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 risk factors tied to adverse cardiovascular outcomes. For more information, visit us at heart.org/covidregistry.

Sandeep Das: 00:33 Hi, and welcome to this episode of our American Heart Association podcast series on COVID-19 and cardiovascular disease. The American Heart Association houses more than 20 quality improvement programs founded on the premise that patient outcomes improve when medical professionals follow the most up-to-date evidence-based treatment guidelines. The challenge of COVID-19 is maintaining consistency and treating to standards for existing conditions, as well as understanding the novel viruses' impact on our care. Together, we're going to examine these challenges more closely and hear from experts on how QI is playing a role in the current situation.

Today I have with me, Dr. Kevin Sheth from Yale New Haven hospital, and I'm going to let him introduce himself in just a second, but first I'll tell you a little about me. I'm Sandeep Das, general cardiologist at the University of Texas Southwestern Medical Center in Dallas, with a primary research focus in quality of care and outcomes. I'm also co-chair of the steering committee of the American Heart Association COVID-19 CVD Registry. Today I have with me, Dr. Kevin Sheth from Yale New Haven hospital. So Dr. Sheth, would you take a few minutes to introduce yourself to our audience?

Kevin Sheth: 01:38 It's my pleasure to be here today. Thank you for the invitation. My name is Dr. Kevin Sheth. I'm a critical care and stroke neurologist at Yale University and Yale New Haven hospital. I spend much of my time taking care of patients with stroke, but also in stroke investigation AND clinical trials, and I'm a member of the American Heart Association Get With The Guidelines stroke steering committee.

Sandeep Das: 02:01 Great, thanks. Really excited to have you. So let me start off with a really broad question. Some of the venous thromboembolic complications of COVID, like DVT and PE, have gotten a lot of attention, but can you give us an overview of the arterial thromboembolic complications you're seeing?

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 you may be referring to is more commonly we're seeing ischemic stroke complications, arterial ischemic stroke complications that occur. There appears to be a biological basis for this, but this is something that's been reported now in several series and observational studies throughout the world, during the course of the pandemic.

Sandeep Das: 03:03 One of the things that really is jumping out, is that we're seeing this in people that we wouldn't typically think of as super high stroke risk. I wonder if you could comment a little bit on what you're seeing for stroke complications in younger patients. Is this something that's associated with just a very high co-morbidity burden, or are you seeing it in people with fewer comorbidities?

Kevin Sheth: 03:25 Well, I think it's something that we're beginning to understand and I think those questions you asked are still some of our central questions. There is a higher rate of stroke infections in this disease, even compared to people in the past who have been infected with influenza, so we know that there's something that appears to be specific to this virus or the body's response to this virus that seems to be associated with a higher frequency of stroke. This does occur commonly in people who have prior established cardiovascular risk factors, such as hypertension, high cholesterol, obesity, and other similar cardiovascular risk factors, but we're also seeing it in populations which may not traditionally have these risk factors, including younger populations, or even patients without traditional risk factors. I think you're correct on both counts. It seems to be both associated with risk factors, and it seems to also be occurring in patients without risk factors.

Sandeep Das: 04:23 One of the things I think people are super scared about right now is what are the potential sequelae of asymptomatic or minimally symptomatic COVID? So people who can get exposed, get sick, but not necessarily get so sick that they're in the hospital, or maybe even not be diagnosed. Are you seeing stroke complications in these?

Kevin Sheth: 04:45

Yeah. Maybe I can touch on that from a number of different perspectives, just briefly. You're right. I think for reasons that we know, if you take just a step back, as the American Heart Association has outlined many times, stroke is a leading cause of disability in the country and it's the 5th leading cause of death, so stroke is a major problem and it changes people's lives. We know that. It's a major problem. When it occur in the context of an infectious pandemic, it becomes significant because it's one thing to have the coronavirus be relatively asymptomatic or even be moderately symptomatic and then get better, but if you have a persistent complication, like you'd get from a stroke, it becomes a serious disease. So I just wanted to frame the question in the first place.

We are seeing this. There are people that are presenting with stroke as their presenting symptom of COVID-19. There are people that have had active COVID-19 infection for several days and then had symptoms of stroke. So we're seeing all forms of that. And when you were talking about stroke, I should say, first of all, there are two kinds of stroke. There's ischemic stroke when you have a blood clot, and there's hemorrhagic stroke, which is traditionally thought of as bleeding within the brain. For the most part, right now, we're talking about ischemic stroke, the kind where you get a blood clot in one of the blood vessels of the brain, one of the arteries. In that kind of a situation, we're seeing both the large vessels get affected and the small blood vessels get affected. This is with people who present with stroke.

