ECRONICON OPEN ACCESS

EC CARDIOLOGY
Review Article

Primary Prevention on Dyslipidemia, on Inflammation and Obesity

Rifat Eralp Ulusoy*

Professor of Cardiology, Darulaceze Cad Turkiye Hastanesi Kardiyoloji Servisi, Istanbul, Turkey

***Corresponding Author:** Rifat Eralp Ulusoy, Professor of Cardiology, Darulaceze Cad Turkiye Hastanesi Kardiyoloji Servisi, Istanbul, Turkey.

Received: May 31, 2019; **Published:** July 18, 2019

Abstract

Two-thousand-eighteen was one of a kind period in terms of 'Preventive Cardiology' trials involving Aspirin, Omega-3 Fatty Acids, Diabetes Mellitus and Dyslipidemia. The research for the link between CVD risk and smoking, potassium intake and the environmental pollution are also continued to be investigated during this period. The role for unique antithrombotic, lipid and anti-diabetic drugs and strategies in reducing CVD risk are making sense. These trials will help us guide people for reducing the impact of CVD risk and new perspectives into preventive CVD risk medicine. We also get use to of new medical concepts such as 'Obesity paradox' as well as 'Cardiovascular Pleiotropic' effects of antidiabetic new drugs.

Keywords: *Dyslipidemia; Inflammation; Obesity*

Introduction

There were numerous publications released in the year 2018 in terms of preventive cardiology. Many observational studies, which were published in 2018 provided accuracy and influence on lifestyle in terms of cardiovascular disease (CVD) risk.

Multiple large-scale studies were published to bring out the role of aspirin in terms of primary prevention of CVD risk.

European Society of Cardiology blood pressure guidelines have a new but almost with the close recommendations with the American Heart Association blood pressure guidelines were also released.

A new outcome from the recently published data with PCSK9 inhibition and GLP-1 agonist therapy and recommendations for Hyperlipidemia and Diabetes management and their use in daily clinical practice was supported with two randomized controlled trials and a consensus report.

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease indicate that there are two major advantages of this recent guideline [1]. Similar to 2013 guideline, it also estimates the CVD risk, but this CVD risk assessment was based on a wider-based CVD risk outcome, which is more relevant to population groups (female, black) and also provides risk estimates that are specific to black populations [1].

What have we learned from the 2018 publications in terms of CVD risk?

- Smoking one cigarette a day is almost equal to smoking 20 cigarettes a day in terms of the CVD risk.
- Stroke risk is directly related to dietary sodium intake in conjunction with reducing the sodium-potassium ratio.

- The diagnosis of familial chylomicronemia and type III hyperlipidemia try to base on simple algorithms, which will strengthen Cardiologist hand in daily practice.
- Mental and daily work stress as well as mobbing and bullying at work is associated with increased CVD risk.
- Air pollution has definitely an impact on CVD risk.
- Comparing the European Society of Cardiology and European Society of Hypertension (ESC/ESH) and American College of Cardiology/American Heart Association (ACC/AHA) Hypertension guidelines for Primary CVD prevention, AHA Hypertension guidelines recommend 130 - 80 mmHg while ESC Hypertension guidelines recommend 140 - 90 mmHg as 'Normal' cut-off values. Secondary prevention of recurrent CVD events in patients with clinical CVD 130-80 mmHg as a 'Normal' cut-off values.
- Two new Diabetes drug classes were investigated hardly. By the end of the year 2018 a consensus report were released including these two new classes of antidiabetic drugs in terms of CVD risk reduction in Diabetes.

Lifestyle and work stress

Three large-scale studies, European study (102,633 cases), Denmark and Sweden (79201 cases) assessed the association of work stress with mortality [2-4]. Work stress indicators were job-strain and effort-reward imbalance. Males increased work stress accompanying to cardio-metabolic disease, as well as bullying at work was associated with increased mortality. However, when all women and men without cardio-metabolic disease facing the same psychology, did not yield the same result.

It was recommended that daily sport activities for CVD risk reduction has to be consistent without giving any intervals (not more than 12 weeks) and at least 30 minutes/day three times a week.

