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Progress in the treatment of cardiovascular diseases News from the American Heart Association Scientific Sessions 2020

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Introduction

The sanitary and epidemiological risk related to the severe acute respiratory syndrome-related coronavirus 2 (SARS-COV-2) pandemic has forced the organisers of major scientific congresses to conduct these events as interactive online meetings. American Heart Association (AHA) Scientific Sessions were not an exception. By choosing the "Virtual Experience" format, the organisers provided online access to live presentations and the possibility to view the congress materials at a later date. This paper presents short descriptions of the most interesting issues that were discussed during the sessions presenting the most interesting clinical trials.

RIVER: Rivaroxaban vs. Warfarin in Atrial Fibrillation in Patients with Bioprosthetic Mitral Valves

Novel oral anticoagulants [non-vitamin K oral anticoagulatns (NOAC)] currently constitute the first-choice treatment in the prevention of venous thromboembolic events in patients with non-valvular atrial fibrillation (AF). While the use of vitamin K antagonists (VKA) is a recognised therapy in patients who underwent mechanical mitral valve replacement with concurrent AF, in the case of patients with a sinus rhythm, the continuation of anticoagulant treatment with the use of VKA for 3–6 months is preferred, even though the 2021 guidelines of the AHA allow the use of antithrombotic therapy exclusively.

The possibility to use rivaroxaban in patients with AF who had a bioprosthetic mitral valve implanted was investigated in the RIVER (Rivaroxaban vs. Warfarin in AFib Patients With Bioprosthetic Mitral Valves) trial. It involved 1005 patients with AF (paroxysmal, persistent or chronic) or atrial flutter (AFL). The intervention was applied in those of the aforementioned patients who had a bioprosthetic mitral valve implanted at least two days before and were natural candidates for anticoagulant therapy. Patients were randomly assigned for treatment with rivaroxaban at a daily dose of 20 mg or with warfarin at a dose calculated according to the international normalized ratio (INR). The primary endpoint was a composite event comprising death and serious cardiovascular event or serious haemorrhage within 12 months.

Rivaroxaban therapy met the expectations — the occurrence of the primary endpoint was recorded after a mean of 347.5 days in the rivaroxaban group and after 340.1 days in the warfarin group ($p < 0.001$ for equivalence — a trend of the superiority of rivaroxaban could be observed in patients who received randomly selected treatment). Death from cardiovascular causes occurred in 3.4% of patients treated with rivaroxaban and in 5.1% of patients in the warfarin group [without a significant difference; hazard ratio (HR) 0.65; 95% confidence interval (CI): 0.35–1.20]. Rivaroxaban significantly better prevented stroke which was diagnosed in the course of observation in 0.6% of patients in this group, while in the warfarin group it occurred in 2.4% participants (HR 0.25; 95% CI: 0.07–0.88). Serious haemorrhage was observed in 1.4% versus 2.6% of patients respectively (without a significant difference, HR 0.54; 95% CI: 0.21–1.35).

The results of the study confirm at least full equivalence of the simpler NOAC therapy to the older standard. The

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evident benefits of the use of NOAC, such as no need for INR dosing and a lower risk of dangerous haemorrhages, encourage continued research into the issue addressed in the RIVER trial [1].

GALACTIC-HF: Registrational Study with Omecamtiv Mecarbil/AMG 423 to Treat Chronic Heart Failure with Reduced Ejection Fraction

Contemporary therapy for chronic heart failure does not generally use inotropic medications (digoxin may be an exception). In particular, medications that improve systolic force by affecting the metabolism of calcium ions were associated with worse survival in clinical trials. Nevertheless, the search for new avenues for the pharmacotherapy of heart failure continues. Direct support for the molecular mechanism of cardiac muscle cell contraction through the activation of myosin is the postulated action demonstrated by omekamtiv mekarbil. It accelerates the formation of strong binding of myosin heads to actin filaments which results in an increased number of these bonds and, consequently, leads to increased force of fibre contraction. The clinical objective of this medication is to improve myocardial contractility in patients with reduced ejection fraction without increasing myocardial oxygen demand.