If you look at some of the early reports that came out earlier this year that first highlighted that you could have neurological complications like stroke, you have to understand that one of the things that was very unique about this whole descriptive setup was that neuro imaging, which is an objective test we always use, so this is like a CAT scan or a brain MRI, is one of the primary ways in which we confirm the diagnosis of stroke clinically. In many of these patients, you couldn't get a neuroimaging, you couldn't do that because, either infection control reasons, you didn't want patients going to scanners, or because, for severely ill patients in the intensive care unit, they were too sick to travel to a scanner. So if you look at those early reports out of China, for example, you'll see that there were a very small number of patients that were imaged.

Over time, through a number of different approaches, once we started to see more patients that were getting imaged, you would also see in patients who were otherwise comatose or in

medical comas, where we couldn't do a neurological exam, we would see strokes. And sometimes you would see so-called subclinical strokes, even when you didn't have signs or symptoms, in some patients once we started getting more frequent neuro imaging. I think the bottom line was, stroke occurs with this disease. Stroke occurs, it's clinically relevant, that it appears to be clinically silent in some cases, and I think we all still try and appreciate exactly how common is this.

Sandeep Das: 07:49 Fantastic. Thank you. One of the things that we see here is there's a lot of variation and anticoagulation practices, and that's kind of the bat signal for folks that do quality improvement when you see practice variation. I wonder if you could comment on prevention of stroke in hospitalized patients. Is there a role for a prophylactic anticoagulation, and at what level?

Kevin Sheth: 08:14 Well, we think it's a very important question, that's to say for certain, and I think we're learning more about that. So, as you know, I think you're absolutely right. There is tremendous variation in practice, in part, based on evolving data. People use DVT prophylaxis, different doses of DVT prophylaxis, people were placed on aspirin or other antiplatelet agents, and in some cases they were placed based on a number of different clinical or biological markers, in some cases on low-dose or high-dose or therapeutic anticoagulation, using a number of different strategies. And so all of these strategies have been used.

The reports to date that has really been out, of course, in part, have been observational and in part, while COVID is very common, the numbers of patients that fall into each of these different bins, where they've been exposed to different anticoagulants, it's relatively small. So to know with a high degree of confidence which strategy is the best strategy, is a little bit unclear. While there are several ongoing trials that hopefully will provide us some insight, this is a great opportunity to have very high-quality, large-scale observational data sets, so we can really ask and answer some of the questions that you're proposing.

And what I'll say, is that we know that there's endothelial dysfunction, so an injury that happens to the blood vessel wall lining that predisposes you to blood clots in this disease, and you also have inflammation in this disease, which also predisposes you the blood clots. So in both of those contexts, using antithrombotic agents, antiplatelet agents, things like aspirin or things like anticoagulation, there is a potential, there's

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 that maybe were underrepresented in the trial. That's fantastic. I totally agree with your perspective there.

One question I have for you, why do you think that, in the US, we're struggling to do as many trials? I've seen very large, tens-of-thousands of patients of observational studies reported, but it seems like we're really struggling to get trials moving forward

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 it easier for patients. Having to pay for parking, travel downtown, get to the clinic for a trial appointment, it's not always easy for patients, especially patients who have disabilities, patients like stroke. So, hopefully, this will be a good catalyst to change some of that. I think it's been some of the reasons, historically, we've had trouble doing very large-scale trials.

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 something that I anecdotally heard quite a bit about. I don't really have a sense of what the true prevalence is, but a lot of people are reporting significant and persistent cognitive impairments after COVID infection. Do you think that may have to do with sub-detectable level strokes, or what do you think might be driving that if you think it's a real major factor?

Kevin Sheth: 18:42 We learned very quickly there were several signatures that the virus is actually penetrating the central nervous system and having effects on the brain in some patients. We already spoke about stroke, and I do think stroke and endothelial dysfunction are components of this disease and some patients more than others, but we've also seen on some of this neuroimaging studies that I described, we've seen where we'd had other neuroimaging signatures that are not necessarily stroke. We've seen bright signals, what we'd call hyperintensities, within the brain, in the gray matter and the white matter of the brain. We've seen white matter disease, and we have, in a small number of patients, even seen brain hemorrhages.

So I think all of that is to suggest that there are signatures that the virus is doing something in the brain in these patients. If you look now, there've been several reports that have been published of neurological sequelae of patients with COVID-19, and stroke is certainly a big part of that, but there are other CNS manifestations, other brain manifestations, that include delirium in the acute phase, that include cognitive changes and dementia over the course of days to weeks to months, that include fulminant encephalitis or brain infection and brain inflammation in some of the more severe cases, so there is a range of neurological complications in this disease. That's clear.