Obesity

Although it was delineated as a clear CVD risk factor, there are still inconsistent reports coming out of the current studies in 2018 [5]. Studies favoring near linear relationship between increasing adiposity and CVD risk, and not favoring (Diet Intervention Examining the Factors Interacting With Treatment Success, CAMELLIA-TIMI 61/Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients - Thrombolysis in Myocardial Infarction 61) trials demonstrated no significant difference in weight loss between a healthy low-fat diet and a healthy low-carbohydrate diet as well as no increase in CVD [6]. These inconsistencies regarding with obesity up till now may highlight another research topic as 'Obesity Paradox' in the literature [5,6].

Salt

This is a well-known CVD and high blood pressure risk. Although it is a well-known CVD risk a systematic review and meta-analysis published in the year 2018 again clearly delineated the association between increased sodium intake and CVD risk [7]. It also highlighted the importance of the Sodium:Potassium (Na:K) ratio and suggested Na:K ratio reduction to decrease the stroke risk by decreasing this Na:K ratio favoring the increase in Na^+ consumption [7]. But while decreasing Na^+ intake we have to keep in mind that we are working with electricity that we need that Na^+ ion enough in our plasma to produce and transmit the electricity to the other tissues.

The PURE (Prospective Urban Rural Epidemiology) study also supported that not all people only need to reduce their daily salt intake to reduce CVD risk but also "insufficient" daily salt intake may also be harmful or life threatening [8]. According to the study, daily salt reduction is recommended in high sodium consumption communities (daily sodium intake > 5 g/day) as well as salt sensitive communities. Besides PURE study also recommend most individuals to increase their daily consumption of potassium rich foods (fruits and vegetables).

Environmental pollution

Epidemiological studies have demonstrated a consistent increased risk for cardiovascular events in relation to both short- and long-term exposure to present-day concentrations of fine particulate matter < 2.5 μm (PM2.5). This particulate exposure is a unique human

killer yielding to global CVD risk and disability attributable to CVD [9]. Several logical mechanistic pathways have been previously described, including enhanced coagulation/thrombosis, a propensity for arrhythmias, acute arterial vasoconstriction, systemic inflammatory responses, and the chronic promotion of atherosclerosis. Short-term elevations in PM2.5 increase the relative risk of acute CVD events by 1% to 3% within a few days. However longer-term exposures over several years increase this CVD risk by a larger magnitude (~10%), which is partially attributable to the development of cardio metabolic conditions (e.g. hypertension and diabetes mellitus) [9].

Smoking

This is a well-established CVD risk factor. Although this was previously established in multiple publishments, there is an urban myth regarding with weight gain following smoking cessation. Korean investigators did a great job regarding with this issue and created a study consisting of >100,000 men and grouped this number into sustained smokers, quitters with BMI (Body mass index) gain, quitters without BMI change, quitters with BMI loss and non-smokers [10]. Compared with sustained smokers the risk of myocardial infarction was significantly reduced in both quitters with BMI gain (HR 0.33) and without BMI changes (HR 0.55) but no significant risk reduction was noted in quitters with BMI loss. Therefore, weight gain after cessation of smoking did not correlate with CVD risk.

Besides this another urban myth, which is smoking very few cigarettes a day is safe in terms of CVD risk is also investigated in a meta-analysis of 141 cohort studies and was published in the British Medical Journal. This study found that people who smoke one cigarette a day have approximately 50% of the risk of CVD or stroke as comparing to those who smoke 20 cigarettes a day. Therefore, one or twenty cigarettes a day did not differ in terms of CVD risk or stroke [11]. Both make people who smoke become a disabled in a period of time or not have enough time to become disabled.

Omega-3 fatty acids

Omega 3 fatty acid deficiency is the 6th highest killer among the United States people according to Harvard University research. Therefore, the effects of omega-3 fatty acids on CVD risk were being assessed heavily again in 2018.

There was inconsistent research released during 2018 both favoring (REDUCE-IT/Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial) and on the contrary to this concept (VITAL/Vitamin D and Omega-3, ASCEND/A Study of Cardiovascular Events iN Diabetes) [11]. The latter two studies (VITAL and ASCEND) both failed to demonstrate a benefit in primary CVD risk prevention in a broad population and individuals with diabetes, respectively, which the daily Omega-3-fatty acid dose intake were adjusted according to American Heart Association for secondary CVD risk prevention. This may yield a patient or population bias again demonstrating that Omega-3-fatty acid daily dose, although it was investigated in secondary CVD risk reduction population, needs further investigations in terms of primary CVD risk prevention.

