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Report from the European Society of Cardiology Congress 2022 in Barcelona: new discoveries in cardiovascular pharmacotherapy

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Abstract

The following paper presents an overview of the key studies presented at the European Society of Cardiology Congress 2022. The DELIVER study provided information on the efficacy of dapagliflozin independent of left ventricular ejection fraction. The ADVOR trial confirmed the beneficial effect of the inclusion of acetazolamide as a diuretic in the initial phase of acute decompensated heart failure. The REVIVED study showed no advantage of percutaneous revascularisation over optimal pharmacotherapy in stable coronary artery disease. The SECURE study demonstrated the benefit of the so-called polypill over taking each drug separately. The PANTHER meta-analysis indicated a better effect of using P2Y12 inhibitors over aspirin in chronic therapy. The ALL-HEART study revealed no benefit in treating asymptomatic hyperuricemia in patients with coronary artery disease with allopurinol. The INVICTUS trial demonstrated the superiority of vitamin K antagonists over non-vitamin K antagonist oral anticoagulants in preventing embolic complications in cases where valvular defects of rheumatic origin co-occur with atrial fibrillation.

Key words: dapagliflozin, allopurinol, percutaneous coronary revascularisation, polypill, acetazolamide

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Introduction

After a two-year hiatus due to the epidemiological situation, the European Society of Cardiology (ESC) Congress 2022 took place in a stationary format in Barcelona. As expected, it became an arena for the presentation of new data that can be applied to daily clinical practice, improve treatment outcomes in patients and accelerate their recovery. The authors of this paper have selected seven most relevant, in their opinion, recent clinical trials that are likely to have the greatest impact on the treatment of patients with heart diseases.

DELIVER (Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction) [1]

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are among the most recent drugs used in the treatment of heart failure (HF). Their positive effect on improving cardiac function was confirmed in the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF as a class Ia recommendation for use in HF with reduced ejection fraction (EF). Their effectiveness in the treatment of HF with preserved and minimally reduced EF has been

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evaluated in two recent studies — EMPEROR-PRESERVED [2] and DELIVER. The latter was designed to determine the efficacy of dapagliflozin treatment in the case of HF with preserved and mildly reduced EF.

The study was participated by 6263 patients with left ventricular (LV) EF above 40% who were randomly allocated to two groups — the first received a daily dose of 10 mg of dapagliflozin in addition to full basic treatment (n = 3131) while the second was treated with a placebo (n = 3132). The primary composite endpoint included death due to cardiovascular causes and HF exacerbation. The inclusion criteria were age above 40 years, confirmed structural heart disease, LVEF above 40% and elevated natriuretic peptide levels (N-terminal prohormone of brain natriuretic peptide [NT-proBNP] > 300 pg/mL or > 600 pg/mL in patients with atrial fibrillation [AF]). The mean age of the patients was 71.7 years, 44% of the subjects were female.

The study was successful, with significantly fewer (by 18%) occurrences of a primary endpoint in patients receiving dapagliflozin. A 21% reduction in the risk of hospitalisation and urgent medical admission due to HF exacerbation was demonstrated; there was no statistically significant decrease in the number of deaths caused by cardiovascular diseases [1].

The DELIVER study is a valuable addition to the EMPEROR-PRESERVED trial [2], published a year earlier, which supplements data on the subgroup of "improved EF", i.e. HF with improved EF, and patients with HF with preserved EF and high LVEF. When correlating the data collected from both studies, it can be seen that the use of flosins is beneficial for every patient diagnosed with HF, regardless of the LVEF values. The results of these studies illustrate exactly how great of a breakthrough in the treatment of HF was the introduction of SGLT-2 inhibitors, which gained importance after the discovery of a significant improvement in cardiovascular risk indicators in diabetic patients. It is worth emphasising that meta-analyses presented at the ESC Congress confirmed the consistent protective effect of flosins across the entire spectrum of phenotypes and LVEF values in patients with HF and that these drugs are now a major element in the pharmacotherapy of patients with preserved LVEF as well.

