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, from National Heart Center and Duke National University of Singapore.
Dr Greg Hundley:	And I'm Greg Hundley, associate editor for circulation from VCU Health Systems in Richmond, Virginia.
Dr Carolyn Lam:	What does cardiac autoimmunity, glycemic control, and cardiovascular disease risk and Type I diabetes have in common? Well, you've got to wait for our feature discussion. This one's such a hot one, don't you agree, Greg? We could hardly finish talking.
Dr Greg Hundley:	Absolutely, and Myra, you're just going to love listening to her.
Dr Carolyn Lam:	Yep, but stay tuned. First, we're going to discuss a couple of papers each. Greg.
Dr Greg Hundley:	Thanks Carolyn. So, the first paper I've got is from Professor Van Rein at Leiden University Medical Center. And basically he's getting at the issue of bleeding in patients with atrial fibrillation. So this is a retrospective cohort that evaluates different anticoagulation strategies for atrial fibrillation. They examined 272,315 patients that had a median age of 75 years and followed them longitudinally over time. These individuals experience 31,459 major bleeding events, and what he did is he evaluated whether they were not taking anticoagulant therapy, whether they were on a vitamin K antagonist, a DOAC, antiplatelet therapies, and then all combinations of the above, including single, double and triple therapy.
	What he observed is relative to taking a vitamin K antagonist alone. The hazard ratios range from 1.13 to 3.73 in those that were receiving dual antiplatelet therapy of vitamin K antagonist plus antiplatelet therapy, a DOAC plus antiplatelet therapy, and then of course triple therapy, which had that highest hazard ratio.
Dr Carolyn Lam:	But were there particular combinations within these groups that had particularly high bleeding risk?
Dr Greg Hundley:	Well, yeah, Carolyn. As we might expect, triple therapy was the worst, but those that were receiving triple therapy, there were two subgroups that were particularly susceptible to having a bleeding episode. First, those that were greater than 90 years of age, and second, those that had CHADS-VASc 2 scores greater than six. Of course, these are very complicated patients, often particularly that latter group. So there are clinical implications. I mean, clearly, this isn't a randomized trial, but what we should take away from this is that if we have one of those two patient groups, age greater than 90, CHADS-VASc score greater than six, that we ought to minimize the time that those individuals are on that triple therapy.

Dr Carolyn Lam:	Talk about and bleeding, I've got a paper, and it's on the performance of the ABC scores for assessing the risk of stroke and systemic embolism or bleeding in patients with atrial fibrillation. This is a study that actually looked at the performance of these scores in an external cohort, which actually hasn't really been done. Now, as a reminder, the ABC score is actually the age biomarker clinical history stroke score, which helps to estimate the risk of stroke or systemic embolism. The ABC bleeding risk score incorporates biomarkers along with the clinical variables to estimate the risk of bleeding.
	All of these were tested in the ENGAGE AF-TIMI 48 trial, which was that multinational randomized trial of the oral factor Xa inhibitor edoxaban in patients with atrial fibrillation and a CHADS-VASc 2 score of two and above. Now, this was from Dr Morrow and the TIMI study group in the Brigham and Women's Hospital, Harvard Medical School in Boston, Massachusetts. Basically what they found was that the ABC stroke and ABC bleeding risk scores performed well in stratifying the risk for stroke or systemic embolic events or major bleeding in this multinational trial.
	Compared to the CHADS-VASc score, the ABC stroke score provided both correct upward and downward reclassification of the stroke systemic embolism risk. Compared with the HAS-BLED score, the ABC bleeding score resulted in a predominantly correct downward reclassification of the bleeding risk.
Dr Greg Hundley:	So, this new ABC score, do we integrate it with HAS-BLED? Do we integrate it with CHADS-VASc 2? How do we use this clinically?
Dr Carolyn Lam:	So first of all, there are some important remaining unanswered questions, and this was really nicely discussed in an accompanying editorial by Dr Hylek from Boston University School of Medicine. Among this, first of all, the ABC scores need to be validated in patients outside of a clinical trial. Remember, this was a clinical trial cohort. Then there are questions about the timing of measurements of the score, the different settings, hospital and otherwise. Do these scores perform equally well across different vascular beds and in diverse patient populations at the same thresholds used?
	So, all these things still need to be addressed. And really, in Dr Hylek's words, the work has just begun.
Dr Greg Hundley:	This is an issue with the theme that might be bleeding, and I'm going to talk about a study from Professor Huisman from Leiden University again, and this is the RE-VERSE AD study. Again, patients that are receiving dabigatran and that may have a GI bleed or patients that are on this therapy and unexpectedly need an emergent surgical procedure, this investigative team evaluated the utility of idarucizumab on reversing that anticoagulant dabigatran. So what did they do? They administered 2.5 milligrams of idarucizumab twice separated by 15 minutes.

