#367 Weekend Warriors, Fluids for Acute Pancreatitis, Colonoscopy Screening & Mortality, and SPRINT trial Revisited (Hotcakes)

[Curbsiders Podcast theme]

Matthew: Welcome back to the Curbsiders. On tonight's show, Paul, we will be discussing some hot cakes. And Paul, guess what, this is coming on Thanksgiving. So, you know what that means? What are we going to call this, hot tofurky cakes? Is that what we settled on?

Paul: I don't think I agree to any of that, no.

Matthew: [laughs] All right, well, if I haven't said it yet, this is the Curbsiders. I'm Dr. Matthew Frank Watto, here with my great friend, Dr. Paul Nelson Williams. And Paul, hotcakes, you want to tell people what that is and then remind them what this show generally is?

Paul: [laughs] Sure. Yeah, the hotcakes is where we and our expert team review practice changing question mark articles that have come out, or tickle our fancy, or that we think might have some educational value to them. And luckily, we brought a bunch of ringers in that are very smart. They'll talk us through the articles and how we should think about them or at least how they think about them. As a reminder we're not doing that during other episodes. We're always The Internal Medicine Podcast, no matter what we're doing. Typically, we use expert interviews to review clinical pearls and practice changing knowledge. But as you mentioned, this is one of the rare instances, where tonight we are the experts, the experts are us. More so, the gigantic team we have assembled here, not just the two of us, Matt.

Matthew: I guess, I should say who's here upfront, because they may hear voices before people present their articles. So, with us we have three great guest hosts and presenters who will be talking through some articles. Dr. Era Kryzhanovskaya, who you may know from the Curbsiders Teach Podcast, one of the two cohosts there, Dr. Nora Taranto, who is the editor of the Digest where most of these articles have been featured, and Dr. Rahul Ganatra, who is our resident-- Paul, are we calling Rahul, a Wizkid in epidemiology or critical appraisal? Critical appraisal, yeah.

Paul: Critical appraisal, Wizkid.

Matthew: I would say that's right.

Paul: I think it's right. Yeah, [Matthew laughs] that feels correct.

Matthew: Era, so first up, you have an article and if you want to tell us at least the first author, and the name of the article, and then let's get some top line results and start the discussion.

Irina: You got it, Matt. So, this is by Dos Santos and colleagues. This is the Association of the Weekend Warrior and Other Leisure-Time Physical Activity Patterns with all cause and cause-specific mortality, a nationwide cohort study. This was published in JAMA IM this summer. And their question was, "Does performing the recommended levels of weekly physical activity in one to two sessions labeled Weekend Warrior versus three or more sessions labeled as regularly active participants' influence mortality?" Now, this trial riffs off of the 2020 WHO published physical activity guidelines, which if you're like me,

we're like, "What is that?" Again, I think I probably should know that. But basically, [Matthew chuckles] adults are supposed to do 150 to 300 minutes of moderate activity or 75 to 150 of vigorous activity per week.

The gap in the literature here was it wasn't clear reaching those recommended WHO guidelines in a concentrated way. It had different health implications than reaching them in a spread out way throughout the week, because there's feasibility implications to doing that concentrated physical activity. They use the term weekend warriors, but I think it's just because it sounds great, because honestly doing physical activity on Tuesday and Wednesday in that concentrated time is the same as doing them on Saturday and Sunday. So, it doesn't have to be the weekend. So, no worries that people's weekend is actually their Tuesday, Wednesday.

Matthew: I like to see some smart branding from the Articles author. That's good.

Irina: Right? Tuesday is the new Saturday or Wednesday is the new Sunday.

Matthew: Yeah. [chuckles]

Irina: This trial also hadn't hit that gap yet of the frequency of physical activity and the total volume of physical activity that was needed. That hadn't been evaluated fully in the literature. So, this was a prospective cohort study including 300,000 adults and their self-reported physical activity via the US National Health Interview Survey from 1997 to 2013. And their data was linked to the National Death Index through December of 2015. In terms of the comparison groups, there are comparisons where participants by self-reported activity level. So, those folks who are physically inactive less than 150 minutes per week of moderate to vigorous physical activity, or physically active greater than 150 minutes of moderate or greater than 75 of vigorous activity.

