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. Caroline Lam, associate editor from The National Heart Center and Duke National University of Singapore. Today we will be discussing the results of an individual level meta-analysis regarding venous thromboembolism and its risk factors, but first, here's your summary of this week's issue.

The first paper provides insights into paracrine signalling pathways that regulate epicardial adipose tissue formation. That is, referring to the adipose tissue located between the epicardium and underlying myocardium that is known to be strongly associated with coronary artery disease. In the current study from Dr. Lira of Icahn School of Medicine at Mount Sinai, New York, Dr. Pu from Boston Children's Hospital, Dr. [Chien 00:00:56] from Karolinska Institute and colleagues, the authors used a novel modified mRNA screening approach to probe the effect of individual paracrine factors on epicardial progenitors in the heart. Using two independent lineage tracing strategies in murine models, they showed that cells originating from the WT1-positive mesothelial lineage, which includes epicardial cells, differentiate into epicardial adipose tissue following myocardial infarction. This differentiation process required WT1 expression and was stimulated by insulin-like growth factor 1 receptor activation. Insulin-like growth factor 1 receptor inhibition significantly reduced its adipogenic differentiation and reduced WT1 lineage cell differentiation into adipocytes following myocardial infarction.

These results thus establish insulin-like growth factor 1 receptor signalling as a key pathway that governs epicardial adipose tissue formation in the context of myocardial injury. And it does this by redirecting the fate of WT1-positive lineage cells. The study also demonstrates the utility of a modified RNA based paracrine library screening to dissect signalling pathways in homeostasis and disease.

The next study brings us closer to understanding the mechanisms underlying diabetes-associated heart failure. In this study by first author, Dr. Wang, corresponding authors, Dr. Abel and Xiang from University of California, Davis and colleagues. High-fat diet feeding was used to induce obesity and diabetes in wild-type mice or mice lacking the beta-2 adrenergic receptor or beta-arrestin 2. High-fat diet feeding was found to selectively increase the expression of phosphodiesterase 4D in the mouse hearts in concert with the reduced phosphokinase A phosphorylation of phospholamban which contributed to systolic and diastolic dysfunction. The expression of phosphodiesterase 4D was also elevated in human hearts with diabetes. The induction of phosphodiesterase 4D expression was mediated by an insulin receptor and substrate as well as by beta-arrestin-2 dependent activation of a beta adrenergic receptor, ERK signalling cascade.

Genetic deletion of beta-2 adrenergic receptor or beta-arrestin-2 or pharmacological inhibition of beta-2 adrenergic receptor with carvedilol or G-protein receptor kinase 2 with paroxetine all significantly attenuated insulin-induced phosphorylation of ERK and phosphodiesterase 4D induction thus preventing diabetes-related systolic dysfunction.
Thus, targeting the insulin beta-2 adrenergic receptor pathway may be a novel way to prevent diabetes-associated heart failure.

The next study addresses the gap in care pertaining to implantable cardioverter-defibrillator or ICD use among Medicare patients with low ejection fraction following myocardial infarction. Dr. Pokorny and colleagues from Duke University Medical Center examined rates of post-discharge ejection fraction assessment and ICD implantation among more than 10,280 Medicare-insured patients age 65 years above with an ejection fraction 35% and below during an index myocardial infarction admission in the ACTION Registry Get With the Guidelines. They found that the cumulative incidence of ejection fraction reassessment within one year of myocardial infarction was 66.8%. Within the first year of post-myocardial infarction, 11% of patients who had an ejection fraction reassessment underwent ICD implantation which was significantly higher than patients without an ejection fraction reassessment. After multivariable adjustment, ejection fraction reassessment remained significantly associated with a higher likelihood of ICD implantation within one year in both revascularized and non-revascularized patients. Based on these findings, the authors recommend that all patients who are potential candidates for ICD therapy be scheduled for follow-up outpatient ejection fraction assessment prior to hospital discharge to bridge these currently observed gaps in care.

