International Heart and Vascular Disease Journal • Volume 8, № 28, December 2020

Journal of the Cardioprogress Foundation

REVIEW ARTICE

The congress of European Society of Cardiology 2020: contribution to the new era of virtual communications

The report presents the results of the annual congress of the European Society of Cardiology that was held trough virtual mode for the first time. In particular, the highlights of 4 updated clinical guidelines of the European Society of Cardiology are summarized. The results of 13 international clinical trials on the efficacy and safety of pharmacological treatment and identification of factors associated with cardiovascular complications are analyzed.

Key words: *congress, clinical guidelines, international research.*

Received: 22.09.2020 **Accepted:** 29.09.2020

The next congress of the European Society of Cardiology was held from August 29 to September 1, 2020. Due to epidemiological situation, the congress was held trough virtual mode. Over 500 scientific and educational sessions have been organized using about 1000 mobile studios around the world. Approximately 58.000 users joined the conference that was 80 % more compared with the number of participants of European Society of Cardiology Congress in Paris in 2019. The website of the European Society of Cardiology contains over 4000 presentations and electronic posters with congress materials.

Traditionally, the Congress presented updated guidelines and the results of new clinical trials.

This year 4 new clinical guidelines were presented:

1. The management of acute coronary syndromes in patients without persistent ST-segment elevation (chairs: Jean-Philippe Collet and Holger Thiele).

2. The diagnosis and management of atrial fibrillation (chairs: Gerhard Hindricks and Tatiana Potpara).

3. The management of adult congenital heart disease (chairs: Helmut Baumgartner and Julie De Backer)

4. Sports and exercise in patients with cardiovascular diseases (chairs: Antonio Pelliccia nd Sanjay Sharma).

A wide range of cardiologists are interested in changes in the guidelines on the management of acute coronary syndromes in patients without persistent ST-segment elevation and atrial fibrillation.

For the rapid diagnosis of acute coronary syndrome, it is recommended to use high-sensitivity cardiac troponin assay immediately and after 1 (optimal) or 2 hours. Once myocardial infarction (MI) has been excluded, invasive coronary angiography should be considered in patients with very high clinical likelihood of unstable angina. Imaging stress testing or computed tomography of the coronary arteries is the best diagnostic option for patients with low to moderate clinical risk. Stress testing with imaging or coro-

nary computed tomography angiography will be the best option in patients with low-to-modest clinical likelihood of unstable angina.

An early routine invasive approach within 24 hours of admission is recommended for patients without ST-segment elevation according to high-sensitivity cardiac troponin assay, GRACE risk score>140, and dynamic new, or presumably new, ST-segment changes as it improves major adverse cardiac events and possibly early survival. A selective invasive approach after positive ischemic testing or cardiac obstruction according to computer tomography is recommended for patients at low risk. Routine pre-treatment with a P2Y12 receptor inhibitor in patients with acute coronary syndrome without ST-segment elevation in whom coronary anatomy is not known and an early invasive management is planned is not recommended given the lack of established benefit. Dual antiplatelet therapy (P2Y12 receptor inhibitor and aspirin) is generally recommended for 12 months, irrespective of the stent type, unless there are contraindications. However, its duration can be shortened (<12 months) or extended (>12 months). The therapy can also be modified by switching P2Y12 receptor inhibitor or de-escalation of dual antiplatelet therapy depending on patient's individual characteristics and the availability of the respective drugs.

The new guidelines on the management of patients with atrial fibrillation suggests that at least a short course of triple therapy (≤7 days) would be desirable in such patients before dual antiplatelet therapy. Only in patients with high risk of ischemic events triple antiplatelet therapy can be prescribed for 4 weeks.

The guidelines emphasize that the diagnosis of AF needs to be confirmed by a conventional 12-lead electrocardiogram tracing or rhythm strip showing atrial fibrillation for≥30 s. Structured characterization of AF, including stroke risk, symptom severity, severity of AF burden, and AF substrate, helps improve personalized treatment of AF patients. The ABC pathway streamlines integrated care of AF patients across healthcare levels and among different specialties (includes A (avoid stroke and anticoagulation), B (better symptom control), and C (cardiovascular risk factors and comorbid conditions management)). The realization of such approach will significantly improve outcomes of patients with AF.

Patient values need to be considered in treatment decision making and incorporated into the AF management pathways; the structured assessment of patient-reported outcome measures is an important element to document and measure treatment success.

