

Results of clinical trials from the latest Congress of the European Society of Cardiology in Paris, 31st August–4th September 2019

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Introduction

The last Congress of the European Society of Cardiology, the world's largest meeting for cardiologists, took place from 31st August to 4th September 2019, together with the World Congress of Cardiology. It was held in one of the most charming European capitals – Paris. Among the many interesting thematic lectures, the participants were most interested in hotline sessions, which presented the results of the latest, long-awaited clinical cardiology research, including innovative treatments using new drugs.

This congress abounded in breakthrough scientific reports which, in the near future, may change the pharmacotherapy standards of the most common diseases in cardiology – heart failure (HF) and coronary artery disease (CAD). Of the many relevant clinical trials, the most interesting ones that may have practical application are described below.

DAPA-HF – dapagliflozin as a new effective drug in HF?

One of the most important studies presented to cardiologists for the first time was **DAPA-HF** (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) [1], a study on the use of dapagliflozin – an inhibitor sodium-glucose co-transporter 2 (SGLT2) as a drug in HF. Researchers examined whether adding dapagliflozin

10 mg OD to standard pharmacotherapy would benefit patients with reduced left ventricular ejection fraction (LVEF), regardless of the type 2 diabetes mellitus (T2DM). The study included patients with HF symptoms in II, III, IV failure class according to the New York Heart Association (NYHA), LVEF not more than 40% and a minimum concentration of the N-terminal pro-B-type natriuretic peptide (NT-proBNP) higher than or equal to 600 pg/mL, as well as greater than or equal to 400 pg/mL, when they were hospitalised due to HF during last 12 months or at least 900 pg/mL for co-existing atrial fibrillation or flutter. Exclusion criteria were chronic kidney disease and estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m², symptomatic arterial hypotension with systolic blood pressure (SBP) less than 95 mm Hg, or type 1 diabetes mellitus. During the 14-day initial assessment, researchers analysed the inclusion and exclusion criteria for patients from the study. After this period, patients were divided into groups receiving dapagliflozin or placebo. The further diagnostic evaluation followed 14 or 60 days after inclusion. Additional visits took place after 4 months, and then every 4 months (from February 15, 2017 to August 17, 2018). The primary endpoint was an exacerbation of HF symptoms associated with unplanned hospitalization or requiring intravenous diuretic therapy, as well as cardiovascular death. Of the initially evaluated 8,134 patients from 20 countries, 4,744 patients were randomised, including 2,373 patients treated with dapagliflozin. The study brought ground-breaking results; dapagliflozin, developed as a hypoglycaemic drug, has been

shown to be suitable for the treatment of HF regardless of the diabetes coexistence. The primary endpoint was seen in fewer people treated with inhibitor SGLT2 (386/16.3%, including 215 patients with diagnosed T2DM) compared to 502/21.17% undergoing standard therapy (including 271 with T2DM), which means a 26% risk reduction [hazard ratio (HR) = 0.74, $p = 0.00001$]. Listed as one of the primary endpoints, unplanned hospitalisation was significantly less common in patients treated with dapagliflozin (231 patients required an additional hospital stay — 9.7%, vs. 318 patients — 13.4% from the control group; HR = 0.7, $p = 0.00003$). Weaker but also statistically significant results were obtained in the area of deaths from cardiovascular causes — 227 patients (9.6%) who received the SGLT2 inhibitor died compared to 273 (11.5%) patients undergoing standard treatment (HR = 0.82, $p = 0.029$). Total deaths were also compared, showing lower mortality in the dapagliflozin group (11.6% vs. 13.9% in the control group; HR = 0.83, $p = 0.022$). Researchers defined the secondary endpoint as hospitalisation for HF or death from cardiovascular causes. Also, in this regard, the results of the study showed the benefits of using dapagliflozin (HR = 0.75, $p = 0.00002$). The authors also considered the severity of HF symptoms in accordance with the Kansas City Cardiomyopathy Questionnaire (KCCQ) scale, demonstrating improvement in the clinical condition after 8 months ($p < 0.001$) in the case of inhibitor SGLT2 treatment. Dapagliflozin had a neutral effect on renal function with no signs reported of the adverse effects of the study drug. Importantly, the protective effect in HF did not depend on the use of ARNI — it was identically strong in patients treated with and without sacubitril/valsartan, suggesting a different mechanism of action. The DAPA-HF study has already shown that adding dapagliflozin to standard therapy reduces the risk of exacerbation of HF symptoms, as well as improves clinical status, which is associated with a reduced number of hospitalisations and reduced cardiovascular mortality in HF patients with reduced LVEF also without T2DM, which is a breakthrough observation and means the identification of a new drug that improves prognosis in HF.