And again, the study population was uncontrolled GI bleeding or those in need of an emergent procedure. The types of GI bleeds that were involved in this study, a third were upper GI bleeds, a third lower, and then a third, it was either unknown, or there was a mixture of both upper GI or lower GI bleeding. So how do we know that dabigatran is effective? We use a DTT time, and 98% of those with an elevated diluted thrombin time had that reduced after receiving these two twin 2.5 milligram doses at a time point of four hours after administration.

Dr Carolyn Lam: Okay, but were there any complications?

Dr Greg Hundley: Yeah, there were. So first of all, something to think about is that this is a high-risk group. In this study, 14.6% of the cohort actually later died either from the bleeding or what have you. Then another thing we need to be thinking about is when we reversed this anticoagulant, do patients experience thrombotic events? So what this group reported is 4.4% did within 30 days. What were those? Myocardial infarction, deep venous thrombosis, and subsequent PE. Then also at the 30-day time point, one patient experienced an ischemic event.

Another question is once you've administered this, you've gone through the procedure. You stopped the GI bleeding, or you've had the surgery. In this particular study, 66% of those individuals had restarted their DOAC. Those events occurred on top of that. So, interesting information. Looking at administration of idarucizumab, and we'll be using this I think frequently as DOACs are used more frequently in the population, particularly dabigatran, so some important data in guiding us on what we might expect when we administer this therapy.

Dr Carolyn Lam: I think going back to atrial fibrillation though, this is my other selected paper, and it's actually results from the GARFIELD-AF Registry. It's from Dr Bassand from University of Besançon in France, and colleagues, and basically, they looked at the early risks of death, stroke, systemic embolism and major bleeding in patients with newly diagnosed atrial fibrillation in the GARFIELD-AF Registry. They basically found that the rates of all three major clinical events was significantly higher during the first month than in the subsequent period set following up to 12 months.

The leading causes of early death were heart failure, sudden death, acute coronary syndromes, infection or sepsis, and respiratory failure.

Dr Greg Hundley: So, what's the take-home message here?

Dr Carolyn Lam: This is observational, so the key thing to understand here, it's a registry. It's observational. We can't really tell chicken from egg with regards to its newly diagnosed AF verses events, which comes first, which causes what. But nonetheless, the increased hazards of an early event and especially cardiovascular mortality in these newly diagnosed AF patients really point to the importance of comprehensive care for such patients and really should alert

physicians to detect warning signs of possible early mortality in these newly diagnosed patients.

Dr Greg Hundley: Very good, Carolyn.

Dr Carolyn Lam: I think that wraps it up. Let's hop to our feature discussion, shall we? I'm so super excited about today's feature paper because it may explain that strong link between hyperglycemia and cardiovascular disease in type one diabetes and all by revealing a potential novel pathway that may have been hiding in plain sight. And yes, I'm stealing the words of editorialists and our associate editor, Dr Naveed Sattar from University of Glasgow, and we're all so pleased to have with us the corresponding author of today's feature paper, Dr Myra Lipes from Joslin Diabetes Center in Boston, Massachusetts. Myra, start us off by telling us a little bit about your study please.

