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# Cardiometabolic University 2017: Meeting Review and Presentation Summaries

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## 1. Introduction

Cardiometabolic University convened December 1-3, 2017 near Dallas, Texas. The conference presented, discussed, and debated all available preventive, diagnostic, therapeutic, and management options for cardiometabolic disease and nutrition in a highly interactive format. This program included didactic lectures, case-based discussions, and faculty panels specifically designed for cardiology, nephrology, and endocrinology fellows. Presentation summaries are provided below.

## 2. Update on risk factors an- d temporal trends in the incidence of acute myocardial infarction

*Presented by Catherine J. McNeal, MD, PhD*

Dr. McNeal introduced statistics showing that cardiovascular disease (CVD) related death has been declining in the last few decades (Benjamin et al., 2017). This likely reflects improved primary prevention efforts. Up to 92% of those who develop clinically significant coronary heart disease (CHD) and greater than 95% of those who had a fatal CVD event had at least one major modifiable risk factor including smoking, diabetes, hypertension, or hypercholesterolemia (Khot et al., 2003).

A variety of new risk factors and risk markers are emerging, including but not limited to coronary artery calcium score, apolipoprotein (a)[Lp(a)], high-sensitivity C-reactive protein, high-sensitivity cardiac troponin, and small dense low density lipoprotein (LDL).

There have been recent changes in the 2017 American College of Cardiology/ American Heart Association (ACC/AHA) guidelines which include using a CVD risk-based approach, lowering blood pressure (BP) goals with normal BP defined as < 120/ < 80 mm Hg, removal of the pre-hypertension category, and a new approach for choosing treatment.

## 3. PCSK9 influences on the lipid panel: clinical strategies for personalized lipid management

*Presented by Peter P. Toth, MD, PhD, FASPC, FAHA, FCCP, FESC, FACC*

Hepatic LDL receptors remove LDL from the circulating plasma to maintain cholesterol homeostasis. Proprotein convertase subtilisin kexin type 9 (PCSK9) starts as a 692-amino acid precursor synthesized primarily by the liver. PCSK9 regulates the surface expression of LDL receptors by targeting them for lysosome degradation, thereby reducing LDL receptor surface concentration, in turn increasing plasma LDL-cholesterol (LDL-C) (Toth , 2016).

There are data supporting a causative role of triglycerides (TG) in atherosclerotic CVD (ASCVD). Increased TG levels activate CE transfer protein (CETP) leading to the downstream effects of decreased LDL size and decreased high density lipoprotein cholesterol (HDL-C). Smaller and denser LDL particles have been shown to predict ischemic heart disease. [Lp(a)] has also been shown to be an independent, causal, genetic risk factor for CVD (John et al., 2009).

Dr. Toth then discussed the action of monoclonal antibodies against PCSK9, which are shown to decrease LDL-C, cholesterol particle remnants, as well as Lp (a) in various trials. The Durable Effect of PCSK9 Antibody CompARed wiTh placEbo Study (DESCARTES) found evolocumab, a PCSK9 inhibitor (PCSK9i), reduced LDL particles. In the Study of Alirocumab in Patients With Heterozygous Familial Hypercholesterolemia who Are Not Adequately Controlled With Their Lipid-Modifying Therapy (ODYSSEY FH I and II), alirocumab, another PCSK9i, resulted in a large reduction in LDL-C. Similar conclusions were replicated in the Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study-2 (RUTHERFORD-2) and Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects -2 (GAUSS-2) studies; the latter also showing a decrease in ApoB and Lp (a), and an increase in HDL-C when compared to ezetimibe. In clinical practice, both ezetimibe and a PCSK9i can be used in combination in statin-intolerant individuals.

## 4. Inhibition of PCSK9: LDL reduction, regression of atherosclerosis, and risk of cardiovascular events

*Presented by Norman E. Lepor, MD, FACC, FAHA, FSCAI*

A meta-analysis reveals that a large number of patients on high-dose statin therapy do not reach LDL-C goals (Boekholdt et al., 2014). Statins increase expression of LDL receptor proteins through activation of sterol regulatory element-binding transcription protein (SREBP), which also unfortunately increases levels of PCSK9. By using a PCSK9i in conjunction with a statin, a synergistic effect is achieved.