Again, they also looked at intensity and volume and compared that to all-cause mortality, cardiovascular mortality, cancer mortality. They only had access to death as reported in that National Death Index, and some major causes of death only. Now, punch line, Matt, were you going to say something?

Matthew: That's what I was going to ask. I was like, "So, let's get the topline results and then we can get under the hood of this a little bit more."

Irina: Yes. So, topline results when we compare to people who didn't exercise at all, all active groups had less mortality, which is like winning. But there were similar mortality outcomes for weekend warriors and regularly active participants. So, again, this is good news for folks who are planning to exercise on one to two days. They looked at this again as hazard ratios for all-cause mortality for weekend warriors being 0.92 and for regularly active participants 0.85. And so, the bottom line for this, people are asking, I think about it as exercise is mortality reducing. So, it doesn't matter if you're doing it frequently in small aliquots or similar amounts, but in concentrated one-to-two-day period, which might be easier to fit in for some folks given their schedule. Really, exercise is beneficial to health and to chronic disease. So, it really just a welcoming feature for those of us who do concentrated physical activity.

Matthew: So, essentially, if you hit the 150 minutes a week of moderate or 75 minutes a week of vigorous activity, there's benefit to you regardless of whether or not it's happening quicker. Era, now, I know you spoke with one of the authors of this trial. So, we're going to get to that. Basically, it sounds like if I exercise 150 minutes a week moderately or 75 minutes a week vigorously, I should be good for reaping some mortality benefits. I want to go to Rahul here and say, Rahul, the design of this trial any sources of chance bias? What do you think about the power, those smart things that you talk about when you're appraising an article? Help us out.

Rahul: This study, a fascinating read, Era. Thank you for giving me an excuse to read this. I've been hearing about this, but hadn't read it yet. So, I was as pleased to have an opportunity to dive in. This study really had a couple of interesting features about it and some good learning opportunities for us in critical appraisal of the literature. I will just telegraph my final thoughts now by saying that there was nothing that really threatened to the conclusions of the paper in my mind and I would welcome if listeners have observed things that maybe I've missed, which happens all the time. Please message us and tweet at us, because critical appraisal works best as a team sport.

There were two or three things that I thought were worth mentioning. This study was a prospective cohort study. And so, that means that the comparison groups were defined by the exposure. In this case, the regular physical activity or the weekend warrior pattern as Era discussed. There was one source that I could identify biasing towards an underestimate of the relationship between those exposures and the outcome of mortality and that was the definition of people who are physically inactive. We're talking a little bit ahead of time that still included people who were exercising up to, I think, 149 minutes a week. So, that is definitely going to include some people who were reaping the benefits of physical activity below the recommended levels in the control group. So, that's likely to buy us away from the association with either activity pattern and a reduction in mortality.

Then another cool thing about this study was the way that the author's attempted to address a problem called reverse causality. This is where rather than the exposure leading to the outcome, the outcome leads to the exposure. This is kind of an interesting problem that it's good to be aware of and be on the lookout for. The way that the author's attempted to deal with this was they excluded people with chronic disease at baseline and the thought here was that if people with chronic disease that might limit their mobility are included, maybe it is the reality that their chronic diseases is what leads to cardiovascular morbidity and mortality, not their activity pattern. So, their plan for dealing with that is excluding those people. There are downsides to that, but that's one strategy.

Then the other thing that they did was they also excluded the first two years of follow up. The reason for that is that you need time for exercise and physical activity to exert its benefit in effect to your mortality from cardiovascular causes. So, a couple of good strengths of this paper. Then I'll also point out that residual confounding is always a concern we have to be vigilant for in any observational research. In this study, there's a nice example of residual confounding by the total amount of moderate to vigorous physical activity. You can see that in table two, where the authors show the outcomes for each of the three exposure groups, people who are inactive, people who are weekend warriors, and people who are regularly active. You can see that the hazard ratios for the regularly active folks are all suggested a reduction in all-cause mortality, cardiovascular mortality, and cancer mortality, but we don't see that

same reduction for weekend warriors. That's because these observations were confounded by the total amount of moderate to vigorous physical activity. In this final model where the authors did control for the amount of physical activity people were getting, we see that that difference disappears.

