#255 Hotcakes: Colchicine, CAD, Gout & Knee OA

Mon, 2/8 3:57PM • 47:34

SUMMARY KEYWORDS

patients, physical therapy, Paul, study, trial, primary outcome, nsaids, gout, hotcakes, important, steroid injections, rahul, naproxen, people, michael, guidelines, injections, bias, laughter, changing

SPEAKERS

Matt, Everyone, Blank, Michael, Stuart, Paul, Rahul

Matt 00:00
Welcome back to the Curbsiders. I'm Matt Watto here without Stuart Brigham tonight, but the great Paul Williams is with me. And this is Hotcakes. So he's going to tell you what we normally do on the show, then what we're doing tonight and a little bit about our guests.

Paul 01:05
Great. Thanks for that, Matt. As a reminder, ordinarily, we are Well, I mean, we're always the internal medicine podcast. But usually we use expert interviews for your clinical pearls and practice changing knowledge for these Hotcakes episodes. The experts are kind of us there really, there's only one expert here and that's Rahul. And then he just kind of drags us along on his coattails for which we are eternally grateful. So we are joined by Rahul Ganatra.

Rahul 01:25
No, no pressure.

Paul 01:27
We are also lucky to be joined by Dr. Michael Sternberg, who is a currency president VCU and a future cardiology Fellow at Virginia Tech Carilion clinic in Roanoke, Virginia. Michael, thank you for joining us.

Michael 01:37
Thanks for having me.

Matt 01:41
So Michael, you're going to present an article later, but first, we got to start off with a pick of the week from Paul and then I think Rahul has a fun animal fact which I will tease I know everyone's gonna be holding their breath until we get to that. So yeah, I have a pick of the week I am choosing the EP that is yet to be released. I'm going to pull Stuart with a pick of the week for something that I'm not entirely

sure what its entirety looks like. But it's based on a single release an EP so that the EP and the single are entitled "Imposter" by the artist Miss Grits who is the stage name of the artist Margaret Stone. It is it's been years since I've been this excited about new song like it is it is, she sort of has this 90s kind of old sensibility and the sort of ethereal of sort of pop stuff but also a lot of fuzzy guitars and she plays a lot with dynamics and sort of Sonic textures and stuff like she's like she's like she was designed in a lab to make music that is right up my alley. Like there's the song Imposter at like two minutes and 30 seconds in. Like I think I feel my soul leave my body Every time. I was doing it is just one of the best things I've heard. So just on the basis of that single song, I'm gonna recommend the Miss Grit EP Imposter and then the single off of it also named Imposter. So check that out if you're in if you're in need of new music.

Rahul 02:53
Paul, I feel like what I listened to is Elevator Music compared to you is just the most vivid description of a song I've heard in a long time.

Matt 03:03
I think you may be in the wrong career Paul, I'm not

Paul 03:07
my patients - my patients tell me that every day

Matt 03:11
Michael, I feel sorry for you having to follow Paul with a pick of the week but did you have a pick of the week we do not expect you to be half as eloquent as Paul is no one ever is.

Michael 03:20
Yeah, that's a tough act to follow. I do have a pic of the week though. It is a TV show Netflix series called Peaky Blinders back from around 2015. It's about a British crime family called the Shelby family right after the end of World War One. And it's not for the faint of heart. It is it's an intense show. But the main character who's played by Paul Anderson is just captivating and my wife and I cannot stop watching the show. It's fantastic.

Matt 03:47
Well to lighten things up after that slightly grim recommendation. Rahul, can you tell us what's happening with dogs these days? Okay, so

Rahul 03:56
Okay, so I tried to keep my finger on the pulse of the COVID-19 literature and on the sort of general interest dog literature. So I was very pleased to have those two Venn diagram circles overlap this week. So the Miami Heat, people may have heard about this in the news, are trying to figure out how to bring back fans to American Airlines Arena. And they are taking advantage of a strategy that we have actually talked about on a prior episode of this show. And that is using COVID sniffing dogs to screen fans for COVID-19 who want to come into the arena. So there's like, you know, news coverage about this. And I don't know anything about the details, but what I see in the news is that they're basically

going to have people line up in a dog that is trained to sniff out COVID-19 is going to walk past them. And if the dog walks past you that is, you're all clear if the dog sits down, that means they've detected the sense and you need to isolate and get tested. So I'm really excited to I know we talked about this kind of as well. One thing, and I'm excited to see that, that somebody's going to try this. I hope they're studying it to see if this like actually works.

Matt 05:06
I think we covered something similar like, like maybe six months ago, and there was I want to say it was at like, somewhere in Philadelphia, even they were doing this might have been at Penn. They were they were trying to teach dogs to sniff out COVID. Just, like does COVID smell like anything? That's my question. But I because there was another article that that one link to that said that it was in, I think the airport in somewhere in Europe, they were like having people wipe their skin with like a wipe, and then they put it in a jar and then they let the dog sniff it. And if the dog like scratches the jar or sits like does there's a couple different signals the dog could give. And if that happens, then that person not getting on a flight.

