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REVIEW ARTICLE

Congress of American Heart Association 2018: results of clinical trials

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This article contains a report of eight most important clinical trials represented during scientific sessions of American Heart Association held in Chicago, US, November 10-12, 2018.

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Last summit of American Heart Association was held in Chicago (USA), November 10-12, 2018. 12654 specialists from over 100 countries took part in over 800 scientific sessions, where were over 1000 speakers – world leaders in the cardiovascular diseases (CVD) studies.

During the congress they discussed: new American guideline on the management of blood cholesterol [1], physical activity guidelines [2], guideline for the evaluation and management of bradycardia and cardiac conduction delay [3]. The results of new most

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important clinical studies that can significantly affect clinical practice are presented in this article.

Cardiovascular Prevention

The **VITAL** study is the first large-scale project on the role of the vitamin D and omega-3 fatty acids supplementation in the primary prevention of cardiovascular disease and cancer in men aged ≥50 years and women ≥55 years.

In 2×2 factorial design 25871 primary healthy US citizens (5106 were African American) were randomized to either vitamin D3 (2000 IU/day) or placebo, and to eicosatetraenoic and docosahexaenoic acids in 1.3 : 1 ratio (1 g per day) or placebo. The primary outcome was any invasive cancer or/ and the summary of major cardiovascular events (myocardial infarction (MI), stroke, CV death). Secondary outcomes included any localization cancer, cancer death, death from MI/ stroke/ percutaneous coronary intervention (PCI)/ coronary artery bypass grafting and/or any component of cardiovascular primary outcome.

During the follow-up of 5.3 years cancer was diagnosed in 1617 participants — 793 of 12927 in vitamin D group and 824 of 12944 in placebo group (relative risk (RR) — 0.96 with 95% coincidence interval (CI) from 0.88 to 1.66; p=0.47). Major cardiovascular event was seen in 805 participants — 396 in vitamin D group and 409 in placebo group (RR 0.97 with 95% CI from 0.85 to 1.12; p=0.69).

The risk of death was not significantly different in the vitamin D group compared with placebo including death from any localization cancer (RR 0.83 with 95% CI from 0.67 to 1.02); breast cancer (1.02 with 95% CI from 0.79 to 1.31); prostate cancer (RR 0.88 with 95% CI from 0.72 to 1.07); colorectal cancer (1.09 with 95% CI from 0.73 to 1.62); the summary of major cardiovascular events and coronary revascularization (RR 0.96 with 95% CI from 0.86 to 1.08); MI (RR 0.96 with 95% CI from 0.78 to 1.19); stroke (0.95 with 95% CI from 0.76 to 1.20); cardiovascular death (1.11 with 95% CI from 0.88 to 1.40) and all-cause mortality (total — 978 cases, RR 0.99 with 95% CI from 0.87 to 1.12). The risk of hypercalcemia and other adverse events wasn't increased during treatment [4]. Therefore, vitamin D did not reduce the incidence of invasive cancer or major cardiovascular events compared with placebo.

During the follow-up of 5.3 years major cardiovascular complications (CVC) were diagnosed in 386 of 12933 in omega-3 fatty acids group and in 419 of 12938 in placebo group (RR 0.92 with 95% CI from 0.80 to 1.06; p=0.24), invasive cancer was diagnosed in 820 and 797 participants, respectively (RR 1.03 with 95% CI from 0.93 to 1.13; p=0.56). Total number of cardiovascular events (RR 0.93 with 95% CI from 0.82 to 1.04); the incidence of any localization stroke (RR 1.04 with 95% CI from 0.83 to 1.31); cardiovascular death (RR 0.96 with 95% CI from 0.76 to 1.21); cancer death (total — 341 cases, RR 0.97 with 95% CI from 0.79 to 1.20); deaths from any other cause (total — 978 cases. RR 1.02 with 95% CI from 0.90 to 1.15) did not differ significantly between groups. But omega-3 polyunsaturated fatty acids decreased the risk of MI (RR 0.72 with 95% CI from 0.59 to 0.90), MI mortality (RR 0.50 with 95% CI from 0.26 to 0.97) and PCI mortality (RR 0.78 with 95% CI from 0.63 to 0.95), especially in patients with low fish consumption and African Americans. The risk of bleeding or other serious adverse effects didn't increase significantly [5]. Generally, additional intake of omega-3 fatty acids did not reduce the risk of cardiovascular events or cancer compared with placebo.