I interpret these results as, if people are able to perform the recommended amount of physical activity, with any regard to how it's spread throughout the week, whether it's regular throughout the week or if it's concentrated on one or two days, this evidence suggests that those people still derive the same mortality reductions. So, exciting study, relevant to a lot of people I know in internal medicine and particularly, the residents I work with.

Matthew: [laughs] Era, the author you spoke with, did he have any other additional insights or things you wanted to share with the audience?

Irina: Thanks, Matt and thank you, Rahul. Yeah, Dr. Leandra [unintelligible [00:13:01] definitely highlighted exactly what you mentioned, Rahul, about making sure that the participants were healthy at baseline that that was kind of the comparison that they needed going forward. I asked him about the generalizability of this trial given that the study population was so healthy and he definitely suggested that it's generalizable for this population and it's also plausible to assume that the benefits of the weekend warrior or other patterns of physical activity, as long as you're meeting that time recommendation is applicable to other populations as well.

He was just really excited that in his epidemiology world that we're seeing the benefits of exercise and by type as well. And some of his group's work has been published in circulation as well and looking at the types of exercise. The more you get, the better it is. I think that's another bottom-line punchline for us with this trial is just remembering that exercise is healthy and so beneficial. If you can only do it in two sessions, then that's great. It still works.

Matthew: I saw another article talking about resistance training at least twice a week or muscle strengthening activities, essentially resistance training also seems like it has a mortality-- and this was in patients older than 65, so it is exciting to see this kind of stuff out there. Hopefully, we can convince people to do it or figure out ways to fit it into their life. But I guess, the weekend warrior, this one-or-two-sessions-a-week pattern makes it easier. Paul, are you a weekend warrior?

Paul: I don't know how to answer that. I also exercise [crosstalk] too.

[laughter]

Paul: So, I will say no.

Irina: I've seen Paul [crosstalk]

Matthew: I thought [crosstalk] get a question. So, that's why I asked it.

[laughter]

Irina: But a Tuesday-Wednesday warrior. [giggles]

Matthew: All right. Well, we have to move on. Rahul. I know you have an article to talk about this. Paul, this one's called the WATERFALL trial. I don't know, if there's an acronym crammed into that or they just nicknamed it the WATERFALL trial. Is that an acronym, Rahul?

Rahul: I don't think that this is an acronym. I think the authors were just being TLC fans and wanted to work a popular song title into this study.

Paul: [laughs]

Matthew: [laughs] So, tell us the author, the name of the trial and let's get into some of the topline results here.

Rahul: Yes, it would be my pleasure. So, this study is by Dr. de-Madaria and colleagues from the Erica consortium. And as you mentioned, it's called the WATERFALL trial. This is aggressive or moderate fluid resuscitation in acute pancreatitis and it appears in the September issue of the New England Journal of Medicine. This paper asks the question, which is a more effective and safe fluid resuscitation strategy in acute pancreatitis? Really aggressive resuscitation and I'll define that in just a moment or more restrained moderate resuscitation depending on volume status. The hypothesis has been for many years that regional pancreatic hypoperfusion in pancreatitis is what leads to necrosis and other local complications. It's been thought from animal studies that this could be mitigated with really aggressive volume resuscitation.

On that basis, professional society guidelines recommend aggressive fluid resuscitations for patients hospitalized with acute pancreatitis. But the human evident space is overall quite weak. And so, these authors designed a randomized controlled trial to test the hypothesis that aggressive fluid resuscitation would be different from moderate fluid resuscitation. Patients were randomized in an open label fashion to either aggressive IV fluid resuscitation, which was a bolus of 20 mg/kg followed by a continuous infusion of 3 mL/kg/hour or moderate IV fluid resuscitation. This was a bolus of 10 mg/kg, so half but only if patients were hypovolemic followed by a continuous rate of half of the aggressive groups, so 1.5 mL/kg/hour. Fluids were stopped once patients were eating and this could be as early as 20 hours in the moderate group and 48 hours in the aggressive group.

