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A report from the American Heart Association Scientific Sessions 2021

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Abstract

The present report summarizes the most interesting new clinical studies that were reported during the American Heart Association Scientific Sessions 2021. The AVATAR study evaluated earlier surgical aortic valve replacement. A study by Cardiothoracic Surgical Trials Network focused on concomitant mitral and tricuspid valve surgery. The CRAVE study provided important data for coffee lovers. Use of empagliflozin in heart failure was evaluated in the EMPULSE and EMPEROR-Preserved trials. A study of an oral PCSK9 inhibitor is an initial step towards full evaluation of the efficacy of this drug. Reversal of ticagrelor action was reported in the REVERSE-IT study.

Key words: cardiac surgery, coffee, empagliflozin, heart failure, PB2452, MK-0616

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Introduction

Due to the epidemiological situation related to the COVID-19 pandemic, the organizers of the American Heart Association (AHA) Scientific Sessions 2021 had to run one of the largest scientific congresses in an online format. During more than 500 presentations, the participants had an opportunity to get informed about the most important clinical studies from all over the world. Below is the digest of the most interesting new clinical studies that were reported during the AHA Scientific Sessions.

AVATAR study — should asymptomatic aortic stenosis be operated on earlier?

Surgical aortic valve replacement (SAVR) and increasingly used transcatheter aortic valve replacement (TAVR) are procedures recommended in symptomatic patients with severe aortic stenosis to relieve symptoms and improve survival, while valve replacement in asymptomatic patients remains a matter of debate. The Aortic Valve Replacement Versus Watchful Waiting In Asymptomatic Severe Aortic Stenosis (AVATAR) study was a prospective, randomized, controlled clinical trial that was conducted also in Polish centres. The study hypothesis was that in patients undergoing aortic valve replacement before development of symptoms or a drop in left ventricular ejection fraction (EF), the incidence of the primary endpoint of death, myocardial infarction, stroke, or unplanned hospitalization for heart failure (HF) would be lower compared to patients treated according to the current guidelines.

The study included 157 patients with severe aortic stenosis that was asymptomatic, also in the exercise test settings. The exclusion criteria included a history of dyspnoea, syncope or angina, EF < 50%, very severe aortic stenosis (peak resting flow velocity > 5.5 m/s), severe aortic regurgitation, aortic dilatation requiring surgery or to > 5 cm, significant mitral valve disease, previous cardiac surgery, atrial fibrillation, severe lung disease, and expected survival below 3 years.

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The study participants were randomized to early surgery (within 8 weeks from randomization, with indications for surgical treatment based on criteria consistent with the current guidelines or conservative treatment. The primary endpoint was consistent with the primary study hypothesis. Secondary endpoints included in-hospital and 30-day mortality, redo aortic valve surgery in the operated patients in both groups, recurrent major adverse cardiovascular events (stroke, myocardial infarction, unplanned hospitalization for HF requiring intravenous diuretic therapy), major bleeding, thromboembolic complications, time to death, and time to the first hospitalization for HF. In addition, the overall serious adverse event rate was analysed.

The mean age of study participants was 67 years, 57% were men, and the mean estimated operative risk by the Society of Thoracic Surgeons (STS) score was 1.7%. The median time from randomization to SAVR in the early surgery group was 55 days, and 53% of patients received a mechanical prosthesis. Surgery was also performed in 25 patients in the conservative treatment group (40% of patients received a mechanical prosthesis), and the median time from randomization to surgery in the conservative treatment group was 400 days. One death within a month from the surgery was noted both in the early surgery group and in the conservative treatment group.

Overall, 39 events were noted, including 13 (16.6%) in the early surgery group and 26 (32.9%) in the conservative treatment group. In the primary intention-to-treat (ITT) analysis, the rate of the primary endpoint of death, myocardial infarction, stroke, or unplanned hospitalization for HF was much lower in patients allocated to early surgery compared to the conservative treatment group (15.2% vs. 34.7%; hazard ratio [HR] 0.46; 95% confidence interval [CI]: 0.23–0.90; p = 0.02]. Sudden death occurred in 6 patients in the conservative treatment group compared to 3 patients in the early surgery group, including one patient who died suddenly when awaiting the surgery. No significant differences in other secondary endpoints were noted between the two groups. The rate of major adverse cardiovascular events was significantly higher in the conservative treatment group compared to the early surgery group (16 [20.5%] in the early surgery group vs. 33 [41.8%] in the conservative treatment group; p = 0.004).