ADVOR (Acetazolamide in Acute Decompensated Heart Failure with Volume Overload) [3]

In the case of HF, exacerbations are a frequent consequence of the disease. They are often manifested by episodes of overhydration of varying degrees, with each successive episode having an increasingly severe course and worsening the patient's prognosis. The basic drugs used in therapy are loop diuretics, which operate in the loop of Henle by inhibiting the transport of chloride and sodium. Better outcomes can be achieved by influencing diuresis with different mechanisms at the same time. The aim of the ADVOR study was to investigate whether the addition of acetazolamide — the carbonic anhydrase inhibitor and a drug that acts in the proximal convoluted tubule, i.e. in a different part of the nephron loop — would be beneficial in patients exhibiting HF exacerbation.

The inclusion criteria were hospitalisation due to exacerbated HF with clinical symptoms of overhydration, NT-proBNP > 1000 pg/mL or BNP > 250 pg/mL, and oral administration of furosemide at a dose of at least 40 mg or 20 mg of torasemide or 1 mg of bumetanide for a minimum of one month prior to randomisation. The exclusion occurred as a result of chronic use of acetazolamide or another drug having an effect on the proximal convoluted tubule (including SGLT-2 inhibitors), systolic blood pressure lower than 90 mm Hg and estimated glomerular filtration rate lower than 20 mL/min/1.73 m^2. The patients were divided into two groups: the first received an additional 500 mg acetazolamide intravenously once a day in addition to loop diuretics for three days (n = 259) and the others (n = 260) received a placebo together with loop diuretics. The mean age of the patients was 78 years. Women comprised 37.4% of participants. The primary endpoint was an effective reduction of overhydration within three days, while the secondary endpoint consisted in death from any cause or re-hospitalisation due to HF within 3 months.

The primary endpoint was achieved in 108 out of 256 (42.2%) patients receiving treatment with acetazolamide and in 79 out of 259 (30.5%) individuals from the placebo group. This represents a 46% improvement in the effective removal of excess water in patients compared to standard therapy based solely on loop diuretics. Death attributable to any cause or re-hospitalisation occurred in 76 out of 256 (29.7%) individuals receiving acetazolamide and 72 out of 259 (27.8%) patients treated with a placebo. There was no statistically significant difference between the two groups. Deterioration of renal function, hypotension and hypokalaemia were also found with similar frequency in both groups.

The ADVOR study demonstrated that the addition of a well-known diuretic — acetazolamide — to standard therapy based on loop diuretics leads to more rapid, yet equally safe, removal of excess water in patients hospitalised due to exacerbated HF, but no statistically significant difference between the incidence of death or hospital re-admission [3].

REVIVED (Percutaneous Revascularisation for Ischemic Left Ventricular Dysfunction) [4]

One of the most frequently performed cardiac procedures is coronary revascularisation. When performed on a patient

with acute coronary syndrome (ACS), it significantly increases their chances of survival. The question is whether it shows equally spectacular results when carried out in the case of stable coronary artery disease (CAD). The ISCHEMIA study revealed a lack of clear prognostic benefits for patients undergoing either percutaneous coronary intervention (PCI) or coronary artery bypass grafting. A major limitation of this trial was the exclusion of patients with a LVEF lower than 35% who could potentially benefit from revascularisation. The REVIVED study was designed to demonstrate whether PCI in patients with HF with reduced EF could improve their prognoses and increase LVEF.

The study included 700 stable patients with a LVEF lower than or equal to 35%, coronary anatomy indicating the possibility of revascularisation and confirmed myocardial viability, who were randomised into two groups — 347 patients were treated by means of PCI and optimal pharmacotherapy, while the control group (353 individuals) consisted of patients treated with pharmacotherapy alone. The primary endpoint involved death caused by any reason or hospitalisation due to HF exacerbation. The secondary endpoint consisted in the assessment of LVEF after 6 and 12 months and the evaluation of patients' quality of life.

The results of the study were surprising. During the 41-month follow-up period, the primary endpoint occurred in 129 patients (37.2%) undergoing PCI and 134 (38.0%) receiving optimal pharmacotherapy alone, with no statistically significant difference between the two groups. At 6 and 12 months, the LVEF was similar in both groups. Quality of life at 6 and 12 months indicated in favour of PCI, but after 24 months, the results in both groups levelled off. It is worth emphasising that REVIVED patients received very good pharmacological treatment, and more than 20% had previously implanted devices.