The most reliable result of the VITAL study is that vitamin D and omega-3 fatty acids did not significantly reduce the incidence of primary outcomes - severe CVD or invasive cancer, despite possible interest in individual frequency differences of secondary outcomes.

Patients with hypertriglyceridemia have increased risk of ischemic events. Highly purified ethyl eicosapentaenoic acid ester reduces triglycerides level without increasing the level of low-density lipoproteins (LDL), which lead to the studies on its effect on ischemic complications.

The **REDUCE-IT** [6] trial included 8179 patients with known CVD (for secondary cardiovascular events prevention, 70.7% of all patients), diabetes mellitus or other risk factors (RF) (for primary cardiovascular events prevention), who were already on statin therapy with fasting level of triglycerides of 1.52-5.63 mmol/l and LDL of 1.06-2.59 mmol/l. Patients were randomized to either 2 g of eicosapentaenoic acid twice daily with food (n = 4.089) or placebo (n = 4.090). During the 4.9 years of follow-up the primary outcomes (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization or unstable angina) were diagnosed in 17.2% of cases in eicosapentaenoic acid group compared with 22.0% in placebo (RR 0.75 with 95% CI from 0.68 to 0.83; p=0.00000001). Secondary outcomes (cardiovascular death, nonfatal MI, nonfatal stroke) - in 11.2% and 14.8% (RR 0.74 with 95% CI from 0.65 to 0.83; p=0.0000006), all-cause mortality

- in 4.3% and 5.2% (RR 0.80 with 95% CI from 0.66 to 0.98; p=0.03) of cases, respectively. The effects of treatment were comparable in secondary and primary prevention cohorts (interaction p=0.46) among men and women (interaction p=0.44) in and outside the US (interaction p=0.38) in patients with and without diabetes mellitus (DM) and those who did not have diabetes initially (interaction p=0.29), as well as in subgroups with exclusion criteria of 2.26 mmol / l (interaction p=0.62) and 1.7 mmol /l (interaction p=0.68) triglyceride level. Prescribed treatment did not affect the course of heart failure. Eicosapentaenoic acid group patients were more commonly admitted compared with placebo due to atrial fibrillation or flutter (3.1% vs. 2.1%; p=0.004) and serious adverse bleeding events (2.7% vs. 2.1%; p=0.06). The frequency of severe adverse events did not differ significantly.

Obtained results cannot be fully explained only by eicosapentaenoic acid effect on lipids and indicate its possible pleiotropic effects (antithrombotic, anti-inflammatory, stabilization of cell membranes and / or atherosclerotic plaques) that shows the new way to reduce the risk of CVC. However, in our country patients need to take 10 capsules per day to reach the dose of 4 g of eicosapentaenoic acid that will lead to an increase in its cost and gastrointestinal disorders.

DECLARE TIMI-58 trial [7] included patients with type 2 diabetes mellitus (DM2) and 6.5%- 12%. level of glycosylated hemoglobin and creatinine clearance ≥ 60 mL/min. Trial included 6974 patients with established CVD (IHD, cerebrovascular pathology, peripheral arteries disease — secondary prevention cohort) and 10186 patients with multiple RF (men ≥55 years and women ≥60 years with at least one additional risk factor: arterial hypertension, dyslipidemia or tobacco use — primary prevention cohort). Patients were randomized to either dapagliflozin 10 mg daily — selective inhibitor of sodium-glucose cotransporter type 2 — or placebo. During treatment dapagliflozin reduced body mass by 1.8 kg and arterial hypertension by 2.7/0.7 mmHg. During the follow-up of 4.2 years primary safety and efficacy outcome — summary of major cardiovascular events (CV death, MI or ischemic stroke) was registered in 8.8% of cases in dapagliflozin and in 9.4% in placebo group (p<0.001 result without superiority of effect — RR 0.93 with 95% CI from 0.84 to 1.03; p=0.17). Secondary efficacy outcome (CV death or heart failure hospitalization) appeared in 4.9% in dapagliflozin and in 5.8% in placebo group (RR 0.83 with 95% CI from 0.73 to 0.95; p=0.005) and indicated lower frequency of heart failure hospitalization (RR 0.73 with 95% CI from 0.61 to 0.88) without significant differences in CV death frequency between groups (RR 0.98 with 95% CI from 0.82 to 1.17). Dapagliflozin was effective in preventing renal events (glomerular filtration rate decrease ≥40% with values <60 ml/min/ per 1.73 m^2, new end-stage renal disease, renal or cardiovascular death) – 4.3% versus 5.6% in placebo group (RR 0.76 with 95% CI from 0.67 to 0.87), but wasn't effective in reducing all-cause mortality — 6.2% versus 6.6%, respectively (RR 0.93 with 95% CI from 0.82 to 1.04). Serious adverse effects that lead to treatment cessation were more common in dapagliflozin group — diabetic ketoacidosis (0.3% vs. 0.1% in placebo group. p = 0.02) and genital infections (0.9% vs. 0.1% in placebo group. p<0.001).