In summary, the AVATAR study showed that early SAVR improved outcomes, resulting in a trend for a lower risk of all-cause death and hospitalization for HF compared to patients who received conservative treatment and were operated on only after symptoms developed. These findings suggest than when aortic stenosis becomes severe, early valve replacement improves outcomes regardless of symptoms [1, 2].

Should tricuspid valve be repaired at the time of mitral valve surgery?

Mitral regurgitation is the most common valve disease worldwide. In the United States, more than 50 000 surgical procedures are performed annually to treat this disease. Mitral regurgitation may be accompanied by tricuspid regurgitation. When planning mitral valve surgery in patients with concomitant severe tricuspid regurgitation, there is a consensus among cardiac surgeons that the tricuspid valve should also be operated on but doubts arise when tricuspid regurgitation is not severe.

This issue was investigated in a study by the Cardiothoracic Surgical Trials Network that included 401 patients with degenerative mitral valve disease with concomitant moderate tricuspid regurgitation or only tricuspid annulus dilatation to ≥ 40 mm. The patients were randomized to isolated mitral valve surgery or concomitant tricuspid valve repair. The primary endpoint during a 2-year follow-up included death, a need for tricuspid valve reoperation, and progression to severe tricuspid regurgitation.

In patients who underwent mitral valve repair combined with tricuspid annuloplasty, the rate of primary endpoint events was lower compared to patients after isolated mitral valve surgery (3.9% vs. 10.2%; relative risk [RR] 0.37; 95% CI: 0.16–0.86; p = 0.02), although no difference in mortality was noted between the two groups. The rate of tricuspid valve disease progression after isolated mitral valve surgery was 6.1% compared to 0.6% in those after combined mitral and tricuspid valve surgery (RR 0.09; 95% CI: 0.01–0.69). The rate of major adverse cardiac and cerebrovascular events, functional status, and quality of life at 2 years were similar in both groups, although the rate of cardiac pacemaker implantation was higher following combined mitral and tricuspid valve surgery compared to isolated mitral valve surgery (14.1% vs. 2.5%; RR 5.75; 95% CI: 2.27–14.60). Duration of cardiopulmonary bypass and duration of hospital stay in patients who underwent combined mitral and tricuspid valve surgery were longer compared to patients who underwent isolated mitral valve surgery.

The results of this analysis do not allow to conclude clearly whether reduction in progression of tricuspid regurgitation using the evaluated strategy translates to a long-term clinical benefit. Possible need for cardiac pacing should be taken into account when calculating the benefit to risk ratio [3].

CRAVE study — does coffee induce arrhythmia?

The Coffee and Real-Time Atrial and Ventricular Ectopy (CRAVE) study was important for all coffee-lovers.

The primary study endpoints were coffee intake-related atrial and ventricular premature beats, and the secondary endpoints included supraventricular and ventricular tachycardia episodes, daily activity defined as the step count, duration of sleep, and average blood glucose level.

The study included 108 volunteers. The median age was 38 years, and 51% of the participants were women. Each study participant was provided an electrocardiogram monitor, blood glucose meter, pedometer, and sleep duration monitor. Data were collected using a mobile app. A DNA sample for genotyping coffee metabolism was collected from each participants. The participants were randomly divided into groups that distinguished between the time system of the coffee they were drinking ("start: on caffeine" and "start: off caffeine" groups).

In subjects who consumed two or more cups of coffee per day, a statistically significant 54% increase in ventricular premature beats was noted ($p = 0.007$). Each additional cup of coffee was associated with a 12% reduction in the occurrence of supraventricular tachycardia episodes ($p = 0.028$), an increase in the daily step count by 587, and a reduction in the duration of sleep by 18 minutes. No significant differences in blood glucose levels were noted. An increase in ventricular premature beats was noted in rapid caffeine metabolizers, and a stronger effect on sleep was noted in slow caffeine metabolizers.