Dr. Lepor discussed conclusions from post-hoc analysis of the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) trial which showed those on alirocumab with ASCVD had a significant reduction in major cardiovascular (CV) events. The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects (SPIRE-2) trials had similar results. These studies also showed that benefit was achieved with lowering LDL-C well below current targets.

## 5. Lipoprotein (a): the final frontier in lipid management

*Presented by Patrick M. Moriarty, MD*

This presentation started with a review of the FOURIER trial which included stable patients with CVD already on statin therapy with LDL-C > 70 or non- HDL-C > 100 mg/dL. Results revealed a very significant decrease in LDL-C with evolcumab, improved CV outcomes, and good tolerance and safety with no increase in neurocognitive side-effects.

Dr. Moriarty then shifted focus to Lp (a) which is composed of apolipoprotein B-100 (apoB-100) covalently bound to apolipoprotein (a). Mechanisms by which Lp (a) confers increased CVD risk may include pro-inflammatory, proatherogenic, and prothrombotic effects (Ellis et al., 2017). The binding of oxidated phospholipids (OxPL) may also confer pathogenicity; the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed association between OxPL-apoB levels and CVD events. A meta-analysis also described the association between OxPL-apoB and the development and progression of aortic stenosis; as well as revealing data which suggest statins may actually increase OxPL-apoB and Lp (a) levels (Tsimikas , 2017).

Various therapies available to reduce Lp (a) include LDL apheresis, niacin, mipomerson, IL-6 antagonists, PCSK9 inhibitors, aspirin, and insulin.

## 6. Diabetes and cardiorenal disease: key relationships with atherosclerosis, myocardial disease, hypertension, and the progression of kidney disease

*Presented by Edgar V. Lerma, MD, FACP, FASN, FPSN (Hon)*

Dr. Lerma started his presentation by emphasizing the clinical links between chronic kidney disease (CKD), diabetes mellitus (DM), and CVD. The complex interactions and understanding of how one organ system contributes to the dysfunction of the other has been captured through the concept of cardiorenal syndrome (CRS). There are 5 types of CRS, classified based on chronicity, mechanism, and the initial dysfunctional organ.

He then shifted focus to diabetes. Hyperglycemia triggers increased oxidative stress which leads to endothelial dysfunction contributing to both renal and cardiovascular disease. It also increases the formation of advanced glycosylation end-products (AGEs) (Aronson and Rayfield., 2002). In addition, with hyperglycemia, vascular smooth muscle cells can differentiate into osteo or chondrocytic-like cells promoting vascular calcification.

Diabetes can contribute to chronic kidney disease (CKD) progression through factors such as inflammation, fibrosis, uremic toxins, and vascular calcification. Dr Lerma concluded that due to the pathogenic overlap of the mechanisms of DM, CVD, and CKD, it is promising to identify therapeutic targets shared between all three.

## 7. SGLT-2 inhibitors: glycemic control, blood pressure reduction, weight loss, and the reduction in cardiovascular death

*Presented by Mark E. Molitch, M.D.*

In a non-diabetic patient, 90% of glucose is reabsorbed by sodium-glucose co-transporter 2 (SGLT-2) transporter in the proximal tubule and the remaining 10% by the sodium-glucose co-transporter 1 (SGLT-1) transporter (Wright, 2001). This reabsorption can only occur until a certain threshold after which glucose cannot be reabsorbed and starts to spill in the urine. In diabetics, the amount of these transporters are actually up-regulated, causing enhanced renal glucose reabsorption contributing to hyperglycemia (Rahmoune et al., 2005).

With inhibition of SGLT-2, this threshold is shifted to a lower level, allowing for the lowering of plasma glucose in an insulin-independent manner. Studying patients with Familial Renal Glucosuria (an autosomal recessive condition causing deficiency of SGLT-2) reveals a normal lifespan, no clinical manifestations, and almost no episodes of hypoglycemia suggesting that inhibiting SGLT-2 receptors with medications may not cause any long-term harm.

