Speaker 1:	00:01	Quality improvement in the time of COVID-19 is brought to you by the American Heart Association with support from Novartis Pharmaceuticals. As physicians, scientists, and researchers worldwide struggle to understand the COVID-19 pandemic, the American Heart Association has developed its COVID-19 CVD Registry, powered by Get With The Guidelines®, to aggregate data and aid research on the disease treatment protocols and

Kevin Sheth: 02:18 Yeah, you're absolutely right. And somewhat mirroring, somewhat in contrast to prior viral infections, we have appreciated that there are significant arterial complications that occur in this disease. There are cardiac ones that you may be familiar with that have to do with inflammation such as Kawasaki's disease and inflammatory syndromes in children that, in some sense, may be considered arterial, but I think what

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a plausible basis for that. The American Heart Association, and we may be talking about this, really has a track record and is using in this platform, a very nice, large-scale, very diverse quality registry that should provide us with some of the highest level data that we can have to date to answer this question about, is antiplatelet, antithrombotic, anticoagulation use safe? Is it effective? Is there a role for it? What's the variation in practice?

Sandeep Das: 10:37 Thanks. So, you have two interesting perspectives because you're a clinical trialist, but you're also someone with extensive experience with the American Heart Association Get With The Guidelines stroke registry, so I'm wondering if you could comment on what you think the relative roles of registry data, versus what we absolutely need to have trials on, and then maybe contrast that with some of this stuff that we're seeing. That single-center administrative data, observational work, and where you see the registry sort of fitting in and that continuum.

Kevin Sheth: 11:13 I think the premise of your question actually had some hints to, at least what I think, might be possible answers embedded in the question. The trials and the registries are both critically important, and they're complimentary. They each have different strengths and weaknesses. So we think of trials, randomized trials, for example, as the gold standard in medicine, and indeed, they provide us with very high quality data, about maybe the best data in many cases about whether or not a particular intervention might work, whether or not aspirin would actually reduce the incidence of stroke, for example, in this disease.

The challenge of the trials is, first of all, they can take a long time, two, they may or may not be adequately powered. What that means is that you have to have sufficient number of stroke events in trial, in order to have a chance of seeing whether or not the intervention will have any effect. And then number three, we know for a number of different reasons, including practical reasons and logistics and chance, sometimes the trial population doesn't mirror the broader population. There may be disparity issues or enrollment issues, and so you can even have results of the trial that they may or may not be generalizable to a much broader population. So these are some of the advantages and disadvantages of trials.

This is really a great window of opportunity for a high-volume, high-quality registry to come in, because one of the things that you'll learn with observational studies, you always have the

problem of biases, potentially, and that's what a randomized trial does a great job of getting rid of, is a lot of biases. One of the ways you can get around the bias in an observational study is actually just with very large numbers, the largest numbers that you can find. Statistics does a great job, not a perfect job, but a great job at minimizing the role of a particular kind of bias, and this is where one place where a high-quality large registry can help.

A second place is that if you have a very vibrant community of active participation, this is where I think the AHA is very strong, where you have hospitals in different geographies, for example, throughout the United States, that also target and serve various patient populations, race, ethnicities, socioeconomic status groups, then you can start to make observations in two aspects. One, on things that touch the whole population, but two, that are actually representative at giving you some insight as to actually what's happening on the ground. That's something that you can't really get from trials.

At the end of the day, as a physician, as a treating physician, but also as an investigator, what I really like to see as the result of both of these kinds of tools, and try to see where they line up and when they don't line up. When you have observations that line up from both a trial and a registry, then oftentimes, you're really now putting together a story where you can make firm conclusions.

Sandeep Das: 14:18 Yeah, that's great. One of the things that I've always thought is that, obviously, in trials, there tends to be a bias in terms of who is willing to enroll in the trial, and that certainly we're seeing certain groups, historically, that had been quite underrepresented in clinical trials. Although I know there's quite a bit of focus on the part of trialists, like yourself, to improve that going forward. So I think, as you say, it's a really nice complimentary effect where you have very robust data from trials with randomization to minimize the effects of bias, but then also at the same time, you have the ability to expand that beyond the trial population by looking at effects in populations

and in contrast to places like the UK that have done that successfully.

Kevin Sheth: 15:27 Yeah. I'd say there are a couple of different aspects to that. First of all, when everybody started earlier this year, 6 months ago, we were in a very different place, and I think we had a lot of understandable fear and anxiety, and safety was really the top concern, and so a lot of things were shut down with a focus on COVID. But I think as we're highlighting here today, there are COVID-related concerns and COVID-unrelated concerns for things that are important in public health. A stroke is certainly one of them, broadly speaking, stroke and heart disease. And so, in some ways, I think we've been trying to figure out how to stop trials, how to start trials, and how to continue to do trials safely.