Michael 05:46
And then who's sniffing the dog? Who's checking if the dog has COVID?

Matt 05:51
 Yeah, yeah, this, this seems, I mean, it's great. It maybe it if it works. It's great. It's better than someone swabbing your nose. Although, I think if you I think there was some mention of like, maybe confirming with a PCR test or something like that.

Paul 06:07
That's a good idea

Stuart 06:08
Yeah

Rahul 06:09
What could possibly go wrong? Laughter

Matt 06:10
What could possibly go wrong? Laughter. Paul, can you start us off we so we have three articles tonight, I want to tease it, we are going to be talking about low dose colchicine for gout, which you're used to, and for chronic coronary artery disease, which maybe you're not used to if you're if you're like me, that wasn't quite on your radar too much. So but first, we're going to talk about chronic osteoarthritis of the knees. Paul, can you tell us about your article and then we'll dig into it?

Paul 06:39
Yeah, I'm excited about this one. It's a little bit old at this point, relatively speaking. So this is "Physical Therapy versus Glucocorticoid Injection for Osteoarthritis of the Knee by Daly Allen at all. And apologies if I mispronounced that in New England Journal medicine. And this is from April 9, 2020. And

if you'll recall around that time, other things were happening medically, that unfortunately, sort of overwhelmed the literature. So this this all this excitement about knee pain kind of got swamped under like hydroxychloroquine. dexamethasone, and there's just other news that unfortunately buried this, but I feel like in primary care, we deal with knee pain all the time. And the question that they wanted to answer is how do glucocorticoid injections and physical therapy compare in terms of efficacy for managing patients who have osteoarthritis of the knee? So I think before I even get into the article, I did want to ask you all just sort of what your how do you choose who gets what I guess so when a patient walk into your clinic or limps into your clinic and says that their knees killing them? They have all the all the stigmata OA. How do you choose which patient will get referred for an inter articular injection or physical therapy? Or both? Do you have any kind of algorithm? Is it based on Gestalt? Like how are you picking?

Matt 07:47
So Paul, this, this happens most days when I'm in clinic, someone has knee pain. And once I find out what they've tried, if it's the person that's already tried NSAIDs and muscle rubs, and they've, they've already been to physical therapy, and they've done topical and NSAIDs and ice and heat and all this stuff, and they're basically all the normal things that I would suggest, then I, then I will often send them to orthopedics. And usually orthopedics is doing their own x rays. And oftentimes, we're starting to work them up like does this person need a surgery, and oftentimes before someone gets a surgery, they'll end up getting an injection. But I do run into a fair number of patients that just do not even want to try physical therapy, they're like "I tried it once it doesn't work." Just give me the drugs. Like that's basically what they're saying or give me the injections.

Michael 08:40
I agree, man, I think people have really, really strong feelings upfront about physical therapy, which sometimes is, is quite surprising.

Matt 08:47
It is

Paul 08:48
Oh, you're setting me up beautifully. Laughter This is exactly the point that I want to make. I think that's exactly right. And a lot of the time how I choose at least at the initial branch point is who's willing to undergo physical therapy versus who would actually sort of like the quicker relief and it's, I've often sort of struggled to have that, that conversation. And basically, I pitched on willingness. One of the reasons I was interested in this article was to see if I had any evidence, I could then add into my discussion my informed decision making with the patient. So that was the thing that got me excited about this. So just for context, the ACR guidelines actually give in particular stories, a strong recommendation based on short term efficacy. And they also recommend I think, against manual therapy. So the most recent guidelines for 2019 that we have learned a little bit more towards particular steroids and they actually seem to happen far more often than PT for knee pain. And even the referrals for physical therapy for knee OA, at least I should say, have been declining over the past couple of years. It's a really, it's an interesting timing is interesting study. So as I mentioned, this is the big question is how does physical therapy compared to steroid injections really at the knee? And this is a design This is a pragmatic,

randomized control trial so it's I don't know that you can do Sham physical therapy, which is something I thought about

Matt 09:57
Yeah, that I know you can do Sham acupoint puncture like patients blindfolded and you pretend to press on the spot, but I don't know.

Paul 10:04
Yeah. So I don't know, it'd be fun to mess around and pretend like you're doing PT and then see if that actually makes a difference. But I guess this study for a different day. But basically, this was this was patients who were recruited from a military health system. So patients and their families, they had to be aged 38 or older. And they presented to one of the two large military hospitals, and they had to have a diagnosis of osteoarthritis by two different criteria by clinical criteria, and then also by radiographic criteria as defined by something called the Kallgren Lawrence grading system, which I have no familiarity with, but it goes from no evidence OA to large osteophytes, and significant joint space narrowing and that kind of stuff. And I think even that inclusion criteria are interesting, we can talk about that. But any case, before I get bogged down, these patients were recruited from primary care offices, and then also for some physical therapy clinics. And so the way they got these patients is if their primary care doctor refers them to orthopedic surgery, or PT, or they presented to a PT clinic, then that's how they actually got recruited into the trial, which I think is, is interesting. So the decision had already been made, the die had been cast, and then these patients were recruited to be randomized into either PT or steroid injections. So I'll be curious to know what Rahul thinks in terms of if there's a possible introduction of bias there at that point.