According to data of large-scale randomized studies inhibitors of type 2 sodium-glucose cotransporter reduce the risk of major cardiovascular events due to atherosclerosis only in patients with established CVD. They also reduce the incidence of heart failure and renal events in a wide range of patients during secondary and primary prevention. However, additional data from ongoing studies are needed to conclude on patients with type 2 diabetes and heart failure without additional RF.

Inflammation is associated with atherothrombosis that was confirmed during kanakinumab treatment - monoclonal antibodies that inhibit inflammation by neutralizing interleukin-1ß. Without affecting the lipid spectrum of blood plasma this extremely expensive drug significantly reduced the incidence of major cardiovascular events compared with placebo [8]. The CIRT study [9] investigated the possibility inhibiting inflammation with similar benefit by using low dose of inexpensive methotrexate (15–20 mg once a week).

4786 patients after MI or with coronary artery disease and DM2 or metabolic syndrome were randomized to either methotrexate or placebo. All patients received folic acid 1 mg daily. The median follow-up was 2.3 years. Unlike previous studies among patients with rheumatoid arthritis or other cause systemic inflammation, methotrexate did not reduce interleukin-1ß, interleukin-6 and C-reactive protein levels compared with placebo. The primary outcome (nonfatal MI, nonfatal stroke or cardiovascular death) was diagnosed in 170 patients in methotrexate and in 167 patients in placebo group (3.46/100 person-years vs. 3.4/100 person-years; RR 1.01 with 95% CI from 0.82 to 1.25). The primary outcome plus hospitalization for unstable angina requiring unplanned revascularization was 4.13 vs. 4.31/100 person-years

(RR 0.96 with 95% CI from 0.79 to 1.16). Methotrexate group had tendency to increase risk of cardiovascular death (0.92 vs. 0.80/100 person-years; RR 1.14 with 95% CI from 0.76 to 1.72) and all-cause mortality (1.80 vs. 1.55/ 100 person-years; RR 1.16 with 95% CI from 0.87 to 1.56). Methotrexate increased liver enzymes, reduced leucocytes, hematocrit level and the incidence of basal cell carcinoma compared with placebo (31 vs. 10 cases; p=0.002).

We need to reduce levels of interleukin-1β, interleukin-6 and C-reactive protein to prevent atherothrombosis without affecting lipid levels in patients with stable atherosclerosis. It is interesting to find out the results of LoDoCo study where the effect of colchicine on interleukin-1β level is evaluated.

We still don't have results of prospective randomized studies on the effectiveness of lipid-lowering therapy in elderly patients despite a significant increase of hypercholesterolemia among them. 3796 patients ≥75 years and with low-density lipoprotein cholesterol (LDL-C) levels ≥3.6 mmol/l without HAD took part in **EWTOPIA75** [10] trial and were randomized to either ezetimibe 10 mg daily plus dietary counseling (n = 1.716) or dietary counseling only (n = 1.695). After 5 years of follow-up LDL-C (p<0.001) and triglycerides (p=0.003) levels were significantly lower in ezetimibe group compared with placebo and level of high-density lipoproteins did not differ significantly (p=0.119). The primary cardiovascular outcome (sudden cardiac death, nonfatal or fatal MI, percutaneous coronary intervention or coronary artery bypass grafting, nonfatal or fatal stroke) was registered significantly less frequent in ezetimibe group (RR 0.659 with 95% CI from 0.504 to 0.862; p=0.002). The risk of cerebrovascular events and all-cause mortality did not differ significantly between groups. Adverse effects in ezetimibe and control group appeared in 10.62% vs. 9.62% of cases.

The results of EWTOPIA75 study for the first time prospectively showed the possibility of atherosclerotic cardiovascular events primary prevention with lipid-lowering therapy among patients ≥75 years. The limitations were: open-label study since the control arm did not receive a placebo pill, the participation of only Japanese who may respond to treatment differently due to polymorphism of NPC1L1 gene. Obtained data may serve as basis for new placebo-controlled studies among more ethnically diverse population.