Dyslipidemia

In the year 2018 there were two major randomized controlled trials (REDUCE-IT, ODYSSEY) highlighting new pharmacologic approach to a classic clinical disease state [12,13]. REDUCE-IT assessed the effects of high dose icosapent ethyl (a derivative of the Omega 3 fatty acid EPA) in 8,179 high CVD risk patients with hypertriglyceridemia who were also receiving a statin. The study's primary endpoint was a composite of CV death, MI, stroke, coronary revascularization and unstable angina. There was a 25% relative risk reduction (HR 0.75; 95% CI 0.68 - 0.83). The study has concluded that in a high risk CVD population with the specific formulation of a derivative of the Omega 3 fatty acid EPA investigated in this trial, both trials (REDUCE-IT, ODYSSEY) explanation for the better outcomes than seen comparing to the other Omega 3 fatty acid trials [12].

The ODYSSEY OUTCOMES study assessed the effects of PCSK9 inhibitors adding to a statin in post-acute coronary syndrome patients. The study reported that Alirocumab adding to a statin in post-acute coronary syndrome patients' (LDL-C level ≥ 70 mg/dL, non-HDL-C level ≥ 100 mg/dL or Apolipoprotein B ≥ 80 mg/dL), reduced the relative risk of recurrent ischemic cardiovascular events by 15% (HR 0.85; 95% CI 0.73 - 0.98) [13].

Two-thousand-eighteen ACC/AHA Guidelines and European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines on the Management of Blood Cholesterol added the use of the PCSK9 inhibitors and PCSK9 inhibition including both Alirocumab and Evolocumab in high blood cholesterol management [14].

Dietary guidelines have also been revised both in the year 2018 and in 2019 as well. We have always insight, shining star 'Mediterranean Diet supplemented with extra virgin olive oil in terms of 'Primary' Prevention of CVD risk. Both pharmacological and non-pharmacological approach yields better cardiovascular disease prevention [15].

Arterial hypertension

Two-thousand-eighteen ESC/ESH guidelines on arterial hypertension differ in some ways than the 2017 ACC/AHA hypertension guidelines. The definitions, treatment thresholds, and treatment targets of ACC/AHA vs ESC/ESH were a little bit more (130 - 80 mmHg vs 140 - 90 mmHg) conservative. None of the guidelines reconciled in 'Normal Blood Pressure' value, but a class I recommendation was given to initiate anti-hypertensive treatment with a two-drug combination, preferably in a single pill (exceptions being those who are frail, at lower CVD risk and those with grade I hypertension).

A class I recommendation was also given to the addition of low-dose spironolactone to current therapy or the addition of further diuretic therapy if intolerant of Spironolactone [15,16]. Both guidelines recommend the use of device-based therapies only on a clinical trial base; nevertheless there were plenty of such trials published in 2018 [16,17].

Diabetes

There was a great effort in Diabetes research in terms of new agents for the prevention of heart failure in diabetics. A novel agent Empagliflozin was investigated in EMPA-REG OUTCOME trial [14]. It was reported that assessing patients with diabetes and established CVD found almost 30% of the patients had a high or very high 5-year risk for developing heart failure [17]. Therefore, the study suggested that SGLT2 inhibitors could be effective in the prevention of heart failure.

Another same group of agent Dapagliflozin was also investigated and reported the supporting findings in terms of reduction in cardiovascular death and hospitalizations for heart failure. However, Dapagliflozin was failed to demonstrate a reduction in major adverse cardiac events comparing to placebo [18].