Now that you know all that the topline findings, this was a negative study. It was stopped early by the data safety monitoring board due to evidence of harm with regard to the primary outcome, which I'll tell you in just a moment, without any evidence of efficacy. So, the primary outcome was a composite that reflects the development of moderate to severe pancreatitis during the hospitalization. This was the development of either local complications, exacerbation of other underlying diseases, a creatinine elevation above 1.9, hypotension or a reduced P/F ratio. That primary outcome, so a composite of bad things occurred in 22% of patients randomized to the aggressive group and only 17% of patients randomized to the moderate group.

No difference in the primary outcome, but the primary safety outcome which is volume overload and this is diagnosed by symptoms, signs, or imaging findings, this happened in 21% of patients randomized to the aggressive group versus only 6% of patients randomized to the moderate resuscitation group.

Matthew: Paul, does it seem to you we've just been wrong about everything about pancreatitis like feeding, fluids like the two main things that we were always taught?

Paul: 100%. We're dating ourselves, but I think we both trained during the time of bowel rest for pancreatitis. You'll recall and it was always, yeah, don't feed them, just dump as much food as they can possibly tolerate into them because of fluid shifts and other nebulous reasons. [Matthew laughs] So, sorry prior patients. [laughs]

Matthew: [laughs] I did think that there were some things. We talked about this trial. I think there were maybe some things that biased towards the safety outcome being more likely in one group than the other, because I just noticed that the fluid resuscitation could be stopped much earlier like at 20 hours in the moderate group and had to be continued for 48 hours in the more aggressive resuscitation group. So, that seems like it would have maybe pushed more patients towards volume overload. And then, since it was open labeled, if you're treating that person, you know they're getting aggressive fluids, maybe you're more likely to pay attention to their fluid status is what I was thinking.

Rahul: Yes, totally. I think those are key observations. For any study we've used on the show, a framework quite often of conceptualizing, is this a positive study or a negative study? It's a little arbitrary, but with respect to the primary efficacy outcome, you could call this a negative study because there was really no difference between the aggressive strategy and the moderate resuscitation strategy. So, then that clues me in to look for sources of that being a false negative. I'm not really finding any. You might wonder if the study was stopped early. Could this have been underpowered for the primary efficacy outcome?

I'm actually not concerned for the study being underpowered because the point estimates actually suggested a higher incidence of the bad primary outcome in the aggressive group. The confidence interval in a study that's underpowered is wide and just crosses unity and you kind of wonder if we had more people with a narrower confidence interval achieve significance. I don't think that would be the case here. The limited data they had from the patients who were enrolled suggested that there really was no benefit of aggressive resuscitation.

Then for the safety outcome, I think you hit the nail on the head that the open labeled nature of the study probably did clue in assessors to look for signs of volume overload. It's a pretty big difference. So, that does make me think that even if there is some ascertainment bias in the rates of the outcome of volume overload based on what the specific outcomes actually were, that probably does represent a real signal. [Irina laughs] I would like to apologize to all the patients and trainees, who I have told aggressive resuscitation is the way to go because I really think that this article provides really strong compelling evidence that there is not really much benefit to flooding people. So, I think that in the tofurkey season, this gets five hot tofurkey cakes for me. I think this is ready to change practice. Yep.

Matthew: That is fantastic and thank you for your tofurkey cakes rating. Actually, we forgot to ask Era for her rating of the weekend warrior article, which I think we must get. Era, so, it's on a scale of 0 to 5, 5 is practice changing, and then 0, no one should even read this. So, that's the scale we're dealing with here.

Irina: Wow, that's hard, Matt. I am somewhere between a 4 and a 5. I think for the folks who I can share this patient specifically who can only get one or two sessions of moderate to vigorous physical activity, this is going to be a game changer. I'm going to recommend this to them and tell them that in terms of mortality, things are about the same, whether it's Tuesday, Wednesday or Monday through Friday.

Matthew: All right.

Nora: So, it's not two hotcakes or five hotcakes.

Irina: Ooh, it's a hundred and-- [crosstalk] Yeah.

Nora: It's a hundred 100 and zero and-- [crosstalk]

Irina: 151 hotcakes. Oh, and the cat goes on the chair. [giggles]

Matthew: Yeah, this is the dream of recording with video, Paul because now people can see the cat, this happens every time we record a podcast. I believe Ollie is on the chair with Paul. All right, Paul tell us about the SPRINT trial. We covered this, Paul. I feel this is really the start of our podcasting relationship, anyway. [Paul laughs] We've known each other for quite a long time.