The GALACTIC-HF trial assessed the risk of the first heart failure-related incident and cardiovascular death in patients receiving omekamtiv mekarbil or placebo combined with the standard therapy. Patients with symptomatic heart failure and reduced left ventricular ejection fraction (≤ 35%) were included in the study. A total of 8,256 patients received the intervention. The mean age was 64.5 years, with balanced sex ratios. More than 3/4 of the group was Caucasian. Nearly 90% of patients were chronically on renin–angiotensin–aldosterone system (RAAS) inhibitors and beta-blockers. The observation lasted less than 2 years.

The primary endpoint, consisting of the first heart failure incident (need for an urgent outpatient appointment or hospital admission due to the intensity of heart failure symptoms) or cardiovascular death occurred in 37% of patients receiving the investigated medication, while in the placebo group — it occurred significantly more often, in 39.1% of patients (HR 0.92; 95% CI: 0.86–0.99, p = 0,03). Cardiovascular death occurred in 19.6% and 19.4% patients respectively (HR 1.01; 95% CI: 0.92–1.11). In the group receiving omekamtiv mekarbil, there was a 10% decrease in the median of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, but the subjective improvement of the quality of life reported by patients in the Kansas City Cardiomyopathy Questionnaire did not significantly differ between the groups.

Significant, albeit moderate, reduction in the incidence of the first heart failure-related incident in the group receiving the investigated medication allows us to consider the possibility of its use in the therapy of heart failure in patients with reduced ejection fraction. However, in the context of the new wave of medications with proven efficacy in the treatment of heart failure (phlorizin, riociguat), the appropriate positioning of omekamtiv mekarbil in treatment schemes requires extended research [2].

AFFIRM-AHF: Ferric Carboxymaltose for Iron Deficiency at Discharge after Acute Heart Failure: a Multicentre, Double-Blind, Randomised, Controlled Trial

The starting point for the AFFIRM-AHF trial was a clinical observation confirmed by multicentre studies [3] on the worse course of chronic heart failure in patients with iron deficiency. Intravenous supplementation of iron and carboxymaltose had a beneficial effect on the quality of life of those patients, as well as on the prognosis [4, 5]. Ferric carboxymaltose is the pharmacological form that allows the controlled administration of iron to target tissues. In a relatively short time, about 80% of the dose is deposited in the bone marrow and the remaining 20% in the liver and spleen.

A group of 1,108 patients with iron deficiency (defined as ferritin level < 100 µg/L, or 100–299 µg/L with iron transferrin saturation < 20%) and left ventricular ejection fraction < 50% admitted to hospital due to acute heart failure was assessed during a 52-week observation. The mean ejection fraction in the analysed group was 33%. The participants were randomly assigned to groups receiving intravenous ferric carboxymaltose complex (FCM) or placebo. Doses were determined based on body weight and haemoglobin (Hb) levels. The medication was administered before hospital discharge and after 6 weeks following the discharge. If iron deficiency persisted and Hb levels ranged from 8 to 15 g/dL, patients received subsequent doses after 12 and 24 weeks. Primary treatment was consistent with contemporary standards — nearly 90% of patients received RAAS inhibitors, beta-blockers and diuretics.

The primary endpoint was a composite event of the total number of hospital readmissions for heart failure or cardiovascular deaths — during the observation period; in the FCM group, the primary endpoint was observed in 293 cases (57.2/100 patients/year). In the placebo group, it occurred insignificantly less often (p = 0.059) — in 372 patients. The study can therefore be considered to have missed its aim; more optimistic themes were observed in the analysis of the composite secondary endpoint — the total number of hospital admissions for cardiovascular reasons and cardiovascular deaths: it was found in 20% less (370) cases in the FCM group and 451 patients in the placebo group [relative risk (RR) 0.80; 95% CI: 0.64–1.00, p = 0.05]. Supplementation with the investigated medication also allowed to

reduce the rate of hospital admissions for cardiovascular causes compared