Dr. Molitch then went over several trials involving SGLT-2 inhibitors. Overall, canagliflozin, dapagliflozin, and empagliflozin have been shown to lower glycated hemoglobin (HbA1c), body weight, blood pressure, but increase LDL-C.

## 8. SGLT-2 inhibitors and progression of cardiorenal disease: update from clinical trials

*Presented by Lawrence Blonde, MD, FACP, MACE*

Type 2 diabetics have increased risk for CV events, including hospitalization for heart failure (HF) and CV mortality. Dr. Blonde began by reviewing the results of older trials which revealed that metformin and pioglitazone have shown CVD benefit, although pioglitazone may be associated with an increase in heart failure (Robert et al., 1998; Dormandy et al., 2005).

He then discussed the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME). The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke [Major Adverse Cardiovascular Event (MACE)]. This occurred in a significantly lower percentage of patients on empagliflozin. Further analysis revealed a decrease in hospitalization in patients with and without HF. However, the applicability of these results with regards to reduced or preserved ejection fraction HF cannot be made.

The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL), a real world trial,

showed that initiation of an SGLT-2 inhibitor rather than any other glucose-lowering drug was associated with a significantly lower risk of all-cause death and hospitalization for HF.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER), Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) & CANagliflozin cardioVascular Assessment Study (CANVAS) trials were discussed as they mirrored results of the EMPA-REG OUTCOME trial, although one alarming finding was an increase in the incidence of lower-extremity amputations in CANVAS.

Both the EMPA-REG OUTCOME and CANVAS trials also showed improvement in a renal composite measure, with future trials underway to confirm such benefits.

## 9. GLP-1 agonists: mechanism of action, glycemic control, weight loss and impact on cardiovascular outcomes

*Presented by Brandon M. Nathan, MD*

Dr. Nathan started by reminding us that CVD begins in childhood referencing the presence of coronary and aortic plaques found in autopsy in 20% of children ages 2-15 years (Berenson et al., 1998).

Glucose-dependent insulinotropic polypeptide (GIP) and Glucagon-like peptide 1 (GLP-1) are responsible for the incretin effect, where gut derived signals result in a higher insulin secretory response than intravenous glucose loads (McIntyre et al., 1964). GIP stimulates GLP-1 which augments insulin secretion, decreases glucagon, slows gastric emptying, and suppresses appetite through effects on pancreatic cells and the hypothalamus. Dipeptidyl peptidase 4 (DPP-4) degrades GLP-1. Reduced incretin effect characterizes diabetes mellitus (DM). Due to the understanding of the incretin effect, DPP-4 inhibitors and GLP-1 receptor agonists (GLP-1 RA) were developed.

He then went over various studies and meta-analyses showing that these medications are successful at reducing mean HbA1c levels. GLP-1 RAs promote weight loss (high dose liraglutide is approved for weight loss in obese adults) while DPP-4 inhibitors are weight neutral (Nauck et al., 2017).

The LEADER trial showed reduction in CV events in diabetic patients on liraglutide, a GLP-1 RA. The SUSTAIN-6 trial had similar results with semaglutide, another GLP-1 RA, showing reduction in CV events, although there was no difference in overall mortality.

Dr. Nathan spent the remainder of his presentation describing increasing trends in childhood obesity and discussing a trial that used exenatide to decrease BMI in severely obese adolescents, concluding that such use is in the early stages, but may become important in the future (Kelly et al., 2013).

## 10. Optimizing diabetes management for cardiovascular outcomes: novel agents and the roles of conventional antidiabetic therapies: it's not all about glycemic control anymore

*Presented by Kris Vijay, MD, MS, FACC, FACP*

There is an increase in the prevalence of diabetes worldwide. Macrovascular complications may precede microvascular ones in the natural history of type-II diabetes mellitus.

The United Kingdom Prospective Diabetes Study (UKPDS) showed that a rise in HbA1c levels predicted higher CV risk. Intensive glycemic control showed decrease of microvascular endpoints by 25%, but did not conclusively show benefit in CV disease. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Veterans Affairs Diabetes Trials (VADT) showed similar findings where intensive glycemic control only improved microvascular (nephropathy and retinopathy) outcomes but not macrovascular ones.