Paul: Yeah.

Matthew: SPRINT trial, episode number 2 of the Curbsiders and now this is going to be episode number 400 something which is sad in some ways, but-

Paul: [laughs] Right.

Matthew: -we're revisiting the SPRINT trial, Paul. So, tell us about it.

Paul: Yeah, no, as we march towards death, I think it's important to reexamine things and that includes [Matthew laughs] the SPRINT trial.

So, this is an update to the SPRINT trial. This is from Yaeger et al found in JAMA Cardiology. This is longer-term all-cause and cardiovascular mortality with intensive blood pressure control, a secondary analysis of a randomized clinical trial. So, this group in essence wanted to know-- the SPRINT trial, as I'm sure we're all familiar with is, I think, to me maybe the most important trials in my recent practice. They looked at intensive blood pressure control versus standard blood pressure control in patients that

are elevated with cardiovascular risk. And that elevated cardiovascular risk was clinical or subclinical cardiovascular disease or chronic kidney disease that had a great large cohort of older patients. So, it looked at patients that were at higher risk and looked at whether intensive systolic blood pressure control versus standard improved mortality. It turns out it did.

But the trial as you recall was ended a little bit early, it was three years in change because there was such a benefit. They're like, "Okay, we know the answer now, we should probably stop doing this." The authors of this particular article wanted to extend things out and see how we were doing while after the trial and extrapolated out data and wanted to see if the benefits of all-cause mortality and cardiovascular mortality persisted even after the actual study period. The child participants were linked to the National Death Index. And so, they looked at those numbers between 2016 and 2020. So, missing out on COVID, which probably would have thrown things off a little bit.

Then for the blood pressure, they extracted the longitudinal data of systolic blood pressure from 2010 to 2020. They only had a smaller cohort of patients they were looking at this. It's still a good chunk, close to 3,000 patients that they were looking at. And so, basically, the cardiovascular mortality benefit was seen in the intensive arm between two to five and a half years and then it attenuated throughout the observational phase. The systolic blood pressure interestingly also went back to around 140 for both groups, whether they were in the intensive arm or whether they were in the standard arm.

Matthew: So, Paul, you're saying basically the blood pressure, if you take your foot off the gas or the brake, the blood pressure just went right back up in the treatment group and then the benefits seem to just disappear by that five-year follow up point.

Paul: I think you nailed it. I think that's why this is important. I think this probably reinforces that the results from SPRINT were real because when the blood pressure was well controlled, you saw the benefits. When it was less controlled those benefits went away. I think the bigger takeaway from this is that-- There're lots of reasons for why it went that direction. These patients return back to their clinicians immediately after the SPRINT trial and were no longer in the study, so they weren't getting these very rigorously protocolized blood pressure measurements, they were not being seen every two months, their treating physicians may not even have the same targets as the SPRINT investigators. There're lots of reasons why the blood pressure may have gone back up. In any case, I think this makes an argument that tighter blood pressure control reduces mortality. I think an argument to be diligent and as you say keep your foot on the gas pedal as you're treating these patients with systolic hypertension.

Matthew: Yeah.

Irina: Was there actually a difference between the observation follow-up period and the actual trial period in the number of antihypertensives that patients were on? Do we know or do we not have that data?

Paul: It's the data may exist. I do not recall if it does.

Matthew: Yeah, I did not come across that either. I wasn't digging around deeply in any supplements. So, that may exist but that wasn't something I read about.

Paul: Or, you wondering if more medications were added on or if medications fell off was your question about that specifically.

Irina: Yeah, kind of like that. It seems likely that some medications probably fell off in the follow-up period.

Paul: If they're no longer getting free boutique ARBs, then-- [crosstalk]

Irina: Right.

Paul: [laughs] It's a fair point. No, genuinely.

Matthew: I think spending most of my time in primary care right now and Paul, maybe you find this as well, I think that oftentimes there's just so much inertia and then sometimes patients aren't believing their blood pressure is really high, people are really hesitant to add on extra medications. I just feel if we ever get to a state where there's constant monitoring of blood pressure like we talked about on the AFib episode recently, Paul, that may help people self-monitor, self-regulate, and be more adherent, because they'd be more aware of it. I think it's a tricky problem to treat. With all that support in the SPRINT trial, it's not surprising that you saw benefit when it was actually controlled. But even then, they couldn't get it down to below 120. Let's remind ourselves. It's hard to treat blood pressure.