Rahul 11:15
Yeah, I mean, this is one of the only sources of bias towards in effect that I could really find in this study, is the fact that a large proportion of the study population came from a setting where you would expect patients pursuing physical therapy are going to be, you know, intrinsically motivated and interested. And I believe that that's going to address their problem. So that I mean, patients had to be willing to undergo corticosteroid injection, if they were randomized to that group in this study. So they were at least willing to do that. But it does make you wonder if you know, the fact that a third of the patients were recruited from physical therapy visits, could have introduced a source of bias towards ineffective physical therapy.

Paul 11:58
Yeah, right. Exactly. Yeah, they were already sold on it, apparently, to the extent that they actually showed up at the door. So it's Yeah, I wonder if there wasn't some bias there, which I think is okay, we'll talk about that. But any case, the patients were randomized to the steroid injections, they were seen at four months in nine months, and they could receive up to three injections, if that's the path that they were randomized to, or for physical therapy, they got manual therapy, reinforcing exercises, stretches, that kind of stuff. And they underwent a treatment over the initial month or so. And then they get additional sessions at four months in nine months. And so they actually had three potential courses of physical therapy. And both groups had education about sort of self-management of their osteoarthritis too, which is also kind of an interesting feature of this study, I think probably worth noting,

quickly is that the mean age in both arms, the patients are about 56 years old. The physical therapy group, actually, after the randomization, interestingly, had worse symptoms at baseline and probably more significant radiographic evidence of disease, but their baseline WOMAC score, so the score they actually used to judge effect was the same for both of those groups,

Matt 13:00
and the WOMAC score that includes pain, stiffness, and physical function.

Paul 13:06
Perfect. Yes. Thank you for that. And that. That's exactly right. And that's the main outcome that they were looking at one year. That was the primary aim.

Matt 13:12
Yeah. And 108 is like a middle tier score, because I think it goes zero to 240.

Paul 13:19
Yep. Yep. And then if you're looking at changes, then a difference of 12 to 16 is considered significant if I earn a change of 12 16% percentage are significant. Yeah, they also looked at other stuff, too, they looked at some functional tasks, they did the Time to Get Up and Go test, they did something called an Alternate Step Test, which I hadn't heard before then also, this global rating of change, just to determine how much the patients felt that they had changed from baseline to the end of the study. And those are all secondary analyses, as well as cost analysis, which in the wash turned out to be the same. Any questions or thoughts? so far? I feel like this part was actually relatively straightforward, even though I said a lot of words there.

Matt 13:54
Laughter Yeah, so adult patients, they had pretty much similar baseline knee pain scores. Seems like they were, you know, medium high scores 180 out of a score of 240. And what was the outcome? Like? How long did they follow the patients, Paul? And what was the primary outcome?

Paul 14:12
Yep, so the primary outcome that they were excited about was at one year, the WOMAC scores were 55.8. And recall, this is from a baseline of 106, for the intra articular injections and 37 in the physical therapy group. And so there was a significant difference between those scores of about 19 points. So that's a p value for what it's worth of 0.008. And then the secondary outcome, the patients had better functional testing scores, though they didn't comment too much about that. Overall, there was actually the persistence in effect is interesting, in that it persisted. The fact that it was better at one year for both physical therapy and inter articular. Steroid injections actually contradict in prior studies where the effects were thought to be more in the short term. The fact that we were seeing both last the full year was interesting, and they had some thoughts as to why that might be. But the big, big ticket item is that the physical therapy did better significantly better than interarticular steroid injections, though both showed improvement at one year when they followed up with these patients. Yeah, this was this was surprising, Michael, were you to say?

Michael 15:09
Yeah, I think the length of follow up here is one of the really big benefits of this study compared to some of the other short-term studies that they mentioned. And also the fact that they, they, you know, offered additional steroid injections, additional PT at preset points throughout that year.

Matt 15:24
Yeah, there was a lot of like touches with the health care system. I think the patient education, they mentioned, the authors were speculating that because they had so much contact with the healthcare system and patient education was given that these patients may have felt more like self-efficacy from that. And maybe that's why their pain scores were better in both groups than you might have expected from previous.

Paul 15:48
That's like, Oh, go ahead.

Rahul 15:49
I was gonna say that's a really important observation, Matt, because the sort of intensity of the exposure to the intervention in both groups was relatively high. They completed a mean of between 11 and 12, physical therapy visits over the course of the year, which is, is quite a lot. And then the patients who were randomized to the corticosteroid injection, they completed a mean of between two and three injections per patient. So kind of a high intensity exposure. I

Paul 16:16
I think the other thing and again, this is not and not imputing. I'm sure everyone's intentions are pure as the driven snow, but the actual the physical therapist who provided the treatment, if I'm understanding the trial correctly, we're also investigators in the trial. So I feel like that they were they probably had a fair amount of investment in the success of physical therapy. And we're sort of like that, I think that they have physical therapy in their hearts and souls. Already, though, again, I'm sure I get I'm not sure that has any significant impact on the trial. I thought that was an interesting point.