Catheter ablation with pulmonary vein isolation is recommended to maintain sinus rhythm after ineffective use or intolerance of a class I or III antiarrhythmic drugs in patients with paroxysmal or persistent AF, regardless of the underlying risk factors. Overall, guidelines emphasize that weight loss, strict control of risk factors, and avoidance of triggers for AF are important strategies to improve outcomes.

Full versions of clinical guidelines are posted on the official website of the European Society of Cardiology: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines.

The summary of the results of the new large international clinical trials are presented below.

The RATE-AF study: the role of digoxin for heart rate (HR) control in patients with permanent AF

The RATE-AF study showed that digoxin can be used as first-line treatment in elderly patients with permanent AF and heart failure symptoms. Authors followed up 160 patients with 76 mean patient age with permanent AF and heart failure symptoms for 12 months. Patients were randomized into 2 groups: the first group received low dose of digoxin, the second — beta-blocker bisoprolol. Heart rate reduction was similar between treatment groups at 12 months: from 100 beats per minute initially to 70 beats per minute after 6 and 12 months. According to Short Form–36 form, both medications similarly affected life quality. Both medications were well-tolerated. For example, at 12 months, the digoxin group scored significantly higher than the beta-blocker group on several domains of the Short Form–36 physical component score, including vitality, physical function, and global health. Heart failure symptoms in the digoxin group improved from a mean baseline New York Heart Association class of 2.4 to 1.5 at both 6 and 12 months; the improvement was more modest in the beta-blocker group, going from NYHA 2.4 at baseline to 2.0 at both 6 and 12 months. N-terminal of the prohormone brain natriuretic peptide levels improved in the digoxin group from a baseline of 1.095 pg/mL to 1.058 at 6 months and 960 at 12 months from 1.041 to 1.209–1.250 pg/mL at 12 months in the beta-blocker group. It is notable that study limitations included small sample size as well as the fact that digoxin is more effective for the heart rate control at rest but not during physical activity.

ATPCI: trimetazidine is not effective in patients with angina pectoris having been treated by percutaneous coronary intervention (PCI)

Routine use of oral trimetazidine added to guideline-recommended medical therapy did not improve patient outcomes following a successful percutaneous coronary intervention (PCI), based on findings from the ATPCI trial. The study included 6.007 patients with myocardial infarction (MI) who had undergone successful planned or urgent PCI at 365 centers in 27 countries. After randomization patients additionally to standard recommended therapy (aspirin and P2Y12-receptor inhibitor in 97% of cases, hypolipidemic medications in 96.6% of cases, renin-angiotensin-aldosterone inhibitors in 82.2% and beta-blockers in 83.9% of cases), as well as calcium channel blockers (in 27.6% of cases) received modified-release trimetazidine 35 mg twice daily or placebo. The majority of patients (77% of all patients were men) suffered from angina pectoris III / IV functional classes according to the Canadian Cardiovascular Society classification (58%). 2517 patients underwent emergency, and 3490 — planned PCI. The duration of follow-up was 47.5 months. The primary outcome occurred in 23.3% of the trimetazidine group compared with 23.7% of the placebo group. Trimetazidine was not superior to placebo in the prevention of several cardiovascular events including cardiovascular death (2.1% versus 2.6%), hospitalization for cardiac events (13.4% versus 13.4%), recurrent/persistent angina leading to adding, switching, or increasing antianginal therapy, or coronary angiography (16.9% versus 16.6%).

According to experts, this result may be due to the fact that all patients received beta-blockers or calcium channel blockers, and had successful PCI. At the same time, 2019 European Society of Cardiology guidelines on the chronic coronary syndrome recommended trimetazidine as a second-line therapy after beta-blockers and calcium channel blockers in patients with chronic coronary syndrome.

DAPA-CKD: the benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors in chronic kidney disease patients without type 2 diabetes

The trial enrolled 4.304 patients with chronic kidney disease (estimated glomerular filtration rate from 25 to 75 mL/min/1.73m2; urinary albumin to creatinine ratio over 200 mg/g). Patients were randomly allocated to dapagliflozin 10 mg or placebo once daily in addition to standard of care (renin-angiotensin-aldosterone system receptor blocker in 97% of cases). The average age of participants was 61.8 years and 66.9% were male. A total of 2.906 (67.5%) patients had type 2 diabetes. The primary composite endpoint was worsening kidney function, defined as>50% sustained decline in estimated glomerular filtration rate or onset of end-stage kidney disease, or death due to kidney disease or cardiovascular disease.