Paul: It's hard to treat blood pressure. The absence of symptoms makes it, I think, especially challenging. It's hard to convince people that it's super important, so something catastrophic happens. I think it's going to be hard to move that needle particularly, I think.

Matthew: Well, fortunately, Paul, we have a really easy trial to interpret to end the show. [Paul laughs] No controversy about this, I didn't see anything about it on the news, and who better to talk us through this than the great Dr. Nora Taranto. So, Nora, do you want to tell us who wrote this article and tell us about it?

Nora: Bretthauer and [unintelligible [00:30:07] wrote this article. It's the Nordic study group. Nordic meaning the Nordic-European Initiative on Colorectal Cancer. And you definitely mean-- [crosstalk]

Matthew: Pause for one moment. Paul, how do you rate the name of this study group?

Paul: Research is hard, but that's an intensity lazy acronym. They should be ashamed of themselves. [Matthew laughs] They should have gotten zero traction until they worked on that.

Rahul: [laughs]

Matthew: All right, Nora, so, you said your article, the Nordic trial, tell us about it.

Nora: Indeed. So, the Nordic trial looked at the effect of colonoscopy screening on the risks of colorectal cancer and related death. The trial results were just published in the New England Journal of Medicine in the end of October. The group looked at whether or not colonoscopies and specifically invitations to colonoscopy screening would decrease the risk of colon cancer, as well as the risk of colon cancer related mortality and overall mortality. There have been many studies looking at the effect of colon cancer screening on the risk of cancer and the risk of death, both colon cancer and overall mortality. But many of these have been either cohort studies, so not randomized control trials or they have looked at screening modalities besides colonoscopy. Colonoscopy is one of the-- [crosstalk]

Matthew: I was going to say, Nora, this was very surprising to me. I was like, "Oh, yeah, colonoscopy, there's got to be tons of randomized trials just showing-

Nora: I know.

Matthew: -that that's like our best. And then you find out that there's not any, which is surprising. It's a very common test.

Nora: Yeah, it is surprising especially I think in the United States where it's the most common modality, I would say, I recommend it to my primary care patients. I don't know about you guys. Perhaps, this has changed a little bit in COVID actually, but I think that's historically been the go-to screening modality here though that may not be the case elsewhere. And so, the study actually looked at populations in Nordic countries as you might have guessed. In Poland, Norway, and Sweden, looked at almost 85,000 men and women between 55 and 64. They compared an invitation to screen group with the usual care group. Importantly, the usual care group was not getting invitations to screen for a colonoscopy, or was not getting colonoscopies, or colorectal screening testing during the-- [crosstalk]

Matthew: Is it true, so, none of the patients in either group had undergone screening, right?

Nora: Correct.

Matthew: That was one of the exclusion criteria. The reason they were able to do that is because it's just not standard practice to invite people for screening colonoscopies in those countries, which was again, I was like, "What? I thought everyone was doing this."

Nora: Yeah. Correct me if I'm wrong any of you, but I think that some of that has changed over the last 15 years. So, there are more colorectal screening protocols in several of these countries. But they did not overlap with the population that was studied in this trial at all. So, it was a pragmatic trial which was designed with the intent of trying to reflect as close to real world clinical practice as possible. The groups were this invitation to screen and usual care. The invitation to screen group had a lower risk of colorectal cancer at 10 years.

Now that didn't translate to a lower risk of colorectal cancer-related mortality or a lower risk of overall mortality. And so, that's an important discrimination there. It was an 18% lower risk of colorectal cancer

diagnosis over those 10 years. The number needed to invite of the screening test was 455 individuals to prevent one case of colorectal cancer. So, Rahul, I'm curious, what do you make of this number needed to invite and just this study, its results overall?