Heart failure

Acute decompensated heart failure is one of the most common causes of admission and diuretics and vasodilators have been its basic treatment for a long time.

In PARADIGM-HF trial sacubitril/valsartan compared with enalapril among patients with heart failure due to reduced ejection fraction ≤40%, reduced cardiovascular death or hospitalization for heart failure [11]. Patients who were recently hospitalized with decompensated heart failure and required intravenous therapy were excluded from PARADIGM-HF, therefore, the efficacy and safety of sacubitril / valsartan in this case is still unknown.

881 patients hospitalized with acute decompensated chronic heart failure or episode of acute chronic heart failure with elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥1600 pg/ml or B-type natriuretic peptide ≥400 pg/ml took part in **PIONEER-HF** [12] trial.

During hospitalization patients were stabilized (systolic blood pressure ≥100 mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension; no increase in intravenous diuretic or vasodilators dose; no intravenous inotropic drugs for 24 hours prior to randomization) and randomized to sacubitril/valsartan (the goal — 97mg/ 103 mg twice a day; n = 440) or enalapril (the goal — 10 mg twice a day; n = 441). Dose titration was based on the BP dynamics during 8 weeks. The primary outcome (time-averaged reduction in NT-proBNP during week 4 and 8 compared with initial level) was 29% lower in sacubitril/valsartan group compared with enalapril (95% CI from 19 to 37; p < 0.0001). Safety outcomes did not differ between groups: rates of worsening renal function (13.6% vs. 14.7%; RR 0.93 with 95% CI from 0.67 to 1.28), hyperkalemia (11.6% vs. 9.3%; RR 1.25 with 95% CI from 0.84 to 1.84), symptomatic hypotension (15.0% vs. 12.7%; RR 1.18 with 95% CI from 0.85 to 1.64) and angioedema (0.2% vs. 1.4%; RR 0.17 with 95% CI from 0.02 to 1.38). Serious composite events (death, HF hospitalization, LV assist device implantation or listing for transplant) were less frequent in sacubitril/valsartan group (RR 0.54 with 95% CI from 0.37 to 0.79; p=0.001), mostly due to lowering the risk of heart failure hospitalization (8.0 vs. 13.8%; p=0.005).

Sacubitril/valsartan reduced NT-proBNP to a greater degree than enalapril among patients admitted with acute decompensated heart failure and reduced ejection fraction without increasing the risk of worsening renal function, hyperkalemia, symp-

tomatic hypotension and angioedema. According to the authors, these findings will allow to start using optimal pharmacotherapy in the hospital instead of initiating angiotensin-converting enzyme inhibitor and prescribe sacubitril / valsartan only at the outpatient stage.

Patients with dilated cardiomyopathy who recovered heart function often ask if it is possible to attempted its withdrawal, for example, during pregnancy. The safety of this action remained unknown.

Patients with dilated cardiomyopathy who recovered their left ventricular ejection fraction from <40% to ⩾50, normal LV end-diastolic volume, N-terminal pro–B-type natriuretic peptide <250 ng/L during treatment took part in opened **TRED-HF** [13] trial. Patients were randomized to either withdrawal of medications (n = 25) or continuation of medications (n = 26). After 6 months patients in the medication continuation arm crossed over to medication discontinuation. The primary endpoint was a relapse of dilated cardiomyopathy within 6 months (reduction in left ventricular ejection fraction of > 10% and to <50%, an increase in left ventricular end-diastolic volume by more than 10% and to higher than the normal range, a two-fold rise in NT-pro-BNP concentration and to more than 400 ng/L or clinical evidence of heart failure at which point treatments were re-established) was diagnosed in 11 (44%) patients only from the withdrawal of medications group (Kaplan-Meier estimate of event rate 45.7% with 95% CI from 28.5 to 67.2; p=0.0001). After 6 months 25 (96%) of 26 patients from continuation group attempted its withdrawal and during the following 6 months, nine patients met the primary endpoint of relapse (Kaplan-Meier estimate of event rate 36.0% with 95% CI from 20.6 to 57.8). No deaths were reported in either group due to careful dynamic monitoring and quick resumption of the therapy if needed.

Many patients with dilated cardiomyopathy who consider themselves recovered have a high probability of a rapid relapse after its withdrawal, which indicate that therapy shouldn't be interrupted.