During a median follow-up of 2.4 years, there were 197 primary endpoint events with dapagliflozin and 312 with placebo (p=0.000000028 for the dapagliflozin benefit in patients with and without type 2 diabetes). Dapagliflozin reduced all three secondary endpoints compared with placebo: 1) worsening renal function or death from kidney failure (0.56 hazard ratio; p<0.0001) ; 2) hospitalization for heart failure or cardiovascular death (0.71 hazard ratio; p=0.0089) ; and 3) all-cause mortality (0.69 hazard ratio; p=0.0035).

The safety and tolerability of dapagliflozin was in keeping with its established profile. In the placebo group, the proportion of patients who discontinued the study drug due to an adverse event or experienced a serious adverse event were 5.7% and 33.9%, respectively. The proportion of patients with these events was similar in the dapagliflozin group — 5.5% and 29.5% respectively. Diabetic ketoacidosis was not reported in any patient randomized to dapagliflozin and occurred in two patients in the placebo group. Neither diabetic ketoacidosis nor severe hypoglycemia were observed in patients without type 2 diabetes.

DAPA-CKD showed that dapagliflozin reduced the risk of worsening kidney function or death from cardiovascular or kidney disease in patients with chronic kidney disease with and without type 2 diabetes. The results highlight the medicine's potential to benefit patients with chronic kidney disease who are in need of improved treatment options.

Aspirin alone was preferential as antithrombotic therapy in patients after TAVI

Ischemic and hemorrhagic complications after transcatheter aortic valve implantation are relatively common and are associated with increased mortality. The goal of the POPular TAVI trial was to evaluate aspirin alone compared with aspirin plus clopidogrel for 3 months among patients who underwent TAVI. Patients with implantation of a drug-eluting stent within the last 3 months or bare-metal stent within

the last month before TAVI were excluded from the study.

The primary co-outcome included all bleeding (including associated with medical procedures). Bleeding at 12 months, occurred in 15.1 % of the aspirin alone group compared with 26.6 % of the aspirin plus clopidogrel group (p= 0.001). Nonprocedure-related bleeding at 12 months, occurred in 15.1 % of the aspirin alone group compared with 24.9 % of the aspirin plus clopidogrel group (p= 0.005).

Secondary outcomes included bleeding and thromboembolic complications (including cardiovascular death, nonprocedure-related bleeding, thromboembolic events stroke, or myocardial infarction) at 12 months occurred in 23.0 % of the aspirin alone group compared with 31.1 % of the aspirin plus clopidogrel group (p<0.001). Cardiovascular death, stroke, or myocardial infarction at 12 months occurred in 9.7 % of the aspirin alone group compared with 9.9 % of the aspirin plus clopidogrel group (p= 0.004).

Therefore, aspirin alone significantly reduced the rate of bleedings compared with aspirin and clopidogrel with absolute decrease of 10 %. At the same time aspirin alone compared with aspirin and clopidogrel did not increase the risk of thromboembolic events. Thus, aspirin alone is recommended in patients after TAVI who does not receive peroral anticoagulants and did not undergo coronary revascularization.

Safety and effectiveness of evolocumab in the treatment of familial hypercholesterolemia in children

HAUSER-RCT is first randomized double blinded placebo-controlled study of PCSK9 inhibitor in pediatric patients with heterozygous familial hypercholesterolemia. The study included 157 patients aged from 10 to 17 years with heterozygous familial hypercholesterolemia from 23 countries from 5 continents. Before the study patients took statins with or without ezetimibe, but the level of low-density lipoprotein cholesterol (LDL-cholesterol) was over 130 mg/dl.

Patients will be randomized in a 2:1 ratio to receive 24 weeks of monthly 420 mg evolocumab or placebo. At week 24, the mean percent change from baseline in LDL cholesterol level was 44.5 % in the evolocumab group and 6.2 % in the placebo group, for a difference of 38.3 % (P<0.001). The absolute change in the LDL cholesterol level was –77.5 mg per deciliter in the evolocumab group and –9.0 mg per deciliter in the placebo group, for a difference of 68.6 mg per deciliter (P<0.001).

Monoclonal antibody directed against PCSK9 (evolocumab) were well tolerated and effectively decreased the level of LDL-cholesterol compared with placebo in pediatric patients with heterozygous familial hypercholesterolemia who already took statins with or without ezetimibe.