PARAGON-HF — angiotensin receptor neprilysin inhibitor in HF with intermediate and preserved LVEF?

Another study on HF, the results of which had been expected, was PARAGON-HF (Efficacy and Safety of ARNI Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction) [2]. It compared the effects of treatment with angiotensin II receptor blocker (ARB) — valsartan 160 mg, and treatment with ARB and neprilysin inhibitor (ARNI) — sacubitril/valsartan (97/103 mg) for 35 months in a difficult-to-treat group of patients with HF with intermediate and preserved LVEF. The study included

4,822 patients aged 50 years and from 43 countries with persistent HF symptoms in NYHA and LVEF class II–IV not less than 45% and elevated NT-proBNP concentration. Individuals were excluded with acute, decompensated HF, LVEF below 40%, SBP values below 110 mm Hg or above 180 mm Hg, and SBP above 150 mm Hg if patients did not take more than 3 antihypertensive drugs. Researchers failed to reach the primary endpoint — only the benefit trend of the new therapy was obtained (reduction of hospitalisations and cardiovascular death by 13%, $p = 0.059$). Similarly, there was a trend to reduce the risk of hospitalisation in the key ARNI group (690 vs. 797 in the valsartan group; relative risk [RR] 0.85, $p = 0.056$). Among the secondary endpoints, there was a statistically significant improvement in clinical status in the ARNI-treated group compared to ARB-treated patients [odds ratio (OR) 1.35, $p = 0.004$], also confirmed on the KCCQ quality of life scale (OR = 1.3, $p = 0.019$). Protective effects on kidney function have also been observed [HR = 0.55; 95% confidence interval (CI) 0.33–0.77, $p = 0.002$]. In the group of patients undergoing complex therapy, a higher tendency to hypotonia ($p < 0.0001$) and angioedema was observed, with less frequent hypokalemia. Subgroup analysis suggested a better effect of the drug in patients with LVEF below 57%. Although the results of the PARAGON-HF study did not indicate the efficacy of ARNI in patients with HF and preserved left ventricular systolic function to improve survival, it improved clinical status, quality of life and kidney function when compared to patients receiving valsartan.

ISAR-REACT 5 — prasugrel versus ticagrelor in patients with acute coronary syndrome after coronaroplasty

ISAR-REACT 5 Study (The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) caused a real sensation [3]. Two antiplatelet drugs (prasugrel and ticagrelor) added to acetylsalicylic acid (ASA) were compared in patients after acute coronary syndrome (ACS) requiring an invasive treatment strategy after coronary angiography, 85% of whom had coronaroplasty. The patients with active bleeding, treated with anticoagulants, after a stroke or transient ischaemic attack (TIA), with renal failure requiring dialysis, with acute or moderate liver failure, and using CYP3A drugs were excluded in this non-commercial study. 4,018 people were included in the study; 2012 received ticagrelor and 2006 prasugrel. The authors determined for the first time in a head-to-head study the impact of these drugs on mortality, ST-segment elevation myocardial infarction (STEMI), haemorrhagic and ischaemic stroke during 12 months of therapy. To the surprise of the initiators of the study, there were significantly fewer (36%) adverse events in the prasugrel-treated group (6.9% vs. 9.3%, $p = 0.006$). When comparing each of the

primary endpoint components individually, benefits were also seen in patients treated with prasugrel in regard to stent thrombosis. In the group of patients treated with prasugrel, there were insignificantly less (12%) incidents of major bleeding (determined by the Bleeding Academic Research Consortium scale – 4.8% vs. 5.4%, $p = 0.46$) compared to those treated with ticagrelor. ISAR-REACT 5 demonstrated that treatment with prasugrel in patients with ACS reduces the risk of death, recurrent heart attack and stroke without increasing the risk of bleeding. These results come from study with a very well-planned protocol in which two antiplatelet drugs were compared for the first time in the context of percutaneous coronary intervention (PCI). The results of the ISAR-REACT 5 study emphasise the importance of solid evidence-based medicine, using direct, precise studies of relevant clinical groups, not stopping at indirect comparisons – using the results of separate trials with not necessarily identical characteristics.

