Host: This is the podcast from *Clinical Chemistry.* I am Bob Barrett.

The August issue of *Clinical Chemistry* reported on the first perspective analysis, revealing an inverse association between Lp(a) in Type 2 diabetes. It confirmed a significant and independent association between increased Lp(a) concentrations and risk of CHD in addition to opening the door to a potentially more precise assessment of diabetes risk.

Dr. Samia Mora is lead author of the report. She is a Cardiologist at the Division of Cardiovascular Medicine and Preventive Medicine at the Brigham and Women's Hospital and an Assistant Professor of Medicine at Harvard Medical School. She is our guest in this podcast.

So, Dr. Mora, tell us about Lp(a). What exactly is it and how is it different from LDL?

Dr. Samia Mora: Well, it's a very interesting question Bob because Lp(a) is just a fascinating molecule. It was first discovered by Berg in 1963, and it's a variant of the LDL particle. So it's basically looks like an LDL particle, but there is attached to it an apo(a) molecule and that's attached to the LDL particle with a disulfide bond.

So it's basically a fancy LDL particle that carries with it this apo(a) molecule on it and this apo(a) turns out – it comes in many different varieties of what we called isoforms. One of the important milestones in the research on this molecule Lp(a) was discovering the sequence of the apo(a) genes and discovering also that there is homology, some similarities between apo(a) and the plasminogen genes.

Now this apo(a) consists of different types of plasminogen, kringle IV-like piece what we call kringles, kringle is like a Danish pastry, if you want to think about it, these like small Danish pastries all lined up together, forming part of the apo(a) molecule and the size of this apo(a) molecule which is basically the number of these Kringle IV repeat determines the Lp(a) level inversely.

So that a bigger apo(a) molecule results in lower Lp(a) levels and relating means mostly to degradation of the particle and it turns out that Lp(a) as well as the apo(a) size is really very heritable and

highly genetically determined, mostly depending on the apo(a) isoform.

Another interesting finding is that Lp(a) is found only in humans and only in some particular types of monkeys. So it's a fascinating molecule really, and we know it's composed of a lot of cholesterol, since it's similar to the LDL particle. And so people measure Lp(a) levels, it contributes also to LDL cholesterol levels in the blood stream.

Host: Now, what is the role of Lp(a) in cardiovascular disease?

Dr. Samia Mora: Well, many groups have found elevated Lp(a) predicted increased risk of cardiovascular disease. Since it was discovered back in the 1960s many studies have since been done in many different population and it turns out pretty consistent. There is about one-and-half up to twofold increased risk for individuals who have the highest levels of Lp(a).

And it seems to carry about the same level of risk compared to other risk factors that we candidly agree upon such as LDL cholesterol or HDL cholesterol or even high-sensitivity c-reactive protein Levels and the Emerging Risk Factors Collaboration recently published a big meta-analysis from over 36 studies included over a 100,000 individuals.

These are really worldwide and they found about 10 to 13% increase relative risk for each standard deviation increase in Lp(a) for both coronary events and for stoke. And it turns out Lp(a) and as I said has an important genetic role, so it turns out families with premature CVD, about 20% of them have elevated Lp(a). So we sometimes check it in individuals who get premature cardiovascular disease at the young age.

We also know that elevated Lp(a) plays a role in increased risk in patients who have renal disease and recently genetic polymorphisms in apo(a) have been found to affect the level of Lp(a) concentration on the blood stream and these polymorphisms that result in higher Lp(a) levels, also result in higher CVD risk and also vice versa.

So there are many pleiotropic effects of Lp(a) and its role in cardiovascular disease. The exact mechanism for how it increases CDV risk remains unclear. Some people postulate that this may relate to the homology, I was talking about earlier between the

apo(a) component and plasminogen, so if postulated that perhaps it's interfering with coagulases, so busting the colt because of the homology with plasminogen.

Other purposed mechanism is that since it's LDL particle that's modified by the apo(a) molecule that its' estrogenic because it's really like an LDL particle and has been found actually in the walls of individuals and also the walls of arteriosclerotic plaque. And a third mechanism possibly is that Lp(a) has been recently recognized to accept oxidized phospholipids more preferentially than the standard LDL particle and so some people postulate maybe a reservoir for this oxidize phospholipids.