EMPEROR-Reduced: the efficacy of empagliflozin in patients with heart failure with reduced ejection fraction with or without type 2 diabetes

The trial enrolled 3.730 patients with heart failure and a left ventricular ejection fraction of 40 % or less, with or without diabetes. Patients were randomly assigned to empagliflozin 10 mg once daily or placebo. The primary endpoint was the composite of cardiovascular death or hospitalization for heart failure.

During a median follow-up of 16 months, the primary endpoint occurred in 361 patients in the empagliflozin group and in 462 patients in the placebo group (p<0.0001). Empagliflozin reduced total hospitalizations for heart failure (p<0.001). The effect of empagliflozin did not depend on the presence of type 2 diabetes mellitus. Empagliflozin reduced total hospitalizations for heart failure (p<0.001). Patients with SGLT inhibitors had lower risk of renal outcomes. Uncomplicated genitourinary tract infections were more common in the empagliflozin group.

The SGLT2 inhibitors have strengthened their role as the new primary treatment for patients with heart failure with low ejection fraction with or without type 2 diabetes mellitus. The results of the second large randomized controlled trial showed significant efficacy and safety of SGLT2 inhibitors in this patient population.

The effect of low-dose colchicine in patients with stable coronary artery disease

Anti-inflammatory pharmacotherapy can significantly decrease the risk of atherothrombosis on a background of standard therapy and secondary prophylaxis.

LoDoCo2 is a double-blind controlled trial in which 5522 patients with stable coronary artery disease have been randomized to colchicine 0.5 mg daily or matching placebo. The median follow-up was 28.6 months. The primary endpoint (cardiovascular death, spontaneous myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization) occurred in 187 patients (6.8 %) in the colchicine group

compared with 264 patients (9.6 %) in the placebo group (p<0.001).

Ischemic events (cardiovascular death, spontaneous myocardial infarction, or ischemic stroke) occurred in 4.2 % of patients from the colchicine group and in 5.7 % of patients (p=0.007) from the placebo group. The incidence of death from noncardiovascular causes was higher in the colchicine group than in the placebo group (0.7 vs. 0.5 events per 100 person-years).

In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo.

The REALITY trial: the impact of restrictive blood transfusion strategy for MI patients with anemia

Restricting blood transfusion in myocardial infarction patients with anemia to those with very low hemoglobin levels saved blood and did not have a negative impact on clinical outcomes, according to findings from the REALITY trial.

According to statistics, 5–10 % of patients with acute myocardial infarction have anemia. Cardiologists does not accept restricting blood transfusion strategy without the evidence of its safety and due to concerns about the effect of low hemoglobin on ischemic myocardium.

The REALITY trial was first large randomized study on the restricting blood transfusion compared with standard therapy in myocardial infarction patients. The study included 668 patients hospitalized at 35 centers in France and Spain with acute myocardial infarction and anemia (hemoglobin 7–10 g/dL). Patients were randomly allocated to either a restrictive transfusion strategy (transfusion withheld unless hemoglobin dropped to 8 g/dL) or a liberal transfusion strategy (transfusion given as soon as hemoglobin was 10 g/dL or below). The target level of hemoglobin was 8–10 g/dL for the restrictive transfusion strategy, and over 11 g/dL for the liberal transfusion strategy. Restrictive transfusion strategy group used 414 blood units less.

The primary clinical endpoint was a composite of major adverse cardiac events (all-cause mortality, MI, stroke or emergency PCI due to myocardial ischemia) at 30 days. The primary clinical outcome occurred in 11 % of cases in the restrictive strategy group compared with 14 % of patients in the liberal strategy group.

The risk of infection between restrictive strategy group and liberal strategy group (0 % vs. 1.5 %), acute lung injury (0.3 % vs. 2.2 %), length of stay (7.0 vs. 7.0 days) did not differ significantly. In terms of cost effectiveness, researchers noted the restrictive strategy had an 84 % probability of being cost-saving while improving clinical outcomes.

The HOME-PE trial: the identification of patients with pulmonary embolism for home management

The HOME-PE trial is randomized, open-label trial that was conducted in 26 hospitals in France, Belgium, the Netherlands and Switzerland. 1.974 patients with normal blood pressure presenting to the emergency department with acute pulmonary embolism were included in the study. The possibility of outpatient treatment was assessed with HESITIA criteria (all 11 criteria were negative; in 39 % of patients) or with the PESI scale (the score was 0; in 48 % of patients).