The next study is the first multi-institutional study in Asia describing current treatment strategies for total anomalous pulmonary venous connection. This retrospective study of 768 patients with total anomalous pulmonary venous connection operated on between 2005 and 2014 is from first authors Dr. Shi, Zhu, and Chen, corresponding authors, Dr. Chen and Zhuang and colleagues from the Shanghai Children's Medical Center and Guangdong General Hospital in China. While most patients underwent conventional repair, a sutureless patient was technique was employed in 10% of patients. Over a median follow-up of 23 months, there were 38 intraoperative deaths and 13 late deaths. A younger age at the time of repair, next an infracardiac total anomalous venous connections, pre-operative pulmonary venous obstruction, prolonged cardiopulmonary bypass time and longer duration of ventilation were all factors associated with increased mortality. Among these 717 survivors, recurrent pulmonary venous obstruction was found in 15% or 111 patients. Risk factors for recurrent pulmonary venous obstruction included pre-operative pulmonary venous obstruction, infracardiac total anomalous pulmonary connection, mixed venous connections and prolonged cardiopulmonary bypass time, a sutureless technique was associated with a lower restenosis rate compared to conventional repair in patients with pre-operative pulmonary venous obstruction but not in newborn patients. Thus, this study provides an important data on the outcomes following surgical correction and risk factors for poor prognosis in total anomalous pulmonary venous connection in Asia.

The final study is the first systematic review and meta-analysis on the association of genetic polymorphisms and outcome of clopidogrel-treated patients with ischemic stroke or transient ischemic attacks. In this paper from first author, Dr. Pan, corresponding author, Dr. Wang and colleagues from Beijing Tiantan Hospital, Capital Medical University in Beijing, China. Authors looked at 15 studies of 4,762 patients with
stroke or transient ischemic attack treated with clopidogrel and this included 3 studies from Europe and 12 studies from East Asia. They found that carriers of the CYP2C19 loss-of-function alleles were at increased risk of stroke compared to noncarriers. Composite vascular events were also more frequent in carriers compared to noncarriers while bleeding rates were similar. There was no evidence of statistical heterogeneity among the included studies for stroke but there was for composite vascular events suggesting that publication bias cannot be ruled out. Genetic variance other than CYP2C19 were not associated with clinical outcomes. The author suggested that their findings may justify genetic testing when clopidogrel is otherwise considered the preferred treatment modality, especially in East Asian patient populations in whom the prevalence of CYP2C19 loss-of-function allele is high.

In an accompanying editorial, Dr. Simon and [inaudible 00:10:11] suggest it maybe time to consider a prospective trial of personalized medicine using CYP2C19 genotyping in acute ischemic stroke and perhaps considering alternative medications in poor or intermediate metabolizers such as in the popular ongoing genetics trial in STEMI patients undergoing PCI. That wraps it up for the summaries this week. Now for our feature discussion.

Today's feature paper talks about the association of traditional cardiovascular risk factors with venous thromboembolism. And it is the first individual level meta-analysis of prospective studies. I am so delighted to have the first and corresponding author here with us, Dr. Bhaktawar Khan Mahmoodie from San Antonio's Hospital in the Netherlands. Hi Khan, thanks for being here.

Dr. Bhaktawar Khan Mahmoodie:

Thank you for inviting me. Thanks a lot.

Dr. Carolyn Lam:

And I am particularly delighted to have associate editor, Dr. Josh Beckman from Vanderbilt University joining us today as well. Welcome Josh.

Dr. Josh Beckman:

Caroline, it is such a pleasure to be here with you. I've been listening to these podcasts and they have been incredible. I've been waiting to be able to jump in and today's paper is an awesome place to start.