In summary, coffee has no effect on the increase in the occurrence of supraventricular arrhythmia. Coffee consumption increases ventricular premature beats in rapid caffeine metabolizers, promoting physical activity but also reducing duration of sleep by 18–36 minutes [4, 5].

EMPEROR-Preserved trial — empagliflozin is beneficial in heart failure with preserved ejection fraction

Based on previously reported results of the Empagliflozin Outcome Trial In Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved), empagliflozin reduces the risk of cardiovascular death or hospitalization due to HF in HF patients with EF > 40%, while in the analysis presented at the AHA Scientific Sessions, the authors examined the effect of empagliflozin on the quality of life in patients with HF with preserved EF (HFpEF), i.e., EF ≥ 50%.

The aim of this analysis was to evaluate the effects of empagliflozin in patients with preserved EF ≥ 50% in the EMPEROR-Preserved trial compared to patients with mildly reduced EF of 41–49% (heart failure with mildly reduced EF, HFmrEF).

The EMPEROR-Preserved trial included 5988 patients with New York Heart Association) class II–IV HF with EF > 40% and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of > 300 pg/mL in those with sinus rhythm and > 900 pg/mL in patients with atrial fibrillation. Thee mean age in the group with EF ≥ 50% (n = 4005; 67%) was 72.8 years compared to 70.1 years in the group with EF 41–49% (n = 1983; 33%) ($p < 0.001$). Diabetes was present in about 50% of patients in both groups ($p = 0.004$). The primary endpoint included cardiovascular deaths and hospitalizations for HF.

Among patients with HFpEF (EF ≥ 50%) receiving empagliflozin, a 17% reduction in the risk of death and hospitalization for HF (318 vs. 270; HR 0.83; 95% CI: 0.71–0.98; $p = 0.024$) and a 22% reduction in the number of first hospitalizations for exacerbated HF (226 vs. 182; HR 0.78; 95% CI: 0.64–0.95; $p = 0.013$) was noted. Reductions in cardiovascular mortality, all-cause mortality and hospitalizations for exacerbated HF in the empagliflozin group compared to placebo were not significant.

Among patients with HFmrEF (EF 41–49%) receiving empagliflozin compared to placebo, the risk of the primary endpoint was reduced by 29% (193 vs. 145; HR 0.71; 95% CI: 0.57–0.88; $p = 0.002$). In addition, a significant 42% reduction in the number of first hospitalizations for HF (126 vs. 77; HR 0.58; 95% CI: 0.44–0.77; $p < 0.001$) was noted.

At 52 weeks, the change in quality of life compared to baseline as evaluated by the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) in patients with HFpEF receiving empagliflozin or placebo was 4.24 compared to 2.78, respectively ($p = 0.006$), while in patients with HFmrEF these values were 4.86 and 3.3, respectively ($p = 0.043$). In addition, a major improvement in the KCCQ Total Symptom Score (KCCQ-TSS) and the Overall Summary Score was found in all empagliflozin-treated patients compared to the placebo group.

When comparing patients with left ventricular EF > 50% in the EMPEROR-Preserved (n = 3501) and PARAGON-HF (n = 4067) trials, a significant reduction in the combined rate of first hospitalizations for HF and cardiovascular deaths was observed in the EMPEROR-Preserved trial (HR 0.82; 95% CI: 0.69–0.98; $p = 0.0263$ vs. HR 0.94; 95% CI: 0.82–1.08;$p = 0.38$).

In patients with HF with preserved EF, empagliflozin treatment resulted in a significant, early, and persistent reduction in the risk and severity of HF exacerbation both in inpatient and outpatient settings. Empagliflozin improved health-related quality of life. This effect appeared early and persisted for at least one year [6, 7].

EMPULSE trial — should we use empagliflozin to treat acute decompensated heart failure?