Matt 16:41
So this was we went through the question, the comparison, we're just talking about the results. And this was a positive trial, right, Rahul, because the physical therapy showed that there was benefit over the steroid injection? So we need to look for potential sources of bias, which we started to talk a little bit about Rahul, for you, what was the? Was it just this recruitment issue? Is that the main source of bias? Were there any other big, big glaring things?

Rahul 17:09
Yeah, I like this framing, I think that, you know, looking for reasons why a study where a difference is shown could be explained by bias or chance is really important, because that is kind of the most accessible way that you know, practitioners like you and I can sort of try to minimize the likelihood of being fooled by something that's not real. So for this study, that showed a benefit of physical therapy, as manifested by a larger decrease in the WOMAC score at one year, we already talked about one source of bias towards in effect, and that's, you know, recruiting patients from physical therapy clinics, I

would welcome you know, observations, if anybody has any ideas for more, I could identify two sources of bias towards a null finding in this study that actually kind of increase my confidence in the reality of this finding. And I'll tell you what they are. The first one is that the degree of crossover between the two groups, I think we tend to bias towards there being no difference between the two. And I think the amount of crossover is also informative. It was twice as many people in the injection group crossed over to physical therapy, it was like 18%, and 9%. And to me, that suggests that that was because their symptom control was worse. So they were looking for other effective treatments. And that's something I think would tend to bias towards the null. And then the other source of bias towards the null is something that Paul mentioned in the very beginning, which was just due to chance, you know, we got unlucky with the randomization and patients in the physical therapy group had more long-standing disease by about a year, they had more frequently reported symptoms of swelling and locking and the knee giving way. And they had slightly worse radiographic findings. So if anything, I would expect those patients to do worse, regardless of what treatment they get. And because there happened to be more patients with severe disease in the PT group, I would expect that to bias away from a benefit of PT.

Matt 19:03
One thing to mention about the duration of symptoms just for clinical practice here, these patients had in the steroid group, they had 85 months of symptoms, and in the, in the physical therapy group, 100 months of symptoms. So these people, these people had symptoms for quite a long time, and going on a decade before they were in this group. And so to refer someone that's had a decade of knee pain to physical therapy is not something like usually, maybe you do that early on. So I think that's something that this definitely for me is going to change practice as far as referring more patients to physical therapy having this to point to and not everyone wants steroid injections there. They're not particularly hard for patients to get though if they want them. You refer them to a clinic that does them. They'll get their x rays; they'll get their injections. But I think this is something we shouldn't leave unturned. So Paul, is this Practice changing for you. And how many hotcakes would you give this?

Paul 20:03
Yeah, we're talking a little bit before. Like, I think, if I'm understanding this study, right, that patient selection is actually bizarre. It's a sort of very unique subset has its patients, as you see above long-standing pain have X rays on file, but have not had recent physical therapy or injections in the past year. Those are exclusion criteria. But despite all that, like I think this is, it's a positive study, I thought it was really actually well done. And I'm happy to have something in my armamentarium to sort of add to the argument that yes, physical therapy is gonna be helpful for you. And we should give this an effort. So I think I'm gonna lean more heavily into it. So I think it is practice changing and based on that, I will give it a four and a half stack. I will play along and say, this is what we do four hotcakes and maybe a pad of butter and some syrup.

Matt 20:43
It's that's four out of five hotcakes. So that is high praise coming from Dr. Paul Nelson Williams. So with that, Michael, can you tell us about your article, we're gonna Now move into talking about culture seen two articles. Michael, you're yours is first. So let's hear about it.

Michael 21:00

Alright, so my article is called Colchicine in Patients with Chronic Coronary Disease. This is also called the LoDoCo2 trial. And it was published in the New England Journal of Medicine in November of 2020. And the question they asked was "does low dose colchicine prevent major adverse cardiovascular events in patients with chronic coronary disease," and they followed these patients for 28 months. So this was a randomized, controlled, double blind trial of around 5500 patients. And they spanned an age from 35 to 82. They had stable coronary disease, and this took place in Australia and the Netherlands. So these patients were randomized to either colchicine 0.5 milligrams per day versus placebo. And this took place after a one month running period to make sure that the patients could tolerate colchicine without too many side effects. So if they tolerated colchicine after a month, then they were divided into placebo or 0.5mg of colchicine per day. The trial excluded patients with moderate to severe chronic kidney disease, severe congestive heart failure, or valvular heart disease, or a known intolerance to colchicine. So overall, this was a very positive trial, the patients taking colchicine had a decrease in the primary outcome, which was a composite outcome of cardiovascular death, myocardial infarction, stroke, or and ischemia driven revascularization. And so 6.8% of the patients in the colchicine arm experienced the primary outcome, whereas 9.6% in the placebo group experienced the primary outcome. And this came out to a hazard ratio of 0.69 and a relative risk reduction of 31%. So a really robust effect here.