Sandeep Das: 20:13 Yeah. So, for long-term complications or secondary prevention, is secondary prevention for a stroke in the context of COVID similar or different from more garden variety, secondary prevention. We think of atherosclerotic cardiovascular disease as the sort of driving force here, but if you had a stroke due to some issue with virus permeability into the brain, what do you tell those patients to do long-term for prevention?

Kevin Sheth: 20:43 Yeah, I think that's an open question. The bottom line is, we don't really know the answer. We know relatively little about that and I think we're going to know a lot more about that in the next 6 to 12 months, in part through these registries and in

part through other mechanisms. The reason is, we talked about those patients that have cardiovascular risk factors, and just like you would for a stroke, a garden variety stroke, a non-COVID stroke, you tell them the same thing as you would in the COVID case. It's very clear those patients are at high risk for these kinds of thrombotic events, and I think all the more reason to have good control of blood pressure, of obesity, of diabetes, of adverse metabolic profile. So lots of good reasons to have good cardiovascular risk factor control. That was true before COVID, that's now true during and after COVID.

I think the real tougher question that you're asking is, what if you're a patient that has no cardiovascular risk factors, really good risk factors? You now had a stroke, you're a young person, you're 45 years old, you've had a stroke. How do you prevent another stroke? How do you do a secondary prevention in those patients? And we would still pay a lot of attention to traditional risk factors, again, because we know they're important and because we have a sense that we know how to treat them, but what can you do in terms of a long-term strategy, or what is the risk of secondary stroke in that population? I would say we have very limited data on that. Even whether or not it's a problem and how big a problem it is, we simply don't know.

I mentioned at the top that brain imaging was a major problem in these patients, and one of the things we'd been involved in with the AHA and others was to develop, actually, a portable MRI machine that you can take to the bedside. We did this in COVID patients, actually, to diagnose things like stroke when patients couldn't either travel to a conventional scanner, or if they were simply just too unstable to be able to travel for a scan or if they were in a coma or a medically-induced coma where we couldn't look at neurological status. So I think one of the nice, broader things about the COVID story, the silver linings of a dark cloud, is that there have been a lot of motivation for technological innovation that can help patient care, and I think that portable MRI-based stroke imaging is something that we might be able to use in COVID and non-COVID contexts.

The other thing that I will just mention briefly, going back to the registry, is that currently, and I think you're one of the leaders in this, but in the COVID-19 era the American Heart Association has this wonderful track record of registries across cardiovascular and stroke modules that have really provided key observations going back several decades now, that have laid the groundwork for developing interventions that improve stroke care and that also improve the quality of stroke care. Right now,

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 relative roles of trials in our space, as well as the role that registries can fill.

So, beyond the role of the individual physician treating the individual patient, obviously, these kinds of infections with long-term sequella have implications for families, caregivers, downstream implications. I wonder if you could comment on the role or impact of diseases like this on caregivers and extended support structures.

Kevin Sheth: 25:44 Well, thanks for asking about that. I think that this is always particularly important for stroke, because stroke never infects individuals. It really affects families and communities. When somebody is changing their level of ability or they have a new level of disability, well, it really does take a village, and that's in

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 that now patients can go to safe units at a SNIF or rehab or long-term facility.

We then needed to make it safe for our physical therapists and our occupational therapists to engage, not just in the hospital, but also in communities. I would say, that's been low. It didn't happen overnight, but we're doing a lot more than we did, say, 3 months ago, and that's both because the people on the

		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.
Sandeep Das:	28:53	Fantastic. And so again, I want to thank you very much for taking the time to come out and talk with us, and appreciate all your hard work. I know Yale was really, really busy early on in the pandemic, so I know that you guys have pulled your way clinically as well, so I appreciate your efforts on that regard as well.
Kevin Sheth:	29:07	Well, thanks for the invitation. It's a wonderful program, and best of luck to all the efforts that you're leading. Thank you.
Sandeep Das:	29:13	Thank you.
Speaker 1:	29:14	Quality improvement in the time of COVID-19 is brought to you by the American Heart Association with support from Novartis Pharmaceuticals. The views expressed in this podcast do not necessarily reflect the official policy or position of the American Heart Association for transcripts of this podcast. And more information on the associations COVID-19 CVD Registry powered by Get With The Guidelines, visit us at heart.org/covidregistry.