Rahul: Yeah. I have a couple things to share with you all. I'm just going to say, I welcome any questions from the group, from listeners. This is a difficult thing to decide what to think about, especially when this flies in the face of what many of us have just assumed was a robust evidence base like fluid resuscitation pancreatitis. So, the primary outcome in this study was the risks of colorectal cancer and related death. Colorectal cancer incidence, there was a reduction with screening. Colorectal cancer death, there was really no change. So, this was not an overwhelmingly positive study in the sense that we saw a mortality reduction that you might expect from colonoscopy.

I think for the sake of discussion, we can call this a negative study, okay? Now, what we have to deal with and what we have to confront is, do we think that this is the truth or do we think that there are reasons that this could have been a falsely negative study? There are some signals for causality in the study that I want to be cautious not to over interpret, but I do think might provide some valuable learning for our listeners. So, there does look like in the adjusted per protocol analysis that there was a dose response between the degree of uptake of colorectal cancer screening with colonoscopy and the effect size of reduction in colorectal cancer deaths. Overall, only 42% of the people in the intervention group actually ended up getting a colonoscopy, which is a big drop off between the number of people who were emailed or who were snail mailed an invitation and who ultimately got a colonoscopy. So, that's an important source of bias towards the no finding.

Then within the four countries that were included, the rates of uptake differed quite a lot from a low of 33% of people in Poland to a high of 61% of people in Norway. And so, in the adjusted-per-protocol analysis, the effect size on colorectal cancer mortality was bigger in Norway than in Poland, which makes me wonder, is this a reflection of the fact that if you do more colonoscopies, the beneficial effect is able to become apparent? That's one possibility. Another possibility is whether or not this study was long enough for the benefit of colorectal cancer screening to become apparent. We know from studies of fecal occult blood testing in colorectal cancer that it takes a long time, more than 10 years for the mortality benefit to become apparent. So, I'm waiting for the final analysis of this study, which I think is planned for 15 years after randomization to answer that question and was this a long enough time horizon to really see a difference?

The last thing I'll say people who want to believe that colonoscopy is what we should be doing, I think are prone to gravitate towards the results of the per-protocol analysis, which did suggest a reduction in colorectal cancer death. So, it's just important to remind all of us what the per-protocol analysis means and what that is. That is looking at the effect of the intervention among people who got colonoscopies. The important thing to be aware with that is that when you only look at people who got the intervention as opposed to the entire city population, the intention to treat population, you are sacrificing some of the benefits of randomization. I don't think it's controversial to say that this study is vulnerable to post-randomization confounding and selection bias because of the fact that only 42% of people in the intervention group ended up getting the colonoscopy. This was a result of this being a pragmatic trial,

where consent was done after randomization in contrast to how randomized trials are usually done, where you consent to patient and then randomize them.

Consent is an important process. That's where patients are told all about the risks and benefits of a study intervention. I have to wonder, would uptake have been higher had patients had the opportunity to undergo consent before randomization? So, this is one of the tradeoffs we make with pragmatic trials. It would be impossible to study something like this at this scale by individually consenting every patient. So, it's tradeoff we made. But I just think it's important for people to know. It is important when you're counseling patients have some estimate of what the effect might be in the individual and it's really hard to extract that from a randomized controlled trial where not a lot of people did the intervention under study.

Matthew: So, you're saying like the consent process that patients essentially getting education about why they may benefit like what we do in clinical practice where we're saying, "Hey, I think you should get a colonoscopy because we can find cancer or polyps that could become cancer, we could find cancer early and that would potentially benefit you." So, it's a little bit what happens in practice. If you just get this thing in the mail, you may not read it. I think that's one of the main limitations to me of this whole thing.

Nora: I do also wonder how the evolution of communication modalities and medicine would affect the results of this, what with so many more patients having access to pretty much real-time communication with medical teams and professionals who are doing community health outreach and saying through the phone, just through email or through electronic medical communications. We recommend this doing behavioral nudges like now the data would change.

Irina: I was going to say, Nora and Rahul, I wonder what y'all say, because this is relative to your comment, Nora, that some people think of this study as more of efficacy of implementation of a screening program as opposed to necessarily like, "Should we be utilizing colonoscopies for colorectal screening, but just like are we evaluating the efficacy of this invitation" and what you all think about that? My second comment is I just want to say with somebody of Polish descent, Poland is not a Nordic country, so I'm not clear what happened there.

