Genetic Susceptibility for Coronary Heart Disease and Type 2 Diabetes Complications

Bob Barrett: This is the podcast from *'Clinical Chemistry'*. I am Bob Barrett. Type II diabetes is a worldwide public health challenge with growing incidents across the world. Cardiovascular disease which can include coronary heart disease, stroke, and peripheral vascular disease, is a major complication of diabetes. Although the association between diabetes and cardiovascular risk is established, the pathologic basis of coronary heart disease in patients with Type II diabetes may differ from that in the general population, and any genetic component is not fully understood.

In the May 2012 issue of *'Clinical Chemistry'* Dr. Seamus Harrison, a Vascular Surgeon from University College London examined recently published advances that attempt to establish the elusive link between Type II diabetes and coronary heart disease.

Dr. Harrison was recently awarded a British Heart Foundation Fellowship to carry out research on application of genomics to cardiovascular diseases, and he is our guest in this podcast from *'Clinical Chemistry'.*

Doctor your article looks broadly at the area of cardiovascular disease in Type II diabetes. Can you tell us a bit about the size of the problem we are facing on a worldwide basis?

Dr. Seamus Harrison: Well, I think starting with a clinical backdrop is very important. I mean Type II diabetes is an enormous problem. It perhaps the most important public health problem of the 21st century and let's hope by 2030, that over 400 million people worldwide will have the condition and its complications can be devastating. In the United States, it's one of the most common causes of blindness, kidney failure and lower-limb amputations.

I mean over half of people without diagnosis of Type II diabetes will die from a cardiovascular complication, so it's really an enormous problem.

Bob Barrett: Your article discusses at some length the recent paper by Chii and colleagues, what's the background to that publication?

Dr. Seamus Harrison: Well, given the enormous burden of cardiovascular disease and people with Type II diabetes, I think understanding the mechanisms of increased risk in these patients is really important and more

importantly, how to protect and effectively prevent cardiovascular disease in those patients.

We know the understand the cardiovascular risk factors such as LDL cholesterol or high blood pressure, do play a role. But there is question as to whether there are alternate pathways specifically in diabetic populations and understanding these pathways might highlight potential targets for noble preventive measures.

Bob Barrett: How does Chii's paper address the problems?

Dr. Seamus Harrison: Well, we know that the cardiovascular disease results from a complicated network of environmental and genetic risk factors which we don't fully understand at present. Let's say in the last three or four years, there has been an explosion of genomic technology and genome-wide association studies which has allowed us to take large steps in our understanding of the genetic determinants of both coronary disease and diabetes.

What is not been addressed by GWAS however is the genetic variants that's specifically underpinned cardiovascular complications in the diabetic population. In this paper, the authors looked at whether or not genetic variance that we knew increase the risk for coronary disease and the general population also increased the risk in populations of diabetic patients.

They also looked at whether or not these variants in combination with established non-genetic risk factors could be used to effectively predict cardiovascular complications in these cohorts.

Bob Barrett: And what were the findings of these research?

Dr. Seamus Harrison: Well, it tested 15 genetic variance in three cohorts of patients of Type II diabetes and there are over a thousand cases of coronary disease and over a thousand controls. They find that of those 15 variants five showed a significant association with an increased risk of coronary disease, specifically in patients with Type II diabetes and the other ten variants they looked at didn't show an association.

Bob Barrett: Does this means that the genetic architecture of coronary disease is different in people with Type II diabetes?

Dr. Seamus Harrison: Well, it's a good question but I am not sure we can answer fully from these data. Three of the variants that were associated with an increased risk, are thought to act through lipid pathways, so we might expect the positive association and they certainly supports the aggressive management Dyslipidemia in patients with Type II diabetes.

I guess the important point to make however is that we probably can't rule out a rule for those variants that didn't show a significant association. As the sample size and the study probably wasn't large enough to confidently show this.

Bob Barrett: What else did they look at in this paper?

Dr. Seamus Harrison: Well, the other thing they looked at and perhaps this is the most interesting part was whether a panel of genetic variants could be used in combination with established non-genetic risk factors, such as LDL cholesterol, and blood pressure to predict the occurrence of cardiovascular complications in patients with Type II diabetes. They find that adding the genetic variants through the more established model, did improve its predictive accuracy, and they suggested there maybe a rule for genetic testing in cardiovascular disease and diabetes.

Bob Barrett: So then should we start applying genetic testing in patients with Type II diabetes on a routine basis?

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Dr. Seamus Harrison: Well, the answer to this in my view is probably no, and there are couple of reasons for this. The first is that although the authors were able to show us statistically significant improvement in the area under receiver operating curve, a metric used to test the predictive efficacy of a test, the improvement was really very small in absolute terms and I thought it would be clinically meaningful and although there was an improvement in risk classification, this was not against any standard classification used in clinical practice. So I think this area of result is pretty difficult to interpret.

The second reason for not implementing testing, just yet is a slightly broader reason. We know that people with Type II diabetes by the very nature of the disease have a very high cardiovascular risk, and can't prevent if strategies rely upon pharmacological intervention to control blood pressure and lipids and

glycosylated hemoglobin as well as their life style interventions.

I think therefore, the most effective way to prevent cardiovascular disease in the diabetic population, is actually to target interventions at all patients with Type II diabetes.

We know that even it's the highest risk group by the score have comparatively more events than those in the little risk group, the greatest burden of events on a population level will be in those people with intermediate risk which I think really supports the universal preventative strategy.

The caveat that would answer this is that if different preventative medications are devised that need to rationed for one reason or other, perhaps safety or economic grounds then stratifying risk may become a more useful strategy.

Bob Barrett: The authors make the point that results from genetic testing could be used early in life before risk factors become apparent. So early targeted treatment may be possible?

Dr. Seamus Harrison: Well, this is an interesting point and I think as a clinician I am not sure how I could justify giving for example a blood pressure medication to somebody with normal blood pressure just because their genotype says they maybe hypertensive later in life. But a question of when to implement genetic testing, and when to implement preventative strategies is a question that I think we haven't been able to answer yet and this is certainly something that we need to looking at over the next couple of years.

Bob Barrett: Well finally doctor, how would you sum this all up?

Dr. Seamus Harrison: Well, I think this was a really interesting paper that brought forward our understanding of the potential for genetic testing in common complex diseases. And I think like many of the other papers that have used similar methodology, the technique probably isn't ready for primetime just yet but we may get there with more genetic variants and understanding either genetic variants and the non-genetic risk factors interact.

Bob Barrett: Dr. Seamus Harrison is a Vascular Surgeon from University College London. He has been our guest in

this podcast from *'Clinical Chemistry'.* I am Bob Barrett. Thanks for listening.

Total Duration: 8 minutes