THEMIS – dual antiplatelet therapy with ticagrelor versus ASA monotherapy in patients with stable CAD and T2DM

The attention of the participants was also focused on the **THEMIS** (The Effect of Ticagrelor on Health Outcomes in DiabEtes Mellitus Patients Intervention Study) study [4], which aimed to demonstrate the benefits of using ticagrelor (dual antiplatelet therapy with ASA) compared to a control group receiving only ASA in patients with T2DM treated for at least 6 months and stable CAD with no history of myocardial infarction. The primary endpoint was a risk of cardiovascular death, heart attack or stroke. 19,220 patients were enrolled in the study, of whom 9,619 received ticagrelor. The inclusion of ticagrelor significantly reduced the risk of a composite endpoint by 10% (HR = 0.9, $p = 0.038$). In the analysis of individual treatment goals, dual antiplatelet therapy reduced the number of myocardial infarction (HR = 0.84, $p = 0.029$) and strokes (HR = 0.8, $p = 0.038$). Acute limb ischaemia was also rarer (HR = 0.45, $p = 0.017$). However, the primary safety-related endpoint proved unfavourable for dual therapy, which more than doubled the number of bleeding complications and the increased the risk of intracranial haemorrhage by 71%. A group of patients **THEMIS-PCI** (THEMIS-Percutaneous Coronary Intervention) [5] treated with the PCI was prospectively separated from the group of patients included in the THEMIS study. This subgroup consisted of 5,558 patients who underwent dual antiplatelet therapy and 5,596 patients from the control group. In this subgroup, the inclusion of ticagrelor reduced the risk of a composite endpoint (cardiovascular death, myocardial infarction or stroke) by 15% (HR = 0.85, $p = 0.013$). In the analysis of individual treatment goals, dual antiplatelet therapy also reduced the number of heart attacks and strokes in the

group of patients treated with PCI. When analysing each of the points, the risk of myocardial infarction was reduced by 20% (HR = 0.8, $p = 0.027$), STEMI by 68% (HR = 0.32, $p < 0.0001$) and stroke by 26% (HR = 0.74, $p = 0.024$). Comparing the composite endpoint including death, myocardial infarction, ischaemic stroke, fatal bleeding and intracranial haemorrhage, it was demonstrated that the inclusion of ticagrelor reduced the risk by 15% (HR = 0.85, $p = 0.005$). Pharmacotherapy with ticagrelor (initially at 2×90 mg, but in the later phase of the study reduced to 60 mg) in THEMIS in CAD and T2DM patients treated with prior PCI has also been shown to reduce the risk of cardiovascular death, MI and stroke despite the bleeding. The results of the study suggest that long-term, even lasting 3 years, ticagrelor therapy with ASA may become useful in patients with stable CAD and T2DM, especially those patients treated with percutaneous coronary angioplasty, with a high risk of thromboembolic events and a low risk of bleeding.

AFIRE – rivaroxaban monotherapy versus dual antiplatelet therapy in patients with CAD and atrial fibrillation

A recent study focused on the treatment of patients with CAD and co-existing atrial fibrillation. The aim of the Japanese **AFIRE** study [6] was to compare the effectiveness of rivaroxaban treatment alone or in combination with antiplatelet agents. The study included 2,200 patients with CAD and atrial fibrillation (with CHADS₂ ≥ 1) one year after coronary angioplasty or coronary artery bypass grafting, and those not requiring intervention with vasoconstriction exceeding 50%. The study excluded patients with a history of stent thrombosis, concomitant active tumour, and poorly controlled hypertension. Patients received rivaroxaban monotherapy at a “Far-Eastern” typical dose of 10–15/day, which corresponded to typical dosing in Caucasian patients, or in combination with one of the antiplatelet agents (also in modified dosing – ASA 81–100 mg, clopidogrel in 50–75 mg or prasugrel 2.5–3.75 mg). Finally, 1,005 patients treated with rivaroxaban only and 968 undergoing dual antiplatelet therapy were randomised. Researchers assessed a composite endpoint including stroke, embolic complications, MI, unstable angina requiring revascularization, or death over a 23-month follow-up period. A 28% lower risk of composite endpoint was seen with rivaroxaban alone (HR = 0.72, $p < 0.001$), as well as a 41% less bleeding event (HR = 0.59, $p = 0.01$). Taking into account the occurrence of cardiovascular incidents and mortality, rivaroxaban monotherapy significantly better protects patients who underwent coronary revascularization a year ago or earlier, which is the first evidence of the risk of the chronic combination of new anticoagulants with antiplatelet agents.

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