Dr Carolyn Lam: Welcome to Circulation on the Run, your weekly podcast summary and backstage pass to the journal and its editors. I'm Dr Carolyn Lam, associate editor from the National Heart Center, and Duke National University of Singapore. Will artificial intelligence replace the human echocardiographer? Aha, well to find out the answer, you have to wait for the incredibly exciting discussion of today's feature paper coming right up after these summaries.

The clinical benefits of the cholesterol ester transfer protein, or CETP inhibitor dalcetrapib depends on adenylate cyclase type 9, or ADCY9 genotype. However, what are the underlying mechanism responsible for the interactions between ADCY9 and CETP activity? In the first paper from today's journal first author Dr Rautureau, corresponding author Dr Tardif from Montreal Heart Institute, and colleagues used a mouse atherosclerosis model inactivated for ADCY9 and demonstrated that loss of ADCY9 protected from atherosclerosis and was associated with improved endothelial function, but only in the absence of CETP. ADCY9 in activation increased weight gain, adipose tissue volume, and feed efficiency, but only in the absence of CETP.

This mouse model reproduced the interactions between ADCY9 and CETP activity observed in patients, and offers new mechanistic insights for the importance of ADCY9 in determining the responses to CETP inhibition. For example, the dal-GenE clinical trial is currently testing prospectively whether patients with coronary disease and the favorable ADCY9 genotype will benefit from dalcetrapib.

The next study addresses the controversy around the cardioprotective effects of Omega-3 polyunsaturated fatty acids, and uncovers signaling pathways associated with eicosapentaenoic acid, or EPA supplementation that may mediate protective effects in atherosclerosis. First author Dr Laguna-Fernandez, corresponding author Dr Bäck from Karolinska Institute, and their colleagues showed that EPA supplementation significantly attenuated atherosclerotic lesion growth. They performed a systematic plasma lipidomic analysis and identified that 18 monohydroxy eicosapentaenoic acid was a central molecule formed during EPA supplementation. 18 monohydroxy eicosapentaenoic acid was a precursor for the plural resolving lipid mediator called resolvent E1.

In the present study, a resolve in E1 was shown to regulate critical atherosclerosis related functions in macrophages through its downstream signaling receptor to transfuse protective effects in atherosclerosis.

Are there racial differences and long-term outcomes among survivors of in-hospital cardiac arrest? In the next paper first and corresponding officer Dr Chen from University of Michigan and her colleagues performed a longitudinal study of patients more than 65 years of age who had an in-hospital cardiac arrest and survived until hospital discharge between 2000 and 2011 from the National Get With The Guidelines Resuscitation Registry whose data could be linked to Medicare claims data. They found that compared with white survivors of in-

hospital cardiac arrest, black survivors had a more than 10% lower absolute rate of long-term survival after hospital discharge. This translated to a 28% lower relative likelihood of living to one year, and a 33% lower relative likelihood of living to five years after hospital discharge for black versus white survivors.

Nearly one-third of the racial difference in one-year survival was dependent on measured patient factors. Only a small proportion was explained by racial differences in hospital care, and approximately one-half was the result of differences in care after discharge, or unmeasured confounding. Thus, further investigation is warranted to understand to what degree unmeasured, but modifiable factors, such as post-discharge care may account for the unexplained disparities.

The next study provides insights into a novel mechanism of atherogenesis that involves protease-activated receptor 2, a major receptor of activated factor 10, which is expressed in both vascular cells and leukocytes. Co-first authors Dr Hara and Phuong, corresponding author Dr Fukuda from Tokushima University Graduate School of Biomedical Sciences, and their colleagues showed that in ApoE-Deficient deficient mice, protease-activated receptor 2 signaling activated macrophages and promoted vascular inflammation, increasing atherosclerosis.

Furthermore, they showed that in humans, plasma-activated factor 10 levels positively correlated with the severity of coronary artery disease, suggesting that the signaling pathway may also participate in atherogenesis in humans. Thus, the protease-activated receptor 2 signaling pathway may provide a novel mechanism of atherogenesis and serve as a potential therapeutic target in atherosclerosis.

The next paper tells us that biomarkers may help to predict specific causes of death in patients with atrial fibrillation. First and corresponding author Dr Sharma and colleagues from Duke Clinical Research Institute evaluated the role of biomarkers in prognosticating specific causes of death among patients with atrial fibrillation and cardiovascular risk factors in the ARISTOTLE trial.