By mid-November 2018 there was a consensus report released by ACC regarding with the use of two new classes of antidiabetic drugs in terms of CVD risk reduction in Diabetes [19]. These were SGLT2 Inhibitors and GLP-1 receptor agonists. These drugs are not the only drugs for Diabetes management but also have other cardiac pleiotropic effects in terms of cardiovascular disease treatment. Therefore, these two classes are also known as cardiovascular agents [19]. Because the growing body of research documenting the CVD risk reduction benefits of these two classes in patients with Diabetes and atherosclerotic CVD seems to go beyond their plasma glucose lowering effects that depends to our current knowledge. If we remember, while we start to use Statins in medicine, we have raised a concept of 'Pleiotropic' effects of statins, which today we can convert it to use the same 'Pleiotropic effects' for these two particular antidiabetic drug classes benefiting the cardiovascular disease management [19]. The consensus document includes the summaries of the major cardiovascular outcome trials with SGLT2 Inhibitors (Empagliflozin, Canagliflozin) and GLP-1 receptor agonists (Liraglutide, Semaglutide, Exenatide, Lixisenatide). Although the major cardiac adverse effect and heart failure risk reduction appears to be lowered by this group, Empagliflozin is the preferred agent according to the evidence based therapy [19]. There is also proven major cardiac adverse risk reduction with GLP-1 receptor agonists; Liraglutide is the most preferred agent in this regard [19]. Beyond these CVD and Heart failure risk reductions, both groups demonstrated in blood pressure and weight reduction and have a low risk of hypoglycemia [19]. Therefore, we have to be stay tuned in the forthcoming time following the studies coming out of these new Diabetes drug classes.

Aspirin

The role of aspirin in primary prevention was one of the most studied topics in 2018. Three major randomized clinical trials, ASCEND (A Study of Cardiovascular Events iN Diabetes: Characteristics of a randomized trial of aspirin and of omega-3 fatty acid supplementation in 15,480 people with diabetes), ARRIVE (A Randomized Trial of Induction Versus Expectant Management) and ASPREE (Aspirin in Reducing Events in the Elderly) assessed the effects of aspirin on primary CVD risk prevention and all-cause mortality [20-22].

Although we can briefly say for these three randomized clinical trials that aspirin is not indicated in primary CVD risk prevention including individuals with diabetes without very high cardiovascular risk and the elderly, it is worth to remember the caveats for each trial.

On the contrary to primary CVD prevention, the protective role of aspirin in secondary CVD prevention is clear according to COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) trial. It was reported that an incidence of cardiovascular death, myocardial infarction, or stroke, occurred in 4.1% of the Rivaroxaban plus Aspirin group vs. 4.9% of the Rivaroxaban alone group vs. 5.4% of the Aspirin alone group ($p < 0.001$) for Rivaroxaban plus Aspirin vs. Aspirin alone; ($p = 0.12$) for Rivaroxaban alone vs. Aspirin alone [23].

Inflammation

Landmark CANTOS (Cardiovascular Risk Reduction Study) trial, which was originally published in 2017 demonstrated a reduction in cardiovascular events in individuals with post-acute coronary syndrome and an hsCRP > 2 mg/L [24]. Further studies confirmed the same findings that elevated CRP plasma level have a higher risk correlation of CVD. Therefore, chronic kidney disease patients might derive more benefit from PCSK9 inhibition and Canakinumab therapy [24].

Conclusion

Two-thousand-eighteen was one of a kind period in terms of 'Preventive Cardiology' trials involving Aspirin, Omega-3 Fatty Acids, Diabetes Mellitus and Dyslipidemia. The research for the link between CVD risk and smoking, potassium intake and the environmental pollution are also continued to be investigated during this period. The role for unique antithrombotic, lipid and anti-diabetic drugs and strategies in reducing CVD risk are making sense. These trials will help us guide people for reducing the impact of CVD risk and new perspectives into preventive CVD risk medicine. We also get use to of new medical concepts such as 'Obesity paradox' as well as 'Cardiovascular Pleiotropic' effects of antidiabetic new drugs.

Bibliography

1. Arnett DK., *et al*. "2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines". *Journal of the American College of Cardiology* 19 (2019): 735-1097.

2. Mika Kivimäki., *et al*. "Work stress and risk of death in men and women with and without cardiometabolic disease: a multicohort study". *The Lancet Diabetes and Endocrinology* 6.9 (2018): 705-713.