The lack of significant difference between the two treatment strategies suggests that complete percutaneous coronary revascularisation should not be pursued at all costs in stable patients with reduced EF without symptoms of CAD exacerbation. Appropriate pharmacological treatment is equally effective and additionally free of the risk associated with the procedure, which, similarly to any invasive intervention, may lead to harmful complications [4]. In the long term, successful pharmacological treatment has a comparable effect in terms of improved quality of life, consistent with the results of the earlier ORBITA trial.

SECURE (Secondary Prevention of Cardiovascular Disease in the Elderly) [5]

For quite some time, there has been a trend of combining multiple drugs in a single tablet focused on improving the outcome of preventive treatment by increasing patient cooperation. The market offers an increasing number of drug combinations designed to enhance therapeutic outcomes. But does the use of a single tablet instead of several actually help the treatment process in any meaningful way? The authors of the SECURE study sought to answer this question by evaluating the benefits of the "polypill" — a single tablet combination (100 mg acetylsalicylic acid, 2.5–10 mg ramipril and 20 or 40 mg atorvastatin) in patients characterised with high cardiovascular risk. The trial covered 2499 patients from 113 centres. Inclusion criteria consisted of a history of myocardial infarction (MI) up to 6 months prior to randomisation, age 75 years or 65 with at least one risk factor (diabetes, mild or moderate kidney disease, previous MI, coronary revascularisation or stroke). The follow-up period was 36 months.

Patients were divided into two groups — the first was treated with combination therapy (n = 1237), while the second received conventional treatment (n = 1229). The primary endpoint included death attributable to cardiovascular causes, non-fatal type 1 MI, non-fatal stroke and urgent coronary revascularisation. This occurred in 118 patients undergoing combination therapy and 156 patients in the conventional treatment group. These data represent a 24% reduction in the risk of occurrence of events classified as primary endpoints. The secondary endpoint consisting of death of cardiovascular origin, non-fatal type 1 MI or non-fatal stroke was observed in 101 individuals receiving polypills and 144 patients participating in the conventional treatment. This indicates a highly statistically significant risk reduction of 30%.

The results of the study demonstrate that combined polypill-type formulations can also be successfully applied in the secondary prevention of cardiovascular diseases. In addition to facilitating the treatment process by improving therapeutic cooperation, they also result in better long-term outcomes by extending patients' lives and helping them to remain in better health than in the case of standard therapy. The use of one-pill medication undoubtedly reduces the risk of skipping or changing any of the doses. As a result, more and more drug combinations and their mixing options are to be expected.

PANTHER (P2Y12 Inhibitors Top Aspirin for Long-term Secondary Prevention) [6]

The use of antiplatelet drugs is the foundation of pharmacotherapy in the case of chronic and ACS. Low-dose aspirin, on which dual antiplatelet therapy protocols are based, is the standard treatment. However, clinical trials have been conducted to test the feasibility of replacing acetylsalicylic acid monotherapy with P2Y12 inhibitors, particularly clopidogrel or ticagrelor.

The authors of the PANTHER meta-analysis attempted to answer the question of whether the application of P2Y12 inhibitors in chronic therapy would be as effective

and safe as the use of aspirin. The study included an analysis of data on 24 325 patients from 7 randomised trials. 12 178 individuals were receiving P2Y12 inhibitors (7545 clopidogrel and 4633 ticagrelor). The control group consisted of 12 147 aspirin users. The mean age of the patients was 64.3 years. 21.7% of the study participants were women. The group receiving P2Y12 inhibitors showed a significantly (12%) lower risk of the primary composite endpoint in the form of death due to cardiovascular causes, MI and stroke. However, no differences in overall or cardiovascular mortality were observed. It is important to emphasise that P2Y12 inhibitors entailed a 23% lower risk of MI. Similar safety was reported for both drug groups as measured by the incidence of major bleeding (1.2% vs. 1.4%) — however, only 0.4% had a history of major bleeding. Interestingly, the risk of haemorrhagic stroke and gastrointestinal bleeding was significantly higher during acetylsalicylic acid therapy.