Dr. Carolyn Lam:

It certainly is. Congratulations on managing such an important paper. Khan, maybe I could start with you. Venous thromboembolism versus arterial thromboembolism. We're very familiar with the latter. We know it comprises coronary heart disease, stroke, peripheral artery disease. We're very familiar with the risk factors such as hypertension, hyperlipidemia, diabetes, smoking. But here you're asking, are these same
risk factors applicable in venous thromboembolism. That would include deep venous thrombosis, pulmonary embolism, where we traditionally classify it into provoked events that is triggered by things we know well like immobilization, surgery and so on. And then there are the unprovoked events that don't have any risk factors. So could you, first of all, point out ... you were looking at venous thromboembolism. What was your hypothesis with regards to the traditional cardiovascular risk factors?

Dr. Bhaktawar Khan Mahmoodie:

Many researchers in the last 10, 15 years, they go questions whether there is connection between venous and arterial thromboembolism. Since then, several studies published on that with controversial results. So our hypothesis for this paper was to see whether there is real associations or are we looking at some kind of associations due to confounding factors such as age and overweight which are risk factors for both.

Dr. Carolyn Lam:

Yeah. And yours is actually the first individual level meta-analyses of prospective studies dealing with this. Tell us what you found in ... Were you surprised by your findings?

Dr. Bhaktawar Khan Mahmoodie:

What we found that actually traditional, modifiable, cardiovascular risk factors like hypertension, diabetes and hyperlipidemia were not risk factors for venous thromboembolism. The exception was smoking, current smoking, which was particularly associated with provoked venous thromboembolism which is probably pro its association with cancer. And cancer itself is a strong risk factor for venous thromboembolism. About whether I was surprised, I was not surprised at all. We saw in several cohort studies and well-defined cohort studies that the association disappeared after adjustment for age and body mass index which are important confounders in these [inaudible 00:14:06]. That's what I expected and we found it and it is confirmed with this large individual level meta-analysis.

Dr. Carolyn Lam:

Great. But what did you think of the association of higher systolic blood pressure not with higher but with lower risk of venous thromboembolism?

Dr. Bhaktawar Khan Mahmoodie:

That was a bit surprising for us too but I think the best explanation we can give at the moment is probably that we have some kind of competing risk. And one suggestion that we gave in the paper as well is that maybe what we already know is that higher blood pressure is a strong risk factor for atrial fibrillation. Most of these people they receive oral anticoagulants. That is subsequently probably a protective factor for venous thromboembolism. We probably deal with some kind of competing risk from another
condition like the atrial fibrillation and use of anticoagulants which we could not unfortunately adjust for in this analysis.

Dr. Carolyn Lam:

Sure. That makes sense. Josh, can I bring you into this? I mean I remember well our multiple and long discussions at the editors meetings. This is one of those papers that is extremely important for its negative, neutral associations isn't it?

Dr. Josh Beckman:

I think this is one of the more important papers in this field in a long time. I am one of those people who has followed this literature and believed, based on the best previous publications, that there was a link between many of the arterial thrombosis or atherothrombotic risk factors and venous thromboembolism. In fact, Circulation published one of these meta-analyses, and I'm going to say only because this little paper is so large with only 21,000 patients demonstrating a clear association. So the first question I would have, we published that back at 2008, the first question I would have is can you describe for the general readership what such a large series of patients allows you to do that was not permitted by the other meta-analyses of say twenty to thirty thousand patients that have been previously in the literature.

Dr. Bhaktawar Khan Mahmoodie:

Thank you Dr. Beckman and thank you also for managing this paper. This is an important question and I think what we were able to do compared to the previous analysis in 2008, we were able to adjust for confounding risk factors. In the course, we included were all with validated venous thromboembolism events and also the events are temporal character, like all the risk factors were measured and then followed-up for event. While in that paper, there were many case-controlled studies added and the results were not adjusted for age and also not adjusted for body mass index. And if we do the same with what's done there, then we have the same results like in our [inaudible 00:17:14] associations, all of these risk factors were indeed positively associated with risk for venous thromboembolism.