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Host: Well, given what we know about Lp(a) and cardiovascular disease, were you surprised with the results in relation to Type 2 diabetes?

Dr. Samia Mora: Well, typically it might be yes. Initially, we had expected they will be the opposite. So we thought that well since higher levels of Lp(a) have been found in over these many studies and cardiovascular disease to be increased risk, we saw diabetes shares a lot of risk factors with cardiovascular disease and we thought it should probably increase risk as well in diabetes.

Cardiovascular and diabetes share genetics as well as other environmental risk factors, and even lipid growth factors for example, HDL cholesterol, triglycerides are both risk factors for cardiovascular disease and for diabetes. So we are really were expecting it in the other direction and based on prior studies, there hasn't been really been much data before on examining the relationship for diabetes and Lp(a).

There have been a few small case control studies and those have been really small and inconsistent, some finding increased risk, some finding lower risk, and we know case-control studies in general aren't the best way to evaluate whether a particular risk factor is associated with disease, because it's susceptible to bias, since in case-control studies you are ready selecting people who have the disease for example, in this case, diabetes and having diabetes it may alter the Lp(a) concentration as a result of having the diabetes as opposed to as a risk factor for diabetes.

So we know prospectus studies are agreed upon to be the best way to refer to determining these risk factor associations and so we conducted first prospective study examining Lp(a) and Type 2 diabetes and we looked at the Women's Health Study, which is a well characterized, very large study of over 26,000 women and we examined whether or not baseline levels of the Lp(a) predicted future risk of diabetes up to 13 years later.

We had about 1,600 cases of Type 2 diabetes during this follow up period and again, like I said, that we are really surprised to find that the Lp(a) concentrations were lower in the cases compared with the non-cases, and inversely predicted diabetes so that individuals who had lower levels of Lp(a) had higher risk of diabetes.

We also found there was a difference between fasting and non-fasting women. So the women who were fasting, there was about 20% lower risk in the quintile 2 to 5 of Lp(a) concentration compared to quintile one and it seems to be a threshold defect versus those who were non-fasting had their blood Lp(a) concentration measured on non-fasting blood samples. They seem to have more of a greater risk and up to 50% lower risk in the top quintile compared to the lowest quintile.

So it seems to be more of a linear affect in those non-fasting women. And we found that predicted risk even after adjusting for all the standard risk factors for diabetes including HbA1c, hemoglobin A1c concentration and we also adjusted for body mass index and other lipid growth factors. So basically adjusted for all the non-risk factors for diabetes and it's still was associated with this inverse risk.

Host: Well your study found that inverse relationship for Lp(a) in future diabetes in U.S. women, then you confirmed your findings in another population. Tell us about your findings and that population of Danish men and women?

Dr. Samia Mora: Yes, so what we did was since we were surprised by our finding, we wanted to make sure this wasn't a random finding, and so first we replicated it in the same Women's Health Study, since we had excluded before the women who had problem with diabetes at baseline, because we wanted to see association with insulin diabetes in the first part of the study.

So we went back and we identified the women who had baseline diabetes and we said, well, let's compare those who have had baseline diabetes with the women who remained free of diabetes during the follow-up served over the 13 years never got diabetes, and we examined those women and we found the same exact result compared to the prospective analysis.

So that also helped us to confirm that this was really a real finding and then we also said, well, does this whole in other populations, let's say populations both men and women, from another country.

So with our collaborators from the Copenhagen City Heart Study we were able to analyze about 10000 Danish men and women. These were adult men and women living in the general Copenhagen population and they had their baseline Lp(a) measured with another assay it turns out and they had about 400 cases of individuals who had Type 2 diabetes and we examined case-control analysis looking at that population to see if it similar results, and we found exactly same result as we found in Women's Health Study. So again, this really helped to confirm that this is a real finding and not just play of numbers.

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Interestingly in the Copenhagen City Heart Study we had men and women, so we are also compared to see were there any sex differences and it turns out they were really no differences, so similar findings in both men and women.

Host: In your opinion are there ways to modify the plasma concentration of Lp(a)?