3. Xu T., *et al*. "Workplace bullying and workplace violence as risk factors for cardiovascular disease: a multi-cohort study". *European Heart Journal* 40.14 (2019): 1124-1134.

4. Herrmann-Lingen C. "Victimization in the workplace: a new target for cardiovascular prevention?" *European Heart Journal* 40.14 (2019): 1135-1137.

5. Imre Csige., *et al*. "The Impact of Obesity on the Cardiovascular System". *Journal of Diabetes Research* (2018): 3407306.

6. Scirica BM., *et al*. "Lorcaserin and Renal Outcomes in Obese and Overweight Patients in the CAMELLIA-TIMI 61 Trial". *Circulation* 139.3 (2019): 366-375.

7. D'Elia Lanfranco Galletti., *et al*. "Effect of dietary sodium restriction on arterial stiffness: systematic review and meta-analysis of the randomized controlled trials". *Journal of Hypertension* 36.4 (2018): 734-743.

8. Czekajło A., *et al*. "Association between dietary patterns and cardiovascular risk factors in a selected population of Lower Silesia (PURE Study Poland)". *Annals of Agricultural and Environmental Medicine* 25.4 (2018): 635-641.

9. Sanjay Rajagopalan., *et al*. "Air Pollution and Cardiovascular Disease". *Journal of the American College of Cardiology* 72.17 (2018): 2054-2070.

10. Kim K., *et al*. "Weight gain after smoking cessation does not modify its protective effect on myocardial infarction and stroke: evidence from a cohort study of men". *European Heart Journal* 39.17 (2018): 1523-1531.

11. Hackshaw A., *et al*. "Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports". *British Medical Journal* 360 (2018): j5855.

12. Bhatt DL., *et al*. "Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia". *New England Journal of Medicine* 380.1 (2019): 11-22.

13. Szarek M., *et al*. "Alirocumab Reduces Total Nonfatal Cardiovascular and Fatal Events: The ODYSSEY OUTCOMES Trial". *Journal of the American College of Cardiology* 73.4 (2019): 387-396.

14. Kluger AY., *et al*. "Cardiorenal Outcomes in the CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME Trials: A Systematic Review". *Reviews in Cardiovascular Medicine* 19.2 (2018): 41-49.

15. Estruch R., *et al*. "Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts". *New England Journal of Medicine* 378.25 (2018): e34.

16. Böhm M., *et al*. "Ambulatory heart rate reduction after catheter-based renal denervation in hypertensive patients not receiving antihypertensive medications: data from SPYRAL HTN-OFF MED, a randomized, sham-controlled, proof-of-concept trial". *European Heart Journal* 40.9 (2019): 743-751.

17. Azizi M., *et al*. "Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial". *The Lancet* 391.10137 (2018): 2335-2345.

18. Clegg LE., *et al*. "Reduction of Cardiovascular Risk and Improved Estimated Glomerular Filtration Rate by SGLT2 Inhibitors, Including Dapagliflozin, Is Consistent Across the Class: An Analysis of the Placebo Arm of EXSCEL". *Diabetes Care* 42.2 (2019): 318-326.

19. Das SR., *et al*. "2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways". *Journal of the American College of Cardiology* 72.4 (2018): 3200-3223.

20. Louise Bowman., *et al*. "ASCEND: A Study of Cardiovascular Events iN Diabetes: Characteristics of a randomized trial of aspirin and of omega-3 fatty acid supplementation in 15,480 people with diabetes". *American Heart Journal* 198 (2018): 135-144.

21. J Michael Gaziano., *et al*. "Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial". *The Lancet* 392.10152 (2018): 988-990.

22. Karen L Margolis., *et al*. "Development of a standardized definition for clinically significant bleeding in the Aspirin in Reducing Events in the Elderly (ASPREE) trial". *Contemporary Clinical Trials Communications* 11 (2018): 30-36.

23. Michiel Coppens., *et al*. "Synergy of Dual Pathway Inhibition in Chronic Cardiovascular Disease. Lessons From the COMPASS Trial". *Circulation Research* 124.3 (2019): 416-425.

24. Paul M Ridker., *et al*. "Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial". *The Lancet* 391.10118 (2018): 319-332.

Volume 6 Issue 8 August 2019