That really brings us to the second point, which is that, in some ways, in large part for historical reasons, regulatory reasons, I think, I would say that as a community, while we've had a lot of advances, we've been a little bit slow in terms of using technologies and procedures to be patient-centered and facilitating doing some of our trials. If you think about it, telemedicine has been around for a couple of decades. Electronic signatures on forms have been about for years, you can buy a house and sign your mortgage and never have to do something in-person, and for years we've made it virtually impossible for you to sign a consent form for a clinical trial, without a face-to-face wet signature. And in some ways, we all know that privacy, safety, confidentiality, those are core elements to doing any kind of research study, but sometimes, I think, the barriers that we've put in are impediments.

One of the things that I hope that the pandemic will stimulate us to do, and I think we're already seeing elements of that, is trying to see how can we enroll patients from a distance? How can we provide them with meaningful consent? How can we do follow-up procedures with remote distancing, using the internet, and telemedicine capabilities? I think if you do those kinds of things, you not only facilitate the trials going forward and facilitate enrollment, but you actually, in many cases, make

Sandeep Das:	18:02	Fascinating perspective. It's really nice to have a trialist on that can speak to that from a personal experience. You mentioned cognitive impairments in patients with COVID, and that's

part through other mechanisms. The reason is, we talked about those patients that have cardiovascular risk factors, and just like y (13. 27.6 reW nBT12 -0 0 12 18hoour-1.217 D j jom

the AHA has been putting together a very exciting, robust COVID-19-specific registry as it relates to heart disease and stroke. That work has been ongoing for many months. It will continue to be ongoing for sometime in the future, and I, as an investigator and as a treating clinician, look forward to the results of the data that will come from those quality registries, because I think, in my mind, it will tell us two or three key things.

Number one, who's getting complications of COVID-19 at a large scale across all demographic population? Number two, we often think we know what we're doing to treat these patients, but sometimes that lines up and sometimes it doesn't, and I think this registry will give us a snapshot as to how we're treating these patients. And number three, I think it'll start to give us some insight as to how we can prevent some of these complications. Does exposure to steroids, exposure to aspirin, exposure to other interventions increase or decrease your risk of stroke and other thrombotic events? I don't know, but I think the AHA registry is going to be one of the best sources the world has, in order to ask and answer some of these questions. I anticipate that these things will start to come out in the coming weeks to months, and that's really exciting.

Sandeep Das: 24:46 One of the things I think that I guess I under appreciated was the extent of CNS involvement in COVID-19 infection. To some extent taking care of these patients clinically, you think of this as just hards, more or less. Straight from the mouth of the expert, where you get a detailed overview of some of the CNS implications that are important and can have potentially profound long-lasting implications. So I appreciate you sharing that. It's also nice to get a chance to talk a little bit about the

sort of normal times. Things are harder with COVID, in part because of physical distancing, and so in many cases, caregivers and family members may not be in the hospital. So there's the in-hospital setting where people feel, I think, a little bit more distant, that makes it emotionally difficult. I think hospitals and communities like ours have tried to use a number of different tools to be able to facilitate visits and interactions.

And then I think what you're really talking about is survivors, or survivors that leave the hospital. So you're going back home, you're now left with a disability. In some cases we've seen COVID effects create strokes and younger patients, and so you have younger patients with disabilities, and that can be life-altering. The short answer is, that's very difficult, but I think a lot of our work, our research, our quality improvement work, and hopefully our broader community's attention, really has to be on educating both patients and providers about resources that are available, and about what recovery pathways look like. It is a big part of the focus and we have a lot of work to do, and I'll tell you, we need a lot more investment in recovery research and recovery initiatives. We can never do enough in that space and it's great to work with places like the AHA that understand that.

Sandeep Das: 27:19 Now, are you having any trouble getting patients into skilled nursing facilities or inpatient rehab, or are you having any trouble getting physical therapy, occupational therapy, speech therapy into the homes? Has that been a problem for you?

Kevin Sheth: 27:32 It hasn't been for us. I should qualify that by saying it was a problem several months ago when we were in the midst of, really, the surge here at Yale and in the system There was a whole process in place that was required in order to get that conveyor belt to work, that required having adequate testing, having adequate testing prior to discharge, coordinating what was adequate testing, where the receding facility, including the several types that you mentioned. So those things needed to be figured out, available, and then implemented. That's been done by and large, and those collaborations worked out very nicely, so thayry. (7.6[w}3.4 (h}2.3 (at}3-6 j s

ground, really dedicated and committed physical therapists, but also we've had great organizational leaders in heart disease and stroke here who have realized that that's an important piece. So it's challenging because everything is slower, everything is backlogged compared to before, but it's still moving forward, and I think the first thing is just calling it out as an important part of the whole continuum of care.

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