Dr. Samia Mora: Well, it's an interesting molecule, Lp(a). So it turns out that statins which usually reduce LDL cholesterol levels, they don't really affect Lp(a) levels too much. It turns out what lowers Lp(a) are only a few things. Niacin lowers Lp(a) by even up to like 20% or 30%.

Interestingly, estrogens can also lower Lp(a), and since we had the study of women and about half of them were using hormones including estrogen, we stratified our analysis in WHS study to see if those women who were not taking estrogen had similar findings to those who were taking estrogen, and we also found some more thing. And then there is a third drug that can actually also lower Lp(a) has recently been found to be the Cholesterol Ester

Transferase Protein or CETP inhibitors can also lower Lp(a).

Another study, early from Women's Health Study found that Aspirin plays a role not in lowering the Lp(a) levels, but that if women had high Lp(a), they had higher CVD risk and if they took aspirin, they actually lowered the risk of CVD even though they didn't affect too much their Lp(a) levels.

Host: What mechanisms might account for the inverse association of Lp(a) with Type 2 diabetes?

Dr. Samia Mora: Potential mechanisms are really at this point exploratory. Even for cardiovascular disease it turns out Lp(a) mechanism is not really clear as to how it causes a cardiovascular disease risk. So it's really a mysterious molecule and a lot of postulation.

As I said earlier, diabetes and cardiovascular disease share some risk factors. However, we adjust it for all the risk factors for diabetes including all the standard risk factors, we also adjusted for inflammatory risk factors and we didn't find any difference in association, suggesting that probably the mechanism of how Lp(a) is associated with diabetes is not through the standard risks factors, probably not through inflammation either.

And then we postulated is it possible related to some resistance, we did not have very sophisticated measures of insulin resistance. However we did have other correlates of insulin resistance including body mass index, triglycerides, hemoglobin A1c and when we are adjusted for all of these, there was really absolutely no change in the finding. So again suggesting, probably less likely insulin resistance, although, it's still possible.

There are some basic scientist departments showing that insulin can suppress the apo(a) function in the parasites post-transcriptionally and apo(a) gene has also been identified as a possible susceptibility gene for Type 1 diabetes. So there is a possible link there.

Other possible mechanisms may include hormonal regulation, so not just through estrogens but it turns out incidents like growth factors and even growth hormone have been implicated in Lp(a) as well as in glucose and lipid metabolism, and it could just be another effect that we haven't yet identified. It's really a well novel finding and showing that there is a

lot more investigation both basic science wise and also clinical studies.

Host: Are there possible explanations for why the association of Lp(a) with Type 2 diabetes differs from its association with cardiovascular disease?

Dr. Samia Mora: It's a puzzle really. We really thought that Lp(a) would have similar relationship with CVD compared with Type 2 diabetes. But then when you look more closely at the two diseases, well they do show lot of risk factors. They are also different. Type 2 diabetes is different from cardiovascular disease and not all risk factors are the same, even lipid risk factor.

For example, while we know HDL cholesterol, triglycerides are both risk factors for diabetes and CVD, however LDL cholesterol is only risk factor for CVD but not for diabetes. So as I said, Lp(a) molecule is a modified LDL particle. So it's possible that's the LDL cholesterol is not a risk factor for CVD, it's possible that modified version of that particle may be a risk factor for diabetes.

And other risk factors are not completely shared between diabetes and cardiovascular disease. For example, family history of diabetes increases the risk for future diabetes, but not for future CVD.

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So there is a lot of common risk factors between the two diseases but they are different and teasing out the differences is important as we have shown in this study that they can actually have completely opposite effect in one disease versus the other.

Host: Okay, thank you Dr. Mora. Now we'll get back to you for some concluding remarks, but we are joined now by two other researchers in this area, who wrote an editorial in the same issue of clinical chemistry. They are Drs. Mahir Karakas and Wolfgang Koenig of the department of Internal Medical Cardiology at the University of Ulm Medical Center in Germany.

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Now, Dr. Koeing what exactly do we know about the role of Lp(a) in cardio metabolic disease?