They looked at the following biomarkers: high sensitivity troponin T, growth differentiating factor 15, N-terminal pro-B-type natriuretic peptide, and interleukin 6. They found that sudden cardiac death was the most commonly adjudicated cause of cardiovascular death, followed by heart failure and stroke or systemic embolism deaths. Biomarkers were some of the strongest predictors of cause-specific death, and may improve the ability to discriminate among patients' risks for different causes of death.

How do the complement and coagulation systems interact in cardiovascular disease? Well in the final original paper this week, first author Dr Sauter, corresponding author Dr Langer from Eberhard Karls University Tübingen, and their colleagues used several in vitro, ex vivo, and in vivo approaches as well as different genetic mouse models to identify the anaphylatoxin receptor C3AR

and its corresponding ligand C3A as platelet activators that acted via intra - platelet signaling, and resulted in activated platelet fibrinogen receptor GP2B3A. This in turn mediated intravascular thrombosis, stroke, and myocardial infarction. This paper, therefore, identifies a novel point of intersection between the innate immunity and thrombosis with relevance for the thrombolic disease of stroke and myocardial infarction.

That wraps up with week's summary. Now for our featured discussion.

Can we teach a machine to read echocardiograms? Well today's feature paper is going to be all about that. I am so excited to have with us the corresponding author of an amazing, and I think, landmark paper, Dr Rahul Deo from the One Brave Idea Science Innovation Center and Brigham and Women's Hospital in Boston, as well as our associate editor Dr Victoria Delgado from Leiden University Medical Center in The Netherlands. Now let me set the scene here. We know that echocardiography is one of the most common investigations that we do in cardiology, and in fact even outside of cardiology, and it is hands down the most accessible, convenient tool to image the heart.

Now let's set this up by remembering that echocardiograms are performed with machines, but led by echocardiologists like me. Now this is really scary Rahul because I think your paper is trying to say ... Are you trying to put people like me out of business?

Dr Rahul Deo: Definitely not. I think what I'm hoping to do is actually two things. One of them is, despite the fact that it's an accessible and safe tool, because it needs people like us, it's probably not used as often as ideally it could be. So part of our hope was to democratize echocardiography by being able to take out some of the expenses from the process so that we can hopefully get more simpler studies done at an earlier stage in the disease process. Because in many ways, at least from my experiences being an attending, it feels like if we could just have gotten to these patients earlier we may have been able to start therapy that could've changed the disease course, but our system can't really afford to do huge numbers of echoes on asymptomatic patients. Really we were trying to find some way of facilitating this by at least helping out on trying to quantify some of the simple things that we do with echocardiography.

Dr Carolyn Lam: I love that phrase, democratizing echo. And you're absolutely right, if we could put it in the hands of non-experts and help them interpret them, we could really lead to detecting disease earlier, and so on and so forth. Wow. But everyone's wondering, how in the world do you go about doing that?

Dr Rahul Deo: One of the things that's really been amazing in these last five years or so is that the field of computer vision, so the field by which computers are trained to mimic humans in terms of visualizing, recognizing, identifying images, has really advanced, and incredibly rapidly. And one of the reasons for that is that the video game type of computing system, the same things that go into Playstations

and such, have resulted in much, much more rapid computing. And that's allowed us to train more complex models.

So that's one of the things that's changed, and also, it's just much easier to get our hands-on training data. So machines can be trained to do things, but they need lots of examples. And the harder the task, the more examples they need. So the widespread availability of digital data has made that easier, though I would say that it wasn't that easy to get our hands on enough echocardiography data to be able to train. But in general, almost any task where there's enough data has been solved on the computer vision side. So this has really been an exciting advance in these last few years. So we thought we could very well just used these same technologies on a clinical problem.

Dr Carolyn Lam: Okay, but Rahul what are you talking about here? Like the machine's actually going to recognize different views, or make automated measurements? That's the cool thing, frankly, that you've written about because we know that the machines can already kind of do EF, ejection fraction, but you're talking about something way bigger. So tell us about that.

Dr Rahul Deo: Yeah, so there are many cute examples in the popular press about machines being able to recognize the differences between cats and dogs, or some breeds of dogs. And so if you think about things that way, it really shouldn't be that much more difficult to imagine recognizing between different views, which probably are much more dramatically different than different breeds of dogs. So you could really just take the same models, or the same approaches, give enough examples, label them, and then say figure out what the differences are.