Matt 22:55
I would say that first of all, I just like to say "LoDoCo" - come on, Paul. Great name.

Paul 23:01
I was just gonna say I think, is it really because I was just gonna say, I think this trial more than anything tells us that the cardiologists have finally exhausted Roman god, names,

Matt 23:10
I'm just gonna now in clinic, I'm gonna be like, so what do you want to do for this patient? LoDoCo? Laughter

Michael 23:15
LoDoCo

Paul 23:16
For locos? Laughter

Everyone 23:17
Laughter - No, yeah, right.

Matt 23:19
Rahul is this is a schema driven revascularization a typical part of the composite of major adverse cardiac events. I know they put revascularization in there I just that ischemia driven revascularization does that mean they, they revascularize them and there was actual evidence of ischemia as opposed to just they just got a stent, just because they felt like putting a stent in.

Rahul 23:42
So really important question. And important observation, I interpreted that to mean that that was patients who basically had unstable angina and then needed to get revascularize. That setting, so when

Matt 23:54
So it wasn't an MI?

Rahul 23:56
Correct, and they did, you know, another important thing to you were kind of laughing about, you know, the specific definition of this, but it's an important point that you bring up, which is, you know, verifying that the original primary outcome in any positive study, you know, verifying that the original primary outcome is the same as the current. And if there's any changes that you kind of understand why. it's really important, because you want to make sure that, you know, we haven't kind of shopped around for a primary outcome, a combination of things that, you know, gives us the effect that we're hoping for, and so the outcome was changed. They say the manuscript a few times in this study, but in my opinion, they did a good job of explaining why they did this in the protocol. And they were basically trying to maintain consistency with other publications in this area. So important point.

Matt 24:44
Yeah, because I saw that I was like, that seems like a red flag changing, changing primary endpoints multiple times,

Michael 24:51
several times, yeah.

Matt 24:53
And Michael, from what I remember from this, reading this article, this is not one of those ones, where it's like, oh, yeah, they gave you a composite outcome, and like there's death and MI and stroke all these scary things. And then it's like it's made that the difference is all driven by one other primary one of the composites that we don't care about. But in this one, I think, when they looked at all the composites, like, everything seemed like it was favored by LoDoCo. Is that...

Michael 25:17
Yeah, they really saw a benefit from each component of the primary outcome. Absolutely. Yeah.

Matt 25:22
Which in sometimes they try to hide it, you know, they try to be like, Oh, we had a great effect on our primary outcome, and then you, then you dig into it, and you're like, Oh, it's just this one thing that I don't even care about.

Paul 25:32
It was just all heart failure, all day.

Michael 25:34

One. One interesting thing about this article that maybe Rahul can comment on is that the primary and the secondary outcomes are very similar. The primary outcome is this composite outcome of MACE that we talked about. And then this, the main secondary outcome is composite of cardiovascular death, spontaneous MI and ischemic stroke. Why would the authors have such similar primary and secondary outcomes?

Rahul 26:00
Yeah, another important question. I'm not sure I have a good straightforward answer to this, you know, to try to tease out as Matt was saying, what is the driver of you know, a difference in a composite endpoint that we're seeing, that's an important function of, you know, testing each of those individually. And they sometimes do see investigators do subsets of the primary outcome. In in this study, the only thing, the only point I'll make about this is the authors did something that I think is quite responsible with regard to testing multiple secondary outcomes. And that is that they used what is called a hierarchical testing procedure, which is a way to try to guard against a false positive finding. And how this works is you say, Okay, here's my secondary outcomes ranked in order of importance, I care the most about, you know, fatal events, debilitating events, and it cared the least about maybe changes in like a surrogate biomarker. And you will only proceed with testing those outcomes if the preceding one is positive. So if the primary outcome shows a difference, then we'll proceed and test the most important secondary outcome. And the author's action. Yeah. And it's kind of a cool thing. And the authors actually stopped when they achieved a secondary endpoint that showed no significant difference. So it's one method to try to guard against something we've talked about before in the show, which is, when you test multiple hypotheses, just due to chance, you're likely to find one that then

Matt 27:28
you Yeah, you eventually find like, was that Virgo - if you're a Virgo aspirin works better. Laughter Remember that? Tony? Tony talks about that. Yeah, there you go. The aspirin one, it was like your sign, your sign determines whether or not you're going to respond to aspirin after a heart attack, something like that? Well, this, you know, Rahul, what I? What was unusual here, and I remember they did this in one of the trials with the I think it was one of the paradigm heart failure trials, they did a run-in phase to make sure patients could tolerate the medicine. Is that legit? That seems like, highly you're highly selecting for a population that might benefit from this medication. I mean, was there secondary gain in this one? That was this? I forgot to check. Was this industry funded? Michael?