Dr. Carolyn Lam:

Let me just state, I mean, there were almost 245,000 participants in your study. With 4,910 thromboembolism events, so this is really huge and gives you a lot of power to look at this thing very carefully.

Dr. Josh Beckman:

It was a 10-fold increase from any of the major publications in this area. It was almost geometrically larger in size which is why, I think its conclusion will be accepted differently than all the previous analyses. Now, let me ask one question about what you
already identified in your discussion as a possible limitation. Is this study applicable to all populations around the globe or do you think it is a bit more focused?

Dr. Bhaktawar Khan Mahmoodie:

I think it is focused at least. We don't have Asian population in these analyses and also the proportion of African-Americans were limited which was only limited to some U.S. cohorts so I think that there is a limitation which is results are probably only applicable for Caucasian population.

Dr. Josh Beckman:

I guess my other question is, one of the reasons that people, I think, advance the argument that there may be overlap between the two kinds thrombosis is that there was evidence that the medication, statin, may ... to a much smaller degree, reduce venous thrombosis as well as reducing arterial thrombosis. Do you think that this is evidence of some common pathophysiology? Or is it like smoking, it's truly working separately from arterial disease?

Dr. Bhaktawar Khan Mahmoodie:

Personally, I think that this association or the finding of statins reduce the risk of thromboembolism could be due to some pleiotropic effects of statins. Like even for stroke, we know that the association of cholesterol with stroke is not so clear-cut as it is with myocardial infarction but still it reduces risk of stroke. And also for venous thromboembolism, the risk reduction of venous thrombosis in the JUPITER trial was like 50%, which is very high, even better than aspirin. But I think that may not be directly related cholesterol levels but more to another pleiotropic effects of statins. It could influence levels of various coagulation [inaudible 00:19:56] in the endothelial stabilization which may be also important risk factors for venous thrombosis.

Dr. Josh Beckman:

One of the reasons that this paper is very important is that we begin to look for therapies and risk factors based on what the disease is caused by. And so the fact that you guys were able to establish, in my opinion, quite clearly what does and what does not contribute to venous thrombosis allows us to begin to think about the disease differently and approach it differently. I would like to provide congratulations. My one little ask of you is that one of the things that I think this podcast is great for is to explain to the readership what goes into this kind of work. Everybody thinks that someone else's research is easier to do than their own, which of course is a ridiculous thing. But can you describe for us what it's like and how long it took from the study initiation to when you completed it? How much work went into trying to get all these studies together to create this individual patient level data?

Dr. Bhaktawar Khan Mahmoodie:
Yeah. That was a great amount of work. Actually, I did a systematic review of the only PubMed publications back in 2014 and it took almost 2 years at least. I was not always active the whole 2 years but still I had to visit several PIs of the studies to get them so far to share their data. Eventually, I had to develop a code that will make it possible without sharing the individual level data by using the same definitions and the same categorization of variables so we call it a two-stage meta-analysis similar to one-stage if the definitions are similar. And eventually, I think that the real part of the analysis and inclusion of studies took like half a year or so. There was a lot of work.

Dr. Josh Beckman:

I think this is a tremendous amount of work and for those members of our readership who do basic research, or translational work, or practice in the clinics, it really needs to be made clear that this is a heroic effort of hundreds and hundreds of hours. And that getting together all of these studies is just an enormous undertaking. And that even though, we can read the paper in 10 minutes and gleam the most important part. It is an incredible amount of work for which you guys are to be congratulated.

Dr. Bhaktawar Khan Mahmoodie:

Thank you for acknowledging this. Thanks a lot.

Dr. Carolyn Lam:

Josh, I couldn't agree with you more and I truly couldn't have said it any better. Thank you both of you for making this just one of the best discussions we've had on this podcast. I'm sure the listeners all agree what a wonderful time we've had.

You've been listening to Circulation on the Run. Please remember to tune in next week.