Dr Vijay then went over the findings of the DPP-4 inhibitor and GLP-1 RA trials including the Evaluation of LIXisenatide in Acute coronary syndrome (ELIXA), LEADER, and SUSTAIN-6 trials as well as trials involving older medications. Of note, for thiazolidinediones, the Insulin Resistance Intervention after Stroke (IRIS) trial suggested that pioglitazone reduces risk of further ischemic events in non-diabetics who have had a recent ischemic cerebrovascular event.

Dr Vijay concluded that since CVD is the main cause of death in diabetes, focus should shift from HbA1c reduction alone to comprehensive CV risk reduction.

## 11. Nutrition and its role in cardiovascular disease: key epidemiologic relationships

*Presented by Parag H. Joshi, MD, MHS*

Due to expense and logistical barriers, there are very few randomized controlled trials in the field of nutrition.

While genetics are associated with increased myocardial infarction myocardial infarction (MI) risk (polymorphisms of the 9p21 gene for example have been shown to contribute to obesity), the Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction (INTERHEART) study suggests that diets higher in fruits and raw vegetables significantly mitigated this genetic risk.

Based on data from the Nurses' Health Study, adherence to lifestyle guidelines involving diet, exercise, and abstinence from smoking is associated with a very low risk of coronary heart disease. In addition, a meta-analysis suggests trans-fats are associated with all-cause mortality, CVD, CHD, ischemic stroke, and type 2 diabetes mellitus (T2DM) (de Souza et al., 2015).

The Prospective Urban Rural Epidemiology (PURE) study involved over 130,000 individuals worldwide and showed that higher fruit, vegetable, and legume consumption was associated with a lower risk of non-cardiovascular, and total mortality. The Primary Prevention of Cardiovascular Disease with a Mediterranean Diet (PREDIMED) study showed reduced acute MI, stroke, and death from CVD with a Mediterranean diet compared to a control (low-fat) diet.

Dr. Joshi concluded that lifestyle modifications should be a primary target to promote well-being and prevent disease.

## 12. Obesity, physical activity, and cardiopulmonary fitness: key roles in survival of the cardiovascular patient

*Presented by Barry A. Franklin, PhD, MAACVPR, FACSM, FAHA*

Dr. Franklin introduced the obesity paradox, namely that among patients with acute MI, higher body mass index (BMI) is associated with a lower mortality. A meta-analysis showed that for patients with established coronary artery disease (CAD), CV and mortality outcomes were better for overweight groups compared with normal-BMI patients (Romero-Corral et al., 2006). These findings suggest that BMI fails as a cardiovascular risk factor.

Studies suggest that usual gait speed, time, or distance covered during walk performance tests are powerful predictors of mortality and future cardiovascular events (Franklin et al., 2015). Regular walking has been shown to decrease all-cause mortality. This led to the recommendation by Dr. Franklin to routinely assess physical activity and observe a patient's gait regularly.

Another meta-analysis showed that every one point increase in metabolic equivalents (METs), was associated with an average 16% reduction in mortality (Boden et al., 2013). Even for those who remain overweight or obese, physical activity may have benefits through increased vagal tone, heart rate variability, and decreased adrenergic activity as well as anti-ischemic, anti-atherosclerotic, and anti-thrombotic changes.

Dr. Franklin then discussed the adverse effects of too much exercise describing a 'Reverse J-shaped Curve' where exercise decreases mortality up to a certain point, after which the benefit is lost (Mons et al., 2014).

He concludes that although there is a possibility that an excess of exercise training could contribute to myocardial fibrosis, coronary calcification, and atrial fibrillation; even for very active athletes, the benefits of exercise training outweigh the risks.

## 13. Understanding the metabolic syndrome and the lipid profile: impact of triglycerides on LDL-C and atherogenicity

*Presented by Michael J. Blaha, MD, MPH*

Genetics, nutrient excess, chronic stress, and physical inactivity leading to abdominal obesity and insulin resistance characterize the metabolic syndrome. This can lead to consequences such as CVD, DM, obstructive sleep apnea, cognitive decline, and sexual dysfunction. Various genes have been suggested to play a role in the progression to metabolic syndrome including those involved in appetite control, insulin sensitivity, lipid metabolism, etc.