Dr Myra Lipes: Sure. So we were interested in examining the role of whether chronic hyperglycemia could trigger cardiac autoimmunity in type one diabetes, because chronic hyperglycemia is associated with subclinical myocardial damage, and we had actually previously observed just unexpectedly in a young adult cohort that ... Actually from Italy, where unexpectedly, we noticed that patients with the poorest glycemic control expressed cardiac antibodies. There's a lot of interesting people who are autoimmune-proned may overreact to injury of certain tissues.

So, type one diabetes, it's a classical autoimmune disorder. So we examined, really tested this hypothesis, in stored samples from the DCCT/EDIC study, and this is a very landmark study where patients were randomized to tight glycemic control, intensive glycemic control. Then another group had just conventional control, and this was done over an average of six and a half years. So during this time, the samples were stored. Every year samples were stored from participants, and this was quite a rich data set that is publicly available. So we studied the development of autoimmunity in two groups that had very distinct separations of the A1C level.

We specifically excluded people who developed kidney disease or cardiovascular disease events during the study. So this is a cohort that had relatively recent onset type one diabetes. They're relatively healthy, and again, groups were matched with cardiovascular risk factors at the beginning and the end of this DCCT period. And of course with our studies, we've also looked genetically because your HLA immune response genes can influence susceptibility to autoimmunity.

These patients were actually matched in HLA genotypes. So what we found was that patients with poor glycemic control, there was expression over time. You could see a time course relationship between expression of antibodies over time on the levels of the antibodies that were different in the two A1C groups. The number of antibodies were different in that with the high group expressing

more antibodies, more different types of antibodies. These are antibodies ... might say antibodies as like proteins in the blood, and they're actually directed against parts of the myocytes, the myofibrillar complex, and a major target is cardiac myosin heavy chain.

We saw the different parts of the myosin heavy chain retarded, and the presence of two or more antibodies, different types of antibodies, different regions of the myosin to different isoforms. Also, we saw antibodies, the troponin, troponin I. So the number of antibodies with different ... with almost a complete absence of antibodies in a tightly controlled group. I might mention the A1C average was 6.5%, so this is a very tightly controlled group whereas the poorly controlled group is at the opposite extreme, the average A1C during DCCT. The mean updated A1C was about 10%.

So, it was a very clean group, two different groups, and we could see that the number of the types, the number over time, very different in the two groups. In fact the profiles of these antibodies were almost very similar to patients with Chagas cardiomyopathy. That was our positive control group. Chagas cardiomyopathy is possibility to be a form of chronic myocarditis directed against cardiac myosin. So the profiles are almost indistinguishable. So on one hand, you have relatively healthy patients with type one before glycemic control, and that was very unexpected that this would look pretty similar.

But very interestingly, and I might say unexpectedly, we saw ... It was very clear that the people with the highest titers of antibody and the most different types of antibodies, particularly two or more, were subsequently ... We noticed that those patients were at high risk for developing CVD events. And that's while the number of events was slow, we noticed that all the patients, some 60%, had two or more antibodies and developed cardiovascular events. Perhaps one more striking example is a single patient in the study could die of cardiovascular death, had a positivity for all five antibodies at highest titer.

Then we looked at coronary calcification just to measure subclinical atherosclerosis. We noticed that the same numbers, two or more, and also the same antibody specificities that were the highest predictors of CVD events were also predictive of coronary ... had detectable coronary calcification. In addition, we looked at the levels trying to find mechanistically what could explain the link between cardiac autoimmunity and an increased risk for atherosclerosis. We looked at CRP, high sensitivity CRP levels.