The frequency of serious adverse events was low in both groups of patients managed at home. Through 30 days of follow-up, there were few adverse events, which included recurrent venous thromboembolism, major bleeding, and death among the patients receiving treatment at home, with a rate of 1.3 % in the HESTIA group and 1.1 % in the PESI group.

The researches also highlighted that both studied methods of prognosis assessment in patients with pulmonary embolism were imperfect and that the physician in charge to make final management decision. Among the patients initially deemed eligible for home treatment, physicians overruled that assessment less frequently in the HESTIA arm (3 % vs 29 %). Thus, the proportion of patients ultimately managed in the outpatient setting was similar in the HESTIA and PESI arms of the trial (38 % versus 37 %). The HESTIA criteria were as safe as Pulmonary Embolism Severity Index (PESI) for the selection of patients for home management.

THEMIS-PAD trial: the combination of ticagrelor and aspirin among patients with stable coronary artery disease, type 2 diabetes and peripheral artery disease

The goal of previously performed randomized THEMIS trial was to evaluate ticagrelor/aspirin compared with placebo/aspirin among patients with stable coronary artery disease and type 2 diabetes. The THEMIS-PAD study included 1687 patients with peripheral arterial disease. Ischemic limb events (acute limb

ischemia; major amputation of vascular etiology; peripheral revascularization) occurred in 1.3 % of cases in the ticagrelor/aspirin group compared with 1.6 % of cases in placebo/aspirin (p=0.022).

Elevated troponin T levels were associated with significantly higher rates of COVID-19 complications

A study from the United States showed that patients admitted with COVID-19 have high incidence of cardiovascular disease and its complications. An earlier French study also demonstrated that high levels of troponin and brain natriuretic peptide were independent predictors of COVID-19 complications.

About 1200 patients were included in the study, and the results of treatment of the first 485 patients were presented at the congress (average age 68 years, 46 % women, 49 % — white, 27 % — African American and 16 % — Latin Americans). The results demonstrated high prevalence of cardiovascular diseases (46 %) and cardiovascular risk factors (over 40 % suffered from arterial hypertension, hyperlipidemia and diabetes mellitus) in patients admitted with COVID-19.

Elevated troponin T levels at admission were associated with death and serious adverse cardiovascular events, which were higher than expected based the experience of other respiratory infections management.

The effectiveness of antihypertensive treatment in patients with normal blood pressure (BP)

The meta-analysis of 48 studies on the effectiveness of antihypertensive treatment included 348 854 patients. Patients were divided into seven subgroups based on systolic blood pressure at study entry (less than 120, 120–129, 130–139, 140–149, 150–159, 160–169, 170 and above mmHg). Over an average four years of follow-up, each 5-mmHg reduction in systolic blood pressure lowered the relative risk of major cardiovascular events by about 10 %. The risks for stroke, ischemic heart disease, heart failure and death from cardiovascular disease were reduced by 13 %, 7 % and 14 % and 5 %, respectively. Neither the presence of cardiovascular disease nor the level of blood pressure at study entry modified the effect of treatment.

According to the researchers, blood pressure lowering with antihypertensive drugs reduces the risks of cardiovascular events, even in patients with normal or slightly elevated blood pressure. However, the fact that the relative effects are similar for everyone does not mean that everyone should be treated. This decision will depend on an individual's likelihood of suffering cardiovascular disease in the future.

Gut microbes are associated with cardiovascular and other diseases

Previous researches have shown that the human gut microbiome is associated with many diseases, but the level of this association is still unclear.

In order to identify diseases associated with microbiome, the study included 422 417 unrelated individuals in the UK Biobank who had undergone genotyping to identify their genetic make-up. The average age of participants was 57 years and 54 % were women.

The researchers assessed possible associations, including 35 single nucleotide polymorphisms that affect human gut microbiome. 7 single nucleotide polymorphisms were significantly associated with 29 diseases, including arterial hypertension, heart failure, hypercholesterolemia, type 2 diabetes, renal failure, and osteoarthritis.

According to experts, the composition of human gut microbiome, including genetic and environmental factors, can be associated with certain diseases, including cardiovascular diseases, as well as its progression and outcomes. Clarification of this risk factor may lead to the development of new personalized risk stratification strategies and preventive measures.