Empagliflozin — a sodium–glucose cotransporter type 2 selective inhibitor — reduced the risk of major cardiovascular events, all-cause mortality and cardiovascular hospitalization in patients with DM2 and established CVD during **EMPA-REG OUTCOME** trial [14]. Mechanisms of empagliflozin remain unclear, but may include natriuresis, reduction of interstitial edema, heart pre- and afterloads, left ventricular wall stress, improved kidney and cardiovascular function and heart's energetical processes.

Left ventricular mass is a strong and independent predictor of MI, heart failure, cardiovascular and all-cause mortality, and left ventricular hypertrophy regression during treatment correlates with clinical outcomes. The effect of empagliflozin 10 mg per day on left ventricular remodeling was estimated in 97 patients with DM2 (glycated hemoglobin ⩾6.5% and ⩽10%) and stable HAD during **EMPA-HEART Cardiolink-6** [15] trial with cardiac magnetic resonance. Left ventricular mass index reduced in empagliflozin and placebo groups after 6 months -2.6 g/m^2 vs. 0.01 g/m^2 (p = 0.01) and left ventricular myocardial mass — 7.71 g vs. 0.39 g, respectively. This effect was more significant in patients with initially higher left ventricular myocardial mass index (interaction p=0.007). The ejection fraction tended to increase in patients without significant end-systolic (p=0.36) and end-diastolic (p=0.55) left ventricular volumes (+2.21% vs. -0.01% in placebo; p=0.07). Empagliflozin therapy did not affect initially low NT-proBNP and troponin I levels.

Empagliflozin promoted early statistically and clinically significant left ventricular remodeling, which could improve outcomes during EMPA-REG OUTCOME trial and other studies with similar medications. The effects of empagliflozin were observed in patients with normotension, preserved left ventricular ejection fraction, no heart failure and during standard therapy (metformin, statins and angiotensin converting enzyme inhibitors or angiotensin II receptor blockers).

Practical integration of most important clinical studies data presented during scientific sessions of the American Heart Association in 2018 may improve most common CVD treatment and prevention.

More detailed information on the scientific event held in November 2018 in Chicago is presented on the official website: https://professional.heart.org

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References

1. Grundy S.M., Stone N.J., Bailey A.L. et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018; Nov 8. [Epub ahead of print]
2. Piercy K.L., Troiano R.P., Ballard R.M. et al. The Physical Activity Guidelines for Americans. JAMA. 2018; Nov 12. [Epub ahead of print]

3. Kusumoto F.M., Schoenfeld M.H., Barrett C. et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardiaand Cardiac Conduction Delay: A Report of the American College of Cardiology/American HeartAssociation Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018; Oct 31. [Epub ahead of print]
4. Manson J.E., Cook N.R., Lee I.M. et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med. 2018; Nov 10. [Epub ahead of print]
5. Manson J.E., Cook N.R., Lee I.M. et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. N Engl J Med. 2018; Nov 10. [Epub ahead of print]
6. Bhatt D.L., Steg P.G., Miller M. et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2018; Nov 10. [Epub ahead of print]
7. Wiviott S.D., Raz I., Bonaca M.P. et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2018; Nov 10. [Epub ahead of print]
8. Ridker P.M., Everett B.M., Thuren T. et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017; 377(12):1119-1131.
9. Ridker P.M., Everett B.M., Pradhan A. et al. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. N Engl J Med. 2018; Nov 10. [Epub ahead of print]
10. Ouchi Y. Ezetimibe in Prevention of Cerebro- and Cardiovascular Events in Middle- to High-Risk, Elderly (75 Years Old or Over) Patients With Elevated LDL-Cholesterol: A Multicenter, Randomized, Controlled, Open-Label Trial. AHA Scientific Sessions, November 10, 2018, Chicago, Illinois. https://professional.heart.org
11. McMurray J.J., Packer M., Desai A.S. et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014; 371(11):993-1004.
12. Velazquez E.J., Morrow D.A., DeVore A.D. et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med. 2018; Nov 11. [Epub ahead of print]
13. Halliday B.P., Wassall R., Lota A.S. et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet. 2018; Nov 9. [Epub ahead of print]
14. Zinman B., Wanner C., Lachin J.M. et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015; 373(22):2117-2128.
15. Verma S. et al. EMPA-HEART Cardiolink-6 Trial: A Randomized Trial Evaluating the Effect of Empagliflozin on Left Ventricular Structure, Function and Biomarkers in People With Type 2 Diabetes (T2D) and Coronary Heart Disease. AHA Scientific Sessions, November 11, 2018, Chicago, Illinois. https://professional.heart.org