Again, these were measured about a decade after the antibody samples were obtained, and we saw that the positivity for multiple antibodies was also associated with markedly elevated ... subsequently elevated high sensitivity CRP levels with levels of six versus something like 1.4 in a group with one or less antibody. So these were very intriguing findings, suggesting a role for autoimmune pathways as a susceptibility to cardiovascular disease in type one diabetes.

Dr Greg Hundley:	Myra, that was absolutely incredible description of the study and all the particulars of the findings. I wonder if I could ask both you and Naveed, where do you see the next steps moving forward with this research in the future? Number one. And number two, is this in any way can be used to segregate patients that may need, for example, really aggressive glucose control with an insulin pump or something of that nature?
Naveed Sattar:	I think we left this study as beautifully described as you see by Dr Lipes. I think the context ... We looked at this from editorial perspective ... is that most people don't realize if you have a middle-aged person with type one, their hazard ratio for cardiovascular risk is about somewhere between four to six fold for men and women respectively, which is much higher than type two. It's often thought that it's the area under the curve for hyperglycemia. But what this paper throws up is actually maybe there's another pathway, which we just didn't understand that this wasn't a permanent autoimmunity closing subclinical myocardial disease and inflammations.
	But potentially, for me though, there's a saying in British that one swallow does not make a summer. So, it would be nice for other groups to replicate this. I think the findings are, as they stand in isolation, fantastically well done. But it would be lovely if other groups had accessible samples, and I knew of several groups that have up towards tens of thousands of samples, maybe even not 10,000. Certainly 10,000 or so plus or minus samples for type and prospective outcomes to potentially validate the findings and extend them.
	And really, if the antibodies do help protect people at higher risk in a meaningful way and improve beyond what we can already do, then you're right. Absolutely. If we can pick up early people who are going to have substantially higher risk, you would want to potentially improve glycemic control, potentially pumps, CGM, closed-loop systems or more intensive statins or lower blood pressure targets or other types of antihyperglycemic agents, which seem to be being tested in type one as well. So that's really one example.
	And for me, the other thing would be really nice is to pull up any inflammation. Is this high systemic inflammation? Is it IL-6 level? Is it something else? What about troponin and BNP levels, et cetera. I'd be interested to hear what Dr Lipes thinks and how do you think to take it forward as well.
Dr Myra Lipes:	So, this is something Dr Sattar said and I completely agree. Actually, right now, we're looking at the DCCT cohort as a whole for already. It's relatively small compared to the population-based studies. But there's 1,400 patients, and the subjects had CMR studies that were published in Circulation. So we're going to actually study next whether we see CMR evidence of systolic dysfunction and looking at the broader DCCT cohort. So, those studies are underway. But of course the ultimate test would be looking at if there were samples available from the Swedish NDRs, Scottish registry.

I think it's something that's not often done prospectively. So that would be incredibly exciting, and that's the important thing. I'd say with type one diabetes, for screening for type one diabetes, the use of autoantibodies and particularly two or more different types of islet autoantibodies, and this is just putting things in a broader context, is the entry criteria for type one diabetes prevention trials and something cardiologists wouldn't be aware of but this particular thing. So in decades, people, researchers, in the field has spent decades optimizing islet antibody assays.

So by analogy, it would be really important to standardize assays so that they can be done in Sweden and Scotland and so that other groups could confirm this, and I'm confident that this could be done, since the setting up of our assays was really built on the experience of people of developing standardized assays and rigorous cutoff points for antibody positivity. So it would be really important to work internationally to try to tap into this.

Dr Carolyn Lam: Oh, my goodness. Myra, Naveed, these are such insightful comments. I think as Greg said earlier, I think we could go on forever discussing this paper, but I'm so sorry. Our time is up. Before we go though, I must point all readers to look at figure five of this marvelous paper. It puts together the whole schema of how autoantibodies can play a role both in myocardial and atherosclerotic cardiovascular disease and type one diabetes.

Thank you so much. Greg and I loved having you. Listeners, don't forget to tune in again next week.

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