Michael 28:18
I actually don't know.

Matt 28:19
Okay, but yeah, let's look it up. And then that way, I can ask you, you can answer it.

Rahul 28:25
Yeah, I asked the same question. So great minds think alike. This was actually funded by the Australian Government and the equivalent of their NIH. So important question to ask about sources of bias. Your question about a running period, you basically described what I would say about this, which is, you know, making sure we understand the effect that that has on the study population, and what that means

for the generalizability of the results. So running periods can be used for good or for evil. And it's not wrong to want to enrich your trial for a population of patients who are going to tolerate the drug. But it's important for us as readers to recognize what that is going to mean about the estimation of adverse events. So if you, you know, screen out everybody who has side effects from a medication, that means that the patients who are left in the trial are patients who are less likely to have adverse events, you guys buy that?

Everyone 29:20
Yeah, yeah.

Rahul 29:21
And that means that we are going to underestimate the prevalence of adverse reactions to a study drug that compared to what we would see in the real world. So it's not a bad thing because it increases follow up and it you know, enriches the study population for people who are likely to benefit. But it's important for us to recognize that what that means is that in the real world translating these results, we're likely to see that this is an underestimation of the adverse effects.

Matt 29:48
Michael, we're gonna we're gonna have to do a follow up episode on stable coronary disease. Paul and I were talking about this earlier but will this be changing your practice or have you seen this Changing practice as someone who's a future cardiology fellow, maybe you're in the know more than we are.

Michael 30:05
I have definitely not seen this used in practice yet. And I think one of the main reasons that people are hesitant to implement this is the, in this study, they found that there was actually an increased incidence of non-cardiovascular death in the colchicine group compared to placebo. And this came out to a hazard ratio of 1.51. And they wrote, the authors really did not have a good explanation for why this was they noted that there were similar rates of cancer in the two groups and similar rates of hospitalization for infection, and GI reasons. So it's kind of unknown.

Matt 30:40
Yeah, this this is all a bit puzzling, because it's like, this seemed fairly favorable, like a number needed to treat in the 30s. These patients were already on like high-dose statin other medications that, you know, we know are protective for secondary prevention. And this seems to be an additive therapy. I guess 10 years ago, or 20 years ago, 15 years ago, this would have been a very cheap therapy to add on to guy now. Now, it's not so cheap, at least for them in the United States. I don't know, Paul, what do you think?

Paul 31:17
No, I agree. I'm kind of shocked that I'm not seeing people showing up in my office after having acute events that have been started on colchicine. Yeah, I feel like I'm just I'm kind of surprised. This has not been sort of more broadly practice changing. But I guess we have some, there's probably a little bit of delay in the uptake by professional societies as they sort of evaluate the evidence. And then also, there's the weird thing that might kill more people from unknown... laughter. Yeah. Which would also

give you pause to I suppose so it's, but yeah, no, I'm surprised. I haven't heard more about it, to be honest.

Michael 31:43
And there's actually there's another colchicine trial published recently, where they gave colchicine to patients after having an acute coronary syndrome. It also showed a very, you know, positive, robust effect. And I'm not sure if it was that trial or another one, but another colchicine trial showed an increased risk of non-cardiovascular death as well.

Matt 32:02
So maybe it's not just a chance, because I was gonna say, I mean, there's always the possibility, anything that you find could be due to chance. But I guess, if it keeps popping up, and more and more trials, you start to question that.

Michael 32:15
Yeah, I think that'll really need to be flushed out prior to this being incorporated into guidelines. All right.

Matt 32:23
Well, Michael, how many hotcakes Do you think you'd give this? I mean, usually, a five is the most hotcakes you can give. That's a full stack. And that means it's like practice changing. You're going to start doing this tomorrow. Zero is like yeah, you're you think it's the worst article you've ever read. It's you can't even believe it was published. Hopefully, we never present any articles like that on this show.

Michael 32:46
But I'm gonna give this 3.5 hotcakes. I think their evidence is really strong. I think the study was well done. But there's just a few unanswered questions still about why the there's an increased risk of death in the patients with colchicine Okay,

Matt 33:01
all right. So the...

Paul 33:02
I think I over committed to my hotcakes now like I'm usually the stingy. I'm second guessing myself.

Matt 33:08
New guy is showing you up there, Paul. Alright, so my study, the final study, this is called the CONTACT trial. Which Paul this is this is a rheumatology study the contact trial if it was the cardiology, it would have been like, high impact trial, something like it would have been a little bit more exciting.

Paul 33:30
Yeah, like the silica of this. Laugher

Matt 33:34

Alright, so this was by Roddy et al. It was also from 2020. And I should mention this, this episode is kind of a, you know, some of our favorite articles potentially practice changing articles from 2020. Since it's relatively early on in 2021 right now. And we did we didn't feel like covering COVID Paul so much. COVID. Laughter

Paul 33:55
I don't have it in me. Laughter

Rahul 33:55
I feel like covering COVID

Matt 33:57
I know I'm sorry, Rahul. Maybe next time.