Dr. Wolfgang Koenig: Well, Lp(a) is a structurally and functionally unique lipoprotein, consisting of a glycoprotein, apolipoprotein(a), which is covalently linked to LDL. Most importantly, Lp(a) is highly heritable. Soon after its discovery in the '60s by Berg, Lp(a) over the

years was shown in case control, but also in prospective epidemiological studies to be associated with coronary heart disease. However, in many studies, the contribution of Lp(a) was modest, and particular in those subjects who had normal LDL levels.

So the main excess risk was seen in those subjects with high LDL, and to an addition, also had high Lp(a). For a long time the database was fairly heterogeneous, which may have to do with the fact that Lp(a) particles are heterogeneous itself, which was smaller rather than larger ApoA-1 isoforms to be stronger risk factors.

Also, there is sadly poor agreement among Lp(a) levels obtained by different assays. So analytical problems, in addition to this above-mentioned biological variation may have contributed to the heterogeneous evidence in many studies.

Of note, Lp(a) is fairly prevalent in the general population with about 20% of them exhibiting levels greater than 15 mg/dL.

Earlier guidelines have suggested that levels above 30 mg/dL should be considered as pathological. Now, despite the evidence from prospective studies showing an association between elevated levels of Lp(a) and various cardiovascular endpoints, the physiological and vascular effects of the particle remain uncertain. But Lp(a) has been shown to enter the arterial intima of humans in vitro, and in animals studies. Researchers have reported that Lp(a) can promote thrombosis, inflammation, and foam cell formation.

Most importantly, it is well known that increased levels of Lp(a) in the circulation interfere with the plasminogen receptor and thus may be prothrombogenic.

Little data is available for diabetes, and so far we only know that Lp(a) also predicts cardiovascular disease in diabetics, but whether or not Lp(a) is also predictive for incident diabetes has been unknown until now.

Host: With that in mind, Dr. Karakas, could you tell us a bit about the study recently published by Dr. Rifai and coworkers?

Dr. Mahir Karakas: Well, the study reports prospective data on Lp(a) concentration and the risk of Type 2 diabetes in two different cohorts; in healthy U.S. women, the Women Health Study or WHS, and then a cohort of Danish men and women with prevalent diabetes, the Copenhagen City Heart Study, CCHS.

In both cohorts, Type 2 diabetes was extensively validated, thereby underlining the excellent methods of the study. And as a finding, as a result of the study, Lp(a) concentration in both cohorts was significantly low end diabetes cases, compared to non-cases. Pearson Correlation Coefficient showed only slight correlation of Lp(a) with other risk factors for diabetes in the WHS. And then WHS, the incident rates for diabetes has significantly lowered in quintiles 2 to 5 compared to quintile 1.

In fasting participants, there was a threshold effect of approximately 20% lower relative risk, in quintile 2 to 5, compared to quintile 1.

Furthermore, in non-fasting participants, there was a more linear effect, up to 50% lower relative risk in quintile 5 compared with quintile 1. Notably, the inverse association of Lp(a) with diabetes remained significant, and was only minimally attenuated after full adjustment for covariates, including LDL cholesterol, triglycerides and HbA1c.

In addition, these findings are replicated in two settings; first in a case control analysis of WHS, when the baseline prevalent diabetes or HbA1c was above 6.5% served as cases, whereas someone free of diabetes during follow-up served is controlled.

In this setting, Lp(a) value below 1 versus above mg/dL was significantly associated with diabetes, with an adjusted odds ratio of about 2.3. Second in the CCHS, Lp(a) value below 1 versus above 1 mg/dL was associated with an adjusted odds ratio of about 1.5.

And there are two aspects of the current study there which are noteworthy. First, the association of Lp(a) with diabetes was stratified for hormone use, and similar results were obtained for both groups. This is of special interest since Lp(a) concentrations have been repeatedly reported to be influenced by hormones. And second, because it has been hypothesized that Lp(a) may be a marker of insulin resistance, the authors adjusted for correlates of insulin resistance, such as lipids, HbA1c, and high-

sensitivity C-reactive protein, but results were not altered.

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So this is the first prospective analysis, revealing an inverse association between Lp(a) and Type 2 diabetes, contrary to what one might have expected, given the fact that Type 2 diabetes and CHD share at least several risk factors.