[laughter]

Irina: But I do love that Poland was included. I'm just unclear about our definitions of Nordic countries. But also, I want to-- [crosstalk]

Nora: You will feed that back. [laughs]

Irina: Yeah. But also, I do want to hear, Nora and Rahul, your thoughts about this evaluating more of an implementation population-based screening, then necessarily are colonoscopies the best colorectal screening test.

Rahul: Yeah, there's a great paper in the New England Journal from 2017 by Miguel Hernan on the ways to do per-protocol interpretations of pragmatic trials. We can link to it in the show notes. A point that they make that I think is really understandable and helpful in this situation is an intention to treat analysis in a pragmatic study is really testing the effect of treatment assignment in a particular trial, not the effect of the intervention itself. Because the effect of colonoscopy screening could be different in an individual patient who has a precancerous polyp and is going to get colon cancer. We always have this tension between trying to take average treatment effects from large randomized trials and translating them into the individual patient. So, I think you are right, Era that this was a test of the invitation to colonoscopy screening in this pragmatic trial and whether or not we can really generalize to the individual patient, we're going to need information beyond what was provided by this study.

Paul: One line to generalizability, And I don't know if you all know the answer to this or are keeping this in your reading. I wonder how sure we are this population is comparable to the population which we serve to. You think about the modifiable risk factors like tobacco use, and obesity, and alcohol consumption. I just wonder if this is one-to-one correlation with their own patient population too and if it's directly applicable or not.

Rahul: Yeah, I don't have the content expertise on this that I'm sure many of our listeners will. So, again, I invite knowledge if anyone has any. But one concern I would have about kind of abandoning colonoscopy as the standard screening modality on the basis of this study is that you might expect that to have ramifications for equity of care in the United States, where we've got a bunch of different populations of varying risks. So, I think we would have to think long and hard about who our patient population is and what the baseline risk is for lesions that might be missed by strategies that don't involve colonoscopy.

Matthew: I think we're going to need a hotcakes rating for this, Nora, because I think we are at the end of the show. And so, will this be practice changing for you and hotcakes rating for this one? What do you think?

Nora: I think I'm going to give it four, because it is a really important trial, but I don't think it will change my practice. I'm excited about several other trials that are in the works, specifically some that are comparing the different screening modalities, colonoscopy and FIT testing.

Matthew: I think those will be helpful to have-- Yeah, I'm not ready. Like we said, this was more of implementation of a screening program that it was convincingly looking at more so than the actual how well colonoscopy works. As Paul pointed out, different population. I think we've done some great work tonight everybody.

Paul: [laughs]

Matthew: Four articles, lots to discuss. Hopefully, the audience learned some things, I know I did. So, I think it's time, Paul, to go do an outro.

Paul: Terrific. We'll do. This has been another episode of the Curbsiders bringing you a little knowledge food for your brain whole.

Matthew: Yummy. It was anyone's to take, but you claimed it.

[laughter]

Paul: I told like I knew that. Get your show notes at *thecurbsiders.com*. And while you're there, sign up for our mailing list to get our weekly show notes in your inbox, plus twice each month, you'll get our Curbsiders Digest edited by the great Doc Nora Taranto, recapping the latest practice changing articles, guidelines, and news in internal medicine.

Matthew: And we're committed to high value practice changing knowledge. And to do that, we want your feedback. So, please subscribe, rate, and review the show on Apple Podcasts or now at Spotify. You can also send an email to *askcurbsiders@gmail.com.* Reminder that this and most episodes are available through VCU Health for free CME at *curbsiders.vcuhealth.org.*

I wanted to give a special thanks to all my wonderful cohosts tonight for helping to write and produce this episode. The technical production for Curbsiders is done by Pod Paste, Elizabeth Proto runs our social media, and finally, Stuart Brigham composed our theme music, which we all love. So, with all that until next time, I've been Dr. Matthew Frank Watto.

Rahul: I've been Dr. Rahul Ganatra.

Irina: And I'm Dr. Era Kryzhanovskaya.

Nora: And I'm Dr. Nora [unintelligible [00:46:30] Taranto.

Paul: And as always, I remain Dr. Paul Nelson Williams. Thank you and goodbye.

[Transcript provided by SpeechDocs Podcast Transcription]