Heart failure is one of the most common chronic diseases associated with high mortality and a major reason for hospital admissions. It was shown that SGLT2 inhibitors improve outcomes in patients with chronic HF but the experience with initiating SGLT2 inhibitor therapy in acute decompensated HF is limited.

The Efficacy and Safety of Empagliflozin In Hospitalized Heart Failure Patients (EMPULSE) study is an international, multicentre, randomized, double blind trial which evaluated the clinical benefits, safety, and tolerance of empagliflozin 10 mg daily compared to placebo in initially stabilized patients hospitalized due to acute decompensated HF, regardless of left ventricular EF. Patients included into the study experienced dyspnoea and had at least two of the following signs of HF exacerbation: congestion on chest X-ray, rales on lung auscultation, clinically significant pulmonary oedema, or dilated jugular veins. Other inclusion criteria were NT-proBNP level ≥ 1600 pg/mL or B-type natriuretic peptide (BNP) level ≥ 400 pg/mL (NT-proBNP level ≥ 2400 pg/mL or BNP level ≥ 600 pg/mL in patients with concomitant atrial fibrillation) and the need for diuretic therapy (minimum intravenous furosemide dose 40 mg or its equivalent).

The study included 500 patients who were allocated in a 1:1 ratio to the study or control group. The analysis of the primary outcome was based on the stratified win ratio approach, with the clinical benefit defined as a combination of mortality, number of HF-related adverse events, time to the first event, and change in the KCCQ-TSS at 90 days compared to baseline. The rate of clinical benefit was 53.9% in the empagliflozin group compared to 39.7% in the placebo group (95% CI: 1.09–1.68; p = 0.0054). Mortality rate was 4.2% in the empagliflozin group compared to 8.3% in the placebo group. The rate of HF-related events was 10.6% in the empagliflozin group compared to 14.7% in the placebo group. Regarding secondary endpoints, a notable change in the KCCQ-TSS was observed, by 4.5 points in the empagliflozin group compared to the placebo group (95% CI: 0.3–8.6; p = 0.035) at 90 days after randomization. Acute kidney injury occurred in 7.7% of patients in the empagliflozin group compared to 12.1% of patients in the placebo group. A statistically significant difference was also noted for the change in body weight at 90 days: –1.5 kg in the empagliflozin group compared to the placebo group (95% CI: –2.8 to –0.3; p =0.014).

In patients with acute decompensated HF, use of empagliflozin compared to placebo was associated with a significant clinical benefit at 90 days regardless of EF and concomitant diabetes. Compared to placebo, empagliflozin treatment was also associated with lower mortality, improvement in quality of life, and higher body weight reduction. No safety issues were identified in regard to empagliflozin therapy. These results may lead to earlier and more frequent initiation of empagliflozin therapy shortly after stabilization of acute decompensated HF, which may improve quality of life in a larger number of individuals with HF [8].

Is it possible to inhibit PCSK9 with an oral drug?

Hypercholesterolemia is a common disease in which the therapeutic goal is to achieve specific low-density lipoprotein (LDL) cholesterol level depending on risk factors. Despite wide availability of cholesterol-lowering drugs, many patients continue to be above these therapeutic goals. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are potent lipid-lowering drugs that reduce LDL cholesterol level by at least 50%, which allows to achieve the therapeutic goal in many patients. Two currently available PCSK9 inhibitors, alirocumab and evolocumab, are still underused due to, among other reasons, their cost and the need to inject the drug every 2 weeks or monthly. A similarly acting oral drug might thus be an interesting alternative.

A phase I study with such a drug, MK-0616, which is a peptide compound administered with agents that improve its gastrointestinal absorption, was reported at the AHA Scientific Sessions 2021.

The study population included 100 subjects. The drug was well tolerated, and treatment-related adverse events were mild and included abdominal discomfort, diarrhoea, indigestion, headache, and maculopapular rash. The efficacy of gastrointestinal absorption-enhancing agents was confirmed, with nearly identical results for labrasol and sodium caprate, and a negative effect of food was observed for a meal consumed within 30 minutes before administration of the study drug. Of the studied dosages, a more than 90% reduction of plasma free PCSK9 for 24 hours was observed despite only 2% bioavailability following oral administration. Similarly, no deaths and serious adverse effects were observed in the second trial. In participants receiving MK-0616, LDL cholesterol level decreased by about 65% at 14 days of therapy.