Host: Now Dr. Koenig, what are the implications of this study and how does it fit into our model of diabetes and coronary heart disease?

Dr. Wolfgang Koenig: The common soil hypothesis put forward by Stern in 1995, implicates the diabetes and atherosclerosis with its clinical manifestations of myocardial infarction and stroke, do have a common underlying pathophysiology, due to the common presence of risk factors like various lipid parameters and in particular, the unequivocal role of information in both diseases.

Thus one would expect that risk factors for one disease, may also exhibit a risk function in the other. However, based on the study by Mora and colleagues in *Clinical Chemistry,* which clearly shows that elevated levels of Lp(a) are protective of diabetes. This seems to be counterintuitive and questions the common soil hypothesis in general. Based on the analysis in that paper, a number of questions still are unsolved.

For example, aspirin reduces Lp(a) production in human hepatocytes by up to 80% by suppression of the Apo(a) gene transcription and that is with their particular interest to see if the predictive value of low Lp(a) levels for diabetes in the Mora paper after stratification for aspirin intake will still be present. Moreover, one might hypothesize that due to this acute distribution of Lp(a), that only extreme values may exert adverse biological effects, either extremely low ones in the case of diabetes or highly increased levels in the case of cardiovascular disease, suggesting a threshold effect and implicating potentially an optimum range of individual concentrations.

This hypothesis is supported by the fact that in the present study in fasting participants, a comparable threshold of approximately 20% lower relative risk was seen for incident diabetes throughout quintiles 2 to 5, compared to the lowest quintile of Lp(a).

Additional analysis that might be suggested to be done, implicate that the measurement of isoforms of Lp(a) which are known to be associated with different magnitudes of risk subjects with ApoA-1 isoforms based on recent made analysis involving 40 studies and 58,000 participants have an approximately two-fold higher risk of CHD or ischemic stroke than those with larger proteins.

Host: Recently in a consensus statement, the European Atherosclerosis Society recommended the screening and treatment for high plasma concentrations of Lp(a). Dr. Karakas, what is the rationale for this recommendation.

Dr. Mahir Karakas: Well, the statement recommends that patients with moderate or high-risk of cardiovascular disease shall be screened once for plasma Lp(a) levels. According to the EAS, bringing a patient's Lp(a) level under 50 mg/dL, there should be a treatment priority after having achieved the targets for the management of low-density lipoprotein cholesterol.

Well, as we have heard from Professor Koenig, a large database has been accumulated concerning the potential role of Lp(a) as a product of cardiovascular risk. And there is the genetic data from pre-studies, suggesting a casual role for Lp(a) and myocardial infarction. However, there are three major concerns regarding this recommendation. My first concern relates that there are heterogeneity of Lp(a). About 20% of people are thought to have plasma Lp(a) levels of over 50 mg/dL, but the gender differences and racial differences have been observed; with whites and Asians having lower levels while black and Hispanics generally has somewhat higher levels.

Recently, the Penn Diabetes Heart Study with 1400 participants and the study of inherited risk of coronary atherosclerosis with 900 participants is very important. Blacks had a two- to threefold higher Lp(a) levels than whites in both diabetic and non-diabetic heart and diabetic women have higher mean Lp(a) levels than diabetic men and there was a highly significant interaction by gender.

So there was a need for further investigation to examine gender and racial differences, the relationships to clinical CHD, especially in diabetes.

My second concern regards Dr. Rifai and colleagues which showed the elevated Lp(a) levels to be clearly

protective in diabetic subjects. So there is a strong need for further research. We have to analyze if genetically elevated levels of Lp(a) are associated with diabetes, thereby suggesting a causal role in pathophysiology. Furthermore, we have to explore potential mechanisms of how Lp(a) could be beneficial in subject at risk of diabetes or its progression once we have diabetes.

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So in light of such data of the present study, the EAS recommendation seems a bit premature until the underlying mechanisms of the possible predictive ability of LP(a) and coronary artery disease and diabetes have been fully elucidated.

