioned, AFib and myocardial injury, have been shown to be associated with higher levels of inflammatory biomarkers in previous studies. And therefore, we thought that treating these patients with an anti-inflammatory drug would be a promising strategy. This strategy is also supported by previous data showing that colchicine has reduced perioperative atrial fibrillation after cardiac surgery in several relatively small but consistent randomized trials. And there have been two major large colchicine randomized trials in patients with coronary artery disease showing that colchicine was able to reduce ischemic events like myocardial infarctions or strokes in patients with coronary artery disease. So, based on this background, we thought that taking colchicine, which is an established anti-inflammatory drug in clinical

practice for gout, pericarditis, and other inflammatory disorders, would be a good strategy.

Patient Population

Okay, so COP-AF was designed to enroll patients after major thoracic non-cardiac surgery. We chose this population because they have a high risk of complications, as already mentioned, and we included patients who were at least 55 years old, who did not have a previous history of atrial fibrillation or taking antiarrhythmic medications. We excluded some minor surgeries. We also excluded the patients who had contraindications to colchicine or patients who needed colchicine, and then came up with a trial population that was randomized one to one to either colchicine 0.5 milligrams, twice daily or placebo. There was a blinded trial, so all the involved personnel and patients were not aware of the study treatment assignment. The first dose was given on the day of surgery, within 4 hours before surgery, and then was continued for a total of ten days, twice daily. And the total follow-up of the study was two weeks.

Key Findings

So we enrolled 3209 patients across eleven countries, 45 sites. We found that the first core primary outcome of clinically important atrial fibrillation was not significantly reduced with colchicine. There was a trend with a hazard ratio of 0.80, but confidence intervals crossed one, and the p-value was not statistically significant. A similar finding that we observed for Mins the second core primary outcome where there was an 11% relative risk reduction. But again, confidence intervals crossed one, and the p-value was not statistically significant. Very similar findings for all the secondary outcomes, which was mainly a composite of several ischemic complications or Mins not fulfilling the definition of myocardial infarction. All these outcomes went in the same direction with usually hazard ratio consistent with the primary outcome, but none of these were statistically significant. When we did some postdoc analysis combining, for example, the two core primary outcomes Mins and AFib in one single outcome, we found a significant reduction of colchicine for this outcome with a p-value of 0.02. There were some other post hoc analysis that were also statistically significant, but the primary

outcomes were not. From a safety perspective, colchicine was very well tolerated, there were few discontinuations of the study drug, and we found that sepsis infection was not increased. However, there was an increase in the risk of noninfectious diarrhea. Patients with colchicine had a 6% absolute increase in the risk of noninfectious diarrhea. Those episodes tended to be benign and temporary. For example, there was no increase in the median length of stay among those who had diarrhea versus those who did not have diarrhea, and there was only one hospital readmission for diarrhea in all affected patients.

Next Steps

So next steps, given that we found this very promising and consistent signal that is also very consistent with the findings that were observed in the large previous trials COLCOT and LoDoCo II. We think that colchicine does have the potential to prevent ischemic events after non-cardiac surgery in general, and so I think we do need more studies in this area. We do need to probably do a larger trial because our trial was slightly underpowered with a lower than expected event rate, especially for the AFib component. And we probably need to tweak the sample size and patient characteristics a little bit to try to come up with an even better patient population and then hope that we can show that colchicine actually really reduces postoperative complications from a cardiovascular cost. Because, as I said initially, this is a really important clinical need. These patients have a very high risk of complications that are much higher than, for example, patients with chronic stable or atherosclerosis. And therefore we do think colchicine has a promising footprint that we just need to further explore."