Paul 34:00
We could use a colchicine-COVID episode next time.

Matt 34:03
Yeah, I'm sure

Michael 34:05
Someone has to be doing it, right? Laughter

Paul 34:06
Yeah. Oh, I thought it was I think it is a thing actually.

Matt 34:10
Okay, so this this was an open label randomized pragmatic trial. The question was, is low dose colchicine or LoDoCo as Paul loves to call it? Is it effective and tolerable as NSAIDs for acute gout flares? So we know NSAIDs work for acute gout flares. And I guess colchicine had just not been studied head to head with it. Surprisingly. Some of the background in the past there were trials, like there was a 2010 study where they're giving patients like 4.8 milligrams of colchicine a day versus 1.8 milligrams of colchicine a day. And they found that the low dose worked just as well and had, go figure, less GI side effects. I can't imagine them... go on Paul

Paul 34:57
Right because I think when we will start I mean, those are still the days where you're titrated to GI intolerance, but you just kept you kept giving colchicine till you start having diarrhea and then you'd back off. Yeah, right. Like I'm a little bit more humane now. So a lot of the common regimens now, Rahul, what do you see usually people doing if they're using colchicine? Is it the 1.2, followed by the 0.6? A couple hours later?

Rahul 35:19

Yes. And that is, you know, I work primarily in the inpatient setting. So it's usually that I'm sort of hearing about that or seeing that is what has been used in the chart. I also see patients get corticosteroids if they don't have a contraindication. Yeah,

Matt 35:34
yeah, so the ACR has guidelines that were updated this year by our friend, Dr. Tahina Neogi. And their guidelines say you can use steroids, NSAIDS, or colchicine, and you sort of choose the therapy based on what the patient can tolerate. And, but any of them should work. So in this study, they were using either the comparison was between NSAIDs, and it was an Naproxen 750 milligrams, you give it as a loading dose, and then you give 250 milligrams three times a day for seven days. And in the colchicine group, they were giving 0.5 milligrams three times a day for four days. And at day seven, they were looking at what their what their symptoms were. And this was on like a 10 point scale at baseline. Both groups had around six out of six and a half out of 10 is what they rated their pain. And then towards the end of the trial both had a score of around one and a half. There was really no significant difference at day seven in pain scores between the LoDoCo and the naproxen group. And patients in this study, they were over 18 years old, they had a clinical diagnosis of either an initial gout flare or a recurrent gout flare. And they excluded patients with advanced chronic kidney disease. Patients who had recent GI bleed because of the NSAIDs patients, on anticoagulation, or if they had like a known allergy or intolerance to either drug. And the results of this, we're calling this a negative trial, right, Rahul? And can you explain because to me, this seems in some ways positive that both LoDoCo and naproxen both had significant reductions in the patient's pain by seven days. But there was no big difference between the groups.

Rahul 37:18
Yeah, and to some extent, this is a little bit of a semantic distinction. Because you're right, in both groups, patients experienced pain relief compared with Day Zero. The only thing that I push people to do with regard to designating positive versus negative is to just make sure that we understand how the study was set up, and what the objective and the hypothesis was. In this study, they powered it as a superiority trial, but they didn't really have a hypothesis about whether colchicine or naproxen would be better. So they, you know, power the study to find a difference of a specified size between the two groups. And because this study did not demonstrate a difference between the two regimens, you know, that's my basis for describing this as a negative or a null study. If this was designed as a non inferiority trial, to show that, you know, one treatment was not inferior to another one, then this absence of a difference we would call a positive study. So it all depends on how the study is set up and what the hypothesis was.

Matt 38:23
And they actually, they took it out to four weeks, and again, there was there was no real difference. You know, one thing that struck me about this, Paul, only at day seven, only about two thirds of the patients were pain free, you know, a lot of patients still had pain, and at four weeks, only 75% of the patients were pain free, which means like a lot of people had lingering symptoms of gout. Yeah, I think that's, I feel like I see that in clinical practice, too. I'm not sure what your experience is. I think we all we often think of acute as in primarily in terms of acute flares and sort of lasting a couple days, it's going to get better. And don't worry, you just pick the right treatment, it goes all the way better, right? Do you see

patients that just it lingers and lingers may have pain, even between the inner critical like acute flares, it just kind of like the pain is never fully resolved? I'm not sure if that's been your experience. This was almost like a sixth sense moment for me where I'm like, No, wait, everyone always gets better. Wait, do they? And then I'm like thinking back to all these patients like wait a minute, no, they, they were still kind of complaining. And I was just like, oh, maybe it's arthritis or something. So yeah, I guess maybe that is and I just wasn't recognizing it. Michael did anything that struck you about this?

Michael 39:28
It makes me wonder if in the United States, whether the patients would take colchicine for longer than four days, because I've seen a lot of times in outpatient practice where we give patients several days of colchicine, oftentimes more than four and we say you know, take it until your until you feel enough relief that you feel like you can stop taking it. And we might not know exactly how many days they take it. Yeah.