And finally I am confounded on the missing investigation evidence of how lowering of LP(a) level affects prevention and progression of coronary heart disease and in my opinion, those are the most important point, we need the clinical end point study for specific LP(a) inhibitor before deciding on the advantages and disadvantages of such a recommendation.

Host: Now which pharmaceutical compounds were available for treatment of high levels of LP(a), Dr. Koenig?

Dr. Wolfgang Koenig: First of all, one compound which has been available for almost 40 years now is nicotinic acid. As early as in the 1970s, a large study, the so-called Coronary Drug Project has been carried out which after a prolonged period of observation has shown a reduction in mortality in those treated with nicotinic acid. Nicotinic acid is safe. It reduces LP(a) level by approximately 30% if given at doses of 2 grams per day but also reduces LDL-cholesterol by 20% and triglycerides by approximately 30%. So it is not specific for reduction of LP(a).

However, the drawback of nicotinic acid is that it is associated with a number of side-effects in particular with itching and flushing which now might be reduced by extended release formulation together with a Prostaglandin antagonist. The most frequently used lipid-lowering drug class statins do not exert a relevant decrease LP(a).

However, they are two smaller clinical trials available that used aspirin in doses of proximately 150 to 200 milligrams per day in patients with coronary artery

 

disease and moderately to highly elevated LP(a) levels and in these studies, aspirin was able to reduce LP(a) production up to 80% by suppression of apolipoprotein(a) gene transcription.

Finally, it needs to be mentioned that unfortunately, lifestyle changes have a very little effect on that LP(a) concentrations.

Host: So are there any investigational drugs for LP(a) treatment?

Dr. Mahir Karakas: Well, there might be a role for mipomersen and new CETP AnacEtrapib like Dalcetrapib and Anacetrapib in the treatment of elevated LP(a) levels.

Mipomersen is a second-generation antisense oligonucleotide developed to inhibit synthesis of Apolipoprotein B-100 into lever and this Apolipoprotein B-100 is mainly expressed in the lever and this is present in all iatrogenic lipoprotein including LDL-cholesterols and LP(a).

In phase one and two studies in multiple patient population including primary hypercholesterolemia and familial hypercholesterolemia, Mipomersen has been shown to result in significant dose dependent and prolonged reductions in LDLC up to 70% even when used as a single agent or in combination with other lipid-lowering medicine.

In addition to LDL-cholestrol, Mipomersen lowers lowered serum apo(b) and LP(a). A dose of 200 mg Mipomersen once weekly was therefore selected for further elution of phase 3 clinical trials.

Recently, the result of the first phase of clinical trials have been presented. It was double-blind, randomized, placebo-controlled global multicenter trial went safety and efficacy of people pursuing on top of lipid-lowering drugs in patients with homozygous familial hypercholesterolemia was determined.

A total of 51 patients were randomized after 26 weeks of treatment and mean reduction in LDL-cholesterol was observed of 25% that the Mipomersen was then treated with just 3% for placebo.

In addition, patients treated with Mipomersen experienced 27% reduction in apo(b) and 21% reduction in total cholesterol. Statistically significant

reductions were also observed in other iatrogenic lipids including LP(a) itself lowered to 31%, but the news is not all positive however. Throughout the various studies, reduction and androgenic lipids mainly LDL-cholesterol so the wide variability of changes ranging from 2 to 82% independent from baseline LDL-cholesterol.

Secondly, a substantial number of patients had elevations in liver enzymes, about 3 times the upper limit of normal indicating unknown liver toxicity. Data regarding the effect of the new CETP inhibitors on Lp(a) levels is much fast. CETP stands for cholesteryl ester transfer protein and is a key protein involved in reverse cholesterol transport.

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Since the CETP inhibitors lead to increases in HDL-cholesterol that may also slightly decrease LDL-cholesterol levels. They are under evaluation as an additional antiatherogenic strategy. There are several studies that prompt to reduction in the apo(b) and Lp(a) levels that are consistent with the respect from HDL changes in the study and very possible to reach up to 50%.

Host: And finally, Dr. Koenig, are there any alternative biomarkers for using primary prevention besides Lp(a)?

Dr. Wolfgang Koenig: During recent years, we have seen an explosion of novel biomarkers being published in many journals, most of them clearly related to diverse pathways that play a role into complex pathophysiology of coronary artery disease. However, only few biomarkers has been adequately validated and do have a large enough database to draw firm conclusions from.