MK-0616 may become an interesting addition to the current preventive therapies but there is still a long way until full evaluation of its clinical efficacy [9].

REVERSE-IT trial — it is possible to reverse the effect of ticagrelor

Antiplatelet therapy is a mainstay intervention for the secondary cardiovascular event prevention. Particularly in high risk patients, the predominant paradigm is to use dual antiplatelet therapy, i.e., a combination of acetylsalicylic

acid and an oral P2Y12 receptor antagonist. Ticagrelor is a direct-acting oral P2Y12 receptor antagonist characterized by reversible receptor binding kinetics. The main limitation of this drug is an increased bleeding risk during the therapy which persists for several days after the drug is stopped. The antiplatelet effect may significantly limit haemostasis in patients with spontaneous or procedure-related major bleeding. The guidelines recommend withdrawal of oral P2Y12 receptor antagonists 3-7 days before a surgical procedure.

The Rapid and Sustained Reversal of Ticagrelor — Intervention Trial (REVERSE-IT) evaluates a new drug that may improve safety of patients treated with ticagrelor. PB2452, also known as bentracimab, is a neutralizing monoclonal antibody fragment that binds ticagrelor and its main active metabolite with high affinity. In healthy volunteers, bentracimab was shown to be safe and effective in reversing the antiplatelet effect of ticagrelor.

The planned recruitment size in the REVERSE-IT study is about 200 patients. Initial results of the study were reported at the AHA Scientific Sessions. The aim of the presented analysis was to evaluate the effect of BP2452 on platelet inhibition and haemostasis in patients who required reversal of ticagrelor action, and to evaluate the efficacy and safety of this agent in patients requiring an urgent surgical procedure or other invasive procedures associated with major bleeding risk.

Of 150 patients, 142 required an urgent surgery or invasive procedure (most commonly coronary artery bypass grafting), and 8 patients had a major bleeding (most commonly intracranial bleeding). The study recruited patients who received ticagrelor during the last 3 days and required urgent reversal of the drug's action, as deemed by the treating physician. Bentracimab was administered as a 6 g intravenous bolus over 10 minutes, immediately followed by an intravenous loading infusion of 6 g over 4 hours and then an intravenous maintenance infusion of 6 g over 12 hours.

The primary endpoints included reversal of ticagrelor action as evaluated using the VerifyNow analyser to determine the reduction in platelet P2Y12-dependent reactivity (P2Y12 reaction unit, PRU) within 4 hours from the start of study drug administration, and achievement of effective haemostasis in the overall study population. Key secondary endpoints included minimum percent inhibition of platelet reactivity index. Other predetermined endpoints included the type and timing of blood product transfusion and the proportion of patients in whom ticagrelor treatment was reinitiated. The safety analysis results included the rate and severity of treatment-related adverse events, thrombotic events following reversal of ticagrelor action, and immunogenicity.

The final analysis of ticagrelor action reversibility included 129 patients, and the analysis of haemostasis included 122 patients. A significant reduction of platelet inhibition following administration of bentracimab was observed, consistent with achievement of the primary study endpoint ($p < 0.001$). The effect of action of PB2452 was observed at 5–10 minutes following initiation of the drug infusion. The effect of bentracimab persisted for 72 hours and then decreased slightly ($p < 0.001$). When evaluating the primary haemostasis endpoint, a high proportion of patients achieving haemostasis was observed (98.4%), which was clearly higher than it would be expected in a similar population not treated with a reversal agent for ticagrelor. Overall, 72 adverse events were reported in 45 of 150 patients. Thrombotic complications were observed in 8 patients (5.3%).

This initial analysis from the REVERSE-IT study suggests that bentracimab may be a reversal agent for ticagrelor in patients requiring an invasive procedure or a surgery, and in patients who experienced a major bleeding. Termination of patient recruitment is planned at the end of 2023 [10, 11].

Conflict of interest

The autors report no conflict of interest.

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