Based on the results of the study, it can be concluded that the use of P2Y12 inhibitors in CAD will grow in importance in the future (particularly if the price decreases), and their broader clinical use should be expected. Currently, their application is limited mainly to dual antiplatelet therapy protocols for stents or ACS and in cases of aspirin intolerance, which is the basis of treatment for chronic coronary syndromes. An example of a group that may benefit from P2Y12 inhibitors are young patients after revascularisation and at high risk of gastrointestinal bleeding. However, the absolute differences in treatment outcomes are small — one out of 123 patients will avoid an incident regarded as a primary composite endpoint.

ALL-HEART (Allopurinol and Cardiovascular Outcomes in Patients with Ischemic Heart Disease) [7]

Allopurinol is a well-known and long-used xanthine oxidase inhibitor exhibiting antioxidant activity. It is used to lower uric acid concentrations in patients suffering from symptomatic gout. It has been prescribed in Poland (and nowhere else) to treat asymptomatic hyperuricaemia with a view to the hypothetical prevention of cardiovascular complications excessively often, without scientific data to recommend it. The authors of the ALL-HEART study decided to examine whether its use would improve the prognosis of patients diagnosed with ischemic heart disease.

Patients with ischemic heart disease were randomised into two groups. In the study group (n = 2853), their standard therapy was supplemented with allopurinol at a dose adjusted to the glomerular filtration rate. The control group (n = 2868) received conventional treatment. The primary endpoint was the death of cardiovascular origin, MI or stroke. This occurred in 11.0% of patients in the group treated with additional allopurinol and in 11.3% of individuals in the control group (p = 0.65). The overall mortality rate was comparable in both groups (10.1% vs. 10.6%; p = 0.77), similar to hospitalisations due to HF (2.6% vs. 3.4%; p = 0.18)

Despite the methodological limitations of the presented study, it is the only high-quality prospective trial evaluating the benefits of allopurinol outside the context of gout. It allows concluding that the use of allopurinol in patients with ischemic heart disease does not improve their prognosis in any way. In view of the above, the application of allopurinol in patients without clinical symptoms of gout is inadvisable and unjustified.

INVICTUS (Investigation Of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies) [8]

The consequences of rheumatic heart disease affect approximately 33 million people worldwide, mostly in poorer countries. Atrial fibrillation is one of the most common complications of the classic rheumatic defect — mitral stenosis — and can also result from other types of defects. Dangerous complications of AF may consist in the blockage of peripheral arteries, including those supplying the brain, which can lead to stroke unless appropriate anticoagulants are administered.

The purpose of the INVICTUS study was to compare the efficacy of rivaroxaban and vitamin K inhibitor treatment in patients with rheumatic heart valve disease (mainly mitral stenosis) and AF. The study was participated by 4531 individuals who were randomly assigned to undergo anticoagulant treatment with rivaroxaban at a dose of 20 mg or 15 mg in the case of creatinine clearance below 50 mL/min, while the second group received vitamin K antagonists at a dose that allowed maintaining an international normalized ratio (INR) between 2.0 and 3.0 (n = 2256). The mean age of the patients was 50 years. 72% of the subjects were female. Among both groups, about 85% of individuals were diagnosed with mitral stenosis, of which about 1/4 was severe, while about 82.5% had mitral regurgitation, of which severe defect accounted for about 22%. Death, stroke, peripheral embolism and MI were identified as primary endpoints. They occurred significantly more often in persons treated with rivaroxaban (8.2%) and those receiving vitamin K antagonists (6.5%). This means that rivaroxaban entails a 25% higher risk compared to conventional treatment. No differences were observed with regard to the rate of hospitalisation due to HF failure. There were also no differences between the two groups in terms of the occurrence of major bleeding, however, the incidence of fatal bleeding was statistically significant in favour of rivaroxaban (4 vs. 15; 0.17% vs. 0.66%).

Despite the development of anticoagulant treatment, the classic vitamin K antagonists still prove to be useful

and are the only choice in specific subgroups of patients (with mechanical valve prostheses and mitral stenosis). As seen in the analysis conducted in the course of the INVICTUS trial, their application in significant valve defects of rheumatic aetiology is associated with a lower risk of stroke and cardiac death, although their significant drawback consists in the need to constantly monitor the INR index, which may be problematic for some individuals. In the case of patients who can maintain high-quality anticoagulant treatment, vitamin K antagonists should remain the treatment of first choice for co-morbid rheumatic heart disease with AF.

Conflict of interest

None declared.

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