Probably the most eminent example of a biomarker that may affect clinical decisions at the moment is C-reactive protein, the classical acute-phase protein produced by the liver upon stimulation by cytokines, in particular IL-6.

A recent meta-analysis published this year in the *Lancet* has shown on an individual patient databases, in more than 100,000 subjects that the predictive ability of CRP is of similar magnitude as the one for systolic blood pressure and it seems even to be superior to non-HDL in predicting future cardiovascular events.

These results were seen even after complex adjustment for a number of potential confounders. Now to test the hypothesis that CRP maybe able to identify subjects at higher risk for cardiovascular disease, based on an increased inflammatory response, the JUPITER Study was carried out and as you know, it has been terminated prematurely due to an overwhelmingly positive outcome after only 1.9 years with the profound relative risk reduction of 44% for the primary composite endpoint, but also significant reductions of all components of the primary end point, including total mortality, which showed a 20% relative risk reduction.

Twenty milligrams Rosuvastatin reduced LDL by 50% and CRP by almost 40%. Based on this compelling evidence, the FDA earlier this year has approved Rosuvastatin to be used in primary prevention in subjects with normal LDL which is below 130 mg/dL, but elevated CRP which means above 2 mg/L and one additional risk factor.

In addition, the European counterpart, the AMIA, has also approved Rosuvastatin not on the basis of increased inflammation, but rather on increased risk in those with Framingham Risk Score of about 20% over 10 years and European Risks Score of about 5% over 10 years. With regards to guidelines, the Canadians were the first to have implemented CRP in their new 2009 recommendations on the treatment of subjects in primary prevention.

Host: Thank you, Dr. Koeing, for reviewing those other biomarkers for us. Well, that takes us back to Dr. Mora, who will have the final word by telling us her thoughts on the clinical implications of her study and what follow-up research she is now conducting.

Dr. Samia Mora I think the take-home point from our standpoint is that it turns out diabetes as more than just a glucose disorder that lipoproteins, even Lp(a) which had been before not really thought to play any role in diabetes, does seem to play a role in the disease process. It really tells us that we should expand our focus not just looking at glycemic factors as risk factors for diabetes, but also look at lipoprotein risk factors.

Our study was the first prospective study and in it we demonstrate that there is this independent and even additive predictive value for Lp(a) for predicting risk of diabetes, even when you compare to standard measures that we commonly now use the hemoglobin A1c measurement to assess risk for

future risk of diabetes as well as for managing people who have diabetes.

And in our study, we found that there is this additive value of Lp(a) so that individuals will have lower levels of Lp(a) less than 10 mg/L or equivalent would be 1 mg/dL, those individuals had severalfold increase risks for Type 2 diabetes if they also had slightly abnormal hemoglobin A1c still within the normal range of hemoglobin A1c but slightly higher than a completely normal individual.

So really future research and clinic implications I think for this molecule would have to depend on evaluating the role of Lp(a) in enhancing our assessment of individuals who are at risk for diabetes as well as also for figuring out its biological role in the disease process and possible therapeutic drugs that way although I would say, it is very premature at this point to examine those.

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I should mention also that there are clinical trials that are being conducted involving both Niacin and the CETP inhibitors and it will be important to see how these therapies affect the Lp(a) levels as well as do they have any affects on diabetes.

So there is still a lot really to be learned about this fascinating molecule and we just don't know how is it exactly playing a role, but we know now that it's playing a role not just for cardiovascular disease, but also for diabetes.

Host: That was Dr. Samia Mora, lead author of the report in *Clinical Chemistry* showing an inverse association between Lp(a) and Type 2 diabetes. She is a Cardiologist at the Division of Cardiovascular Medicine and Preventive Medicine at the Brigham and Women's Hospital, and is an Assistant Professor of Medicine at Harvard Medical School.

We are also joined by Drs. Mahir Karakas and Wolfgang Koenig of the Department of Internal Medical Cardiology at the University of Ulm Medical Center in Germany. They have been our guests in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening.

Total Duration: 36 Minutes