Dr. Blaha revisited lipids where the importance of non-HDL-C measurement was emphasized. He described studies which suggest that non-HDL-C is more predictive of ASCVD risk than LDL-C. When non-HDL-C and LDL-C are discordant, risk follows non-HDL-C (Boekholdt et al., 2012; Jacobson et al., 2014).

While there are advanced lipid profile tests, such testing may not be required if non-HDL-C levels are used. The failure of the Friedewald equation to accurately calculate LDL-C when triglycerides are elevated was explained, along with the introduction of a novel calculation method by Martin which gives more accurate values for LDL-C (Martin et al., 2013). Major labs around the US have already adopted the "Martin" LDL equation.

## 14. The skinny on weight loss: practical approaches for the aardiovascular apecialist

*Presented by Peter A. McCullough, MD, MPH*

As BMI increases, diet and exercise becomes inadequate, and meal replacement, weight-loss medications, and eventually bariatric surgery may be required to return to a normal weight.

There are data suggesting a correlation between obesity and the risk for heart failure. Dr. McCullough elaborated on the pathophysiology of obesity cardiomyopathy where central hemodynamic and cardiac structural abnormalities, as well as alterations in ventricular function may predispose obese individuals to heart failure (Lavie et al., 2013). The cardiometabolic syndrome also contributes specifically to diastolic dysfunction through decreased cardiac efficiency, decreased adenosine triphosphate (ATP) production, lowered myocardial perfusion, and impaired relaxation (von et al., 2016).

He then discussed bariatric surgery, which has many CV effects including lowered blood pressures, increased left-ventricular ejection fraction, improved diastolic function, and lower rates of atrial fibrillation. Studies not only show reduction in heart failure admission after bariatric surgery, but also showed reduced relative risk of heart failure with bariatric surgery compared to intensive lifestyle treatment (Shimada et al., 2016). Overall, bariatric surgery is associated with a decrease of 40% all-cause mortality, 56% CAD death, and 92% diabetes-related death, and should be considered as a valid and effective treatment in the morbidly obese (Adams et al., 2007).

## 15. Diet, microbiome and heart health

*Presented by Zhaoping Li, MD, PhD*

The human body contains only 10 trillion human cells, but 100 trillion microorganisms. These organisms are considered to be the human microbiota and play a role in resistance to pathogens, energy harvesting, vitamin synthesis, maintenance of the intestinal-epithelial barrier, as well as anti-inflammatory processes.

Both the variety and levels of specific organisms in the human microbiome vary by age. A variety of factors can influence the composition of the microbiome. As an example, Dr. Li reviewed literature that showed dramatic differences in the gut microbes of babies based on factors including method of delivery, mode of nutrition, gestational age, location of birth, maternal stress and antibiotic usage (Bokulich et al., 2016; Borre et al., 2014).

A study was discussed where colonization of germ-free mice with microbiota from obese mice caused increased weight gain on the same diet compared to mice who remained colonization free, thus identifying gut microbiota as a contributing factor to the pathophysiology of obesity (Turnbaugh et al., 2006).

The US and British Gut Project showed that 'junk food' causes decreased microbiota diversity, decreased Biphidobacteria, and an increased Firmicute to Bacteroides ratio, all associated with increased obesity. Overall, maintaining a healthy microbiome is essential for the prevention of obesity and all its various comorbidities.

## 16. Summary

Through identification of common pathological pathways, the interconnected nature of cardiovascular disease, kidney disease, and diabetes was explored. Trends in cardiometabolic diseases, changes to guidelines, and updates in management were reviewed. This included discussion on lipids, the pathogenicity of Lp(a), and novel therapies such as PCSK9 inhibitors. Newer diabetic therapies that not only lower glucose but improve cardiovascular and renal outcomes, including SGLT-2 inhibitors and GLP-1 receptor agonists, were evaluated. The importance of nutrition and the impact of exercise were emphasized with evidence-based information guiding recommendations and discussions throughout the entire conference.


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## Conflict of interest

The author declares that he has no conflicts of interest.

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