Matt 39:50
And the guidelines say and this is just for practice, if you're if you're treating an acute gout flare, just some neat things that I came across in the guidelines that maybe you're slightly Different. So one thing that's slightly different is that the guidelines now say you can, they gave a conditional recommendation to start a urate lowering therapy during an acute flare. And it was it's case by case. And I think that's something that was different than what I was taught, at least when I was being trained many years ago now. And so you can now you have the option to start it, but you need to overlap some sort of an anti inflammatory therapy. So either steroids and NSAIDs, or colchicine, you need to overlap them for at least three to six months. And you want to make sure that the patient's urate level is less than six, uric acid levels less than six before you stop those. So that was a

Michael 40:41
long time. That's a long time lapse.

Matt 40:43
Yeah, but that and that was surprising to me. But that is consistent with what Dr. Neogi told us. I just didn't the what the big change for me is the fact that you need to you can now start during a flare, which is something and they say just you have a captive audience and they're motivated. You're like, wait, you have something that can make this not happen again. I'm motivated. Take it right now, because I'm in pain. So maybe I'll do it. I don't know. Have you done that yet, Paul?

Paul 41:09
Yeah, yeah, it's I more and more commonly it our rheumatology colleagues have encouraged us to do so. So now I'm trying to be a bit more aggressive, especially if someone's having recurrent flares. Now, I'll pull the trigger what I'm seeing in the office for that regard. Yeah.

Matt 41:20
And usually, the dose, the dose of culture, seeing I think it can vary like how much you give, but you could continue that low dose, like, in the US, it seems like we just have the 0.6 milligram dose is what I see. And you continue to do that, like once or twice a day. And it would vary, it can vary based on renal

function. So I, for me, I think one of the ways this might this study might be practice changing is, is the fact that like giving a loading dose of naproxen is something I hadn't saw. I thought that was kind of neat. And then dosing it three times a day instead of the normal just like, usually, I'm giving patients like twice a day, 500 milligrams, but maybe I would, I would switch the dose and spread it out the way they did in this trial, Rahul, any major sources of bias or any, any major things you think the audience needs to look at here?

Blank 42:09
Yeah, I mean, in some sense, the fact that there was no difference between naproxen and culture seen in this study is kind of a useful thing, because it supports that, as you were saying that both groups had a decline in their pain rating from baseline to day seven. So that suggests that both of these could be, you know, potential treatment options for gout, that the way that I would make this decision in practice is basically patient factors and looking at the adverse events. And as you might expect, patients in the culture scene group had more diarrhea. And they also had more headache, which the authors hypothesize might be, because naproxen maybe is treating headache that just, you know, we all experienced, because life is hard. When I think about sources of bias in this study, one thing that was missing, that I think was an omission that makes it a little bit hard to evaluate is the author's didn't report, the time from symptom onset to randomization and treatment. In the text, they say that two thirds of patients started treatment after symptoms had been ongoing for 24 hours. So that's probably pretty comparable to real world practice. Yeah. But it does make me wonder if you know, starting, you know, beyond 24 hours might have attenuated any difference that might exist if the treatments were started earlier. Yeah, something that we don't know here.

Matt 43:32
Yeah, because the guidelines also mentioned this, like pill-in-pocket, the concept where if someone had colchicine the first signs of a flare, they don't need to wait to see a doc, they can just start to take it.

Rahul 43:43
Yeah. And then the other thing that I think could bias towards the novel is I would have liked to see the breakdown for how gout was diagnosed in each group. The author's note that to be to be considered to have gout in this study, patients can be diagnosed either by joint tap, by uric acid levels, by imaging or by clinical criteria. So that's a relatively permissive definition of gout. And it probably included some misclassification of patients who had other acute arthroplasties. And so I would expect that to you know, if anything that's inflammatory, I would expect that to be addressed by both but that that's another source of potential bias towards the Null.

Matt 44:23
So I don't think this article, you know, as many hotcakes as I'd give it, I'd probably give it something like a three and a half to follow Michael's lead, because I did think it would be it would inform my practice in a way, the way that I think about prescribing either NSAIDS or colchicine for an acute flare, these are doses that I wasn't typically using, so I might start to use this dosing. And it also made me go back and look at the gout guidelines. But for the reasons you said roll you know, I don't I don't necessarily think this was like a you know, it was a negative. It was a negative trial. If nothing, none of it was That's surprising the fact that both these drugs work for acute gout flare. So that's why I wouldn't give it a

higher number. So with that, any closing comments, Michael Paul, before we get into the outro here, I think that we've done hero's work tonight.

Michael 45:16
I think you know, colchicine the new drug of the future based on this episode.

Paul 45:20
Yes. A new kid in town. This has been another episode of the Curbsiders, bringing you a little knowledge food for your brain hole.

Matt 45:35
Yummy?

Paul 45:36
Great, I wasn't sure who was gonna do it. But that was a pleasant surprise.