And I think one of the challenges with these systems is they're often black boxes. They can't tell us exactly what it is that they're using, but when it comes to something like recognizing whether something is an apical four chamber view or a parasternal long axis view, we actually don't care that much as to how it is that the computer gets there. We just wanted them to do it accurately, and that's one of the places for some of these computer vision models. It's a field broadly called deep learning, and it's just great at achieving complex tasks.

So, once you recognize views, then the other thing that computers have been shown to be able to do is recognize specific objects within an image. For example, you could give an entire football field and you could find a single player within it. You could recognize where the players are, where the ball is, where the grass is. So computers can distinguish all those things too. And then once you know where something is, you can trace it and you can measure it. So in that sense it's very similar to what a human reader would do, it's just broken down into individual steps, and each one of those needs to be trained.

Dr Carolyn Lam: You put that so simply so that everyone could understand that. That's so cool. You mentioned, though, accuracy. I could imagine that a machine would likely interpret one image the same way again and again, and that addresses

something that we really struggle with in echo doesn't it? Because, frankly, one reader against another, we always know. Ejection fraction has got a plus minus seven or something, and then even within the same reader you could read the same thing and say something one day, and say something the other. So this is more than just automating it, is it?

Dr Rahul Deo: Yeah, so it's certainly making it more consistent, and the other thing that we were able to do, I mean once you can teach it to identify and traces the contours of the heart in one image you can have it do it in every single image within the video, and every single video within the study. So now, I mean it's quite painful. I know this from my own experience in terms of tracing these things, so a typical reader can't trace 150, 200, 300, 500 different hearts, that's not going to happen. So instead, they'll sort of sift through manually, pick one or two, and if there's variability from one part of the study to the other, that really won't be captured.

And in this case, the computer will very happily do exactly what you ask it to do, which is to repeat the same thing again and again and again, and then be able to average over that, capture variability. So that's one of the tasks that is much more easy to imagine, setting a computer who won't talk back to you and won't resist and won't refuse to actually taking on the mundane aspect of just getting many, many, many more measurements. And that could happen not only in a single study, but also could happen more frequently. So you could imagine that, again, there's just not that resistance that's coming from having to have an individual do these things.

Dr Carolyn Lam: Oh, my goodness, and not only does he not ... well he, machine, not say no, I mean they don't need to take time off or weekends off. We could get immediate reports directly. Oh my goodness. Victoria I have to bring you in on this. We knew as editors when we found this paper that this is something we just have to publish in Circulation that's going to be groundbreaking. Could you tell us a little bit more about what you think the implications of this is?

Victoria Delgado: I think that this is a very important paper because it's a very large study and it's sets, I would say, three important questions that we deal every day in clinical practice. One is how to reduce burden in very busy echo labs by facilitating the reporting of the echoes and the interpretation of the echoes. Second: to have an accurate measurement and quantification of the images that we are acquiring, and third: this is recognition of the pattern.

And I think that this very important, particularly in primary care because, for example in Europe here, echocardiography is not really in the primary care and the patients are being referred to secondary level hospitals or third level hospitals. That means that the waiting days sometimes is too long. If we train the general practitioners, for example, to do simple echocardiograms with the handheld systems which are also the technologies that are coming and are

really available in your iPhone, for example, on your phone, you can get an echocardiographic evaluation of a patient that comes to a general practitioner.

And if you don't have too much knowledge on interpretation, these tools that can have recognition of the pattern of the disease can trace a red flag and say, okay this patient may have this disease or may have this problem, you should consider sending or referring this patient to us at Leiden Hospital where he's going to have a regular check-up and a complete echocardiogram. That could lead to less burden in very busy labs and only refer the patients in a timely manner to the centers when they have to be referred, when the others can wait of can be referred much later.

I think that that's important, and next two technologies that are coming now and it will be very important, some groundbreaking technologies. One is the handheld systems, the ones that you can have in your phone, the ones that you can have in your tablet for example. And the other one is going to be the artificial intelligence to, if not diagnose completely, at least to recognize the pattern that there is a pathology where we need to focus, and we need to act earlier.

Dr Rahul Deo: I think that one place we would like to see this used is in a primary care setting where you have individuals who have risk factors that we know would be risk factors, for example, for let's say heart failure with preserved ejection fraction. But really, my experience in that phase of clinical practice is there's a lot of resistance from patients to get on the medications. So hypertension is, at that point, often, I just got worked up because I had a hard time finding parking, and so on, and so on, where there's just a natural resistance.

So if you could imagine having objective measures describing, let's say how their left atrium is doing at that point, how it looks the next year, what the change in therapy is doing, all these things, you actually can bring in that quantification at a low enough cost that makes it actually practical, then that would be one place we could imagine motivating or intensifying therapies on the basis of something like this.

And I think one area we have to admit we didn't solve is we haven't solved the ability to facilitate getting the data in the first place. We do know that there are these focused workshops around trying to get some simple views, and more and more of our internal medicine residents are able to get some of these, but we can't dismiss that this is still an important challenge in terms of being able to get the images. What we want to do is say, well you can get some images and we can help you interpret them and quantify in an effort to try to motivate therapies being initiated or intensified in a way that's sometimes difficult to do in the current system.

Dr Carolyn Lam: So, Rahul and Victoria, you both mentioned that one of the key aspects is the acquisition of the echo. Not just the machine that does it, but also who takes

the images that will then be automatically analyzed. So, Rahul, do you think that sometimes you're going to invent something that will replace even the acquisition, or maybe even simplify it so that we may not need Doppler anymore?

Dr Rahul Deo: One of the things that we thought about was, we wanted to limit ourselves to views that might be easier to acquire, in part because we wanted to reduce the complexity of the study and yet still try to capture as much information as possible. And getting back to the first part of your question, you could imagine that recognizing a view is not that different from recognizing that a view is 10 degrees off from where it should be. You could imagine training a computer to do just that very same thing too. It could recognize a slightly off axis apical four chamber view and guide you into correctly positioning the probe, and you could even imagine a robotic system that does this and just takes the person out of it all together. In part because a very skilled sonographer can quickly look at something and say, oh I just need to tilt my wrist this way and move it this way. I was always humbled by that because I never could quite do that myself.

But in the same way, and in the way, that's happening is that an image is recognized, and then the reference image is held in one's brain, and then they just know from experience what needs to be done to turn one into the other. But that very well-oiled machine could very well be taught to do that exact same thing too.

Dr Carolyn Lam: Oh wow. That is just totally amazing. I know the listeners are being blown away by this just as I am. Let me just end by asking for any last words, Victoria and Rahul, of the clinical application of this. When are we going to have this primetime? What do you think?

Victoria Delgado: I think that this is coming. This is one, for example, of the first studies showing the feasibility of this technology. In terms of accuracy, probably we need improvement, but that depends very much on the quality of the echocardiographic data that we obtain. And in the future, I think that we are going to rely more and more on this technology, and we will have the expert view for those cases that are ambiguous or where the technology has limitations. But in terms of accuracy, for example, I can imagine one of the clinical scenarios that we face in everyday clinical practice is the evaluation of the effect of the treatment in heart failure patients for ejection fraction, and in patients, for example, treated with chemotherapy to see changes in ejection fraction.

That, if we do it manually as we do now, we know that we have limitations in terms of the own viability of the observer. If you leave it for artificial intelligence, maybe that viability may be reduced, and you may be better in terms of adjusting the medication if needed. Because you removed completely what would be the individual viability. So these are the fields that probably I see more and more application of this technology in order to improve the

reproducibility of the measurements and accuracy. But yeah, for that we need probably very good image quality, and I see in echocardiography we always tend to say, yeah the image quality is not that good. I'm sure that echocardiography can give you much more than just using through the echocardiography. You can use contrast, you can use many other techniques in order to improve the image quality. And artificial intelligence, the better the image quality is, probably the better it's going to be as well, the accuracy of the measurements and the recognition of disease.

Dr Carolyn Lam: Wow, and Rahul?

Dr Rahul Deo: I completely agree with Victoria. I think that we're going to have to be clever about where we incorporate something like this into the current clinical workflow. You have to choose your problem carefully, you have to understand it. Any system like this is going to make some mistakes. To figure out how to minimize the impact of those mistakes, and at the same time add benefit and potentially enable things that wouldn't even be done. So I think that the fun stuff is yet to come here in terms of really incorporating this in a way that can really change clinical practice.

I want to add one thing that I really haven't mentioned. And we, at this point, really just focused on trying to mimic the stuff that we're already doing. Part of the motivation of this work is to try to potentially see things that we can't even see right now and try to potentially predict onset of disease or early latent forms of something that would really be difficult to detect by the human eye. And we've seen examples of that in some of the other fields around radiology, and I think that's going to be a place that would be augmenting beyond what we're even doing currently.

But of course, the challenge is that the system has to be interpretable enough that we understand what it is that it's seeing, because otherwise I'm sure we'll be reluctant to embrace something clinically that we don't understand.

Dr Carolyn Lam: You've been listening to Circulation on the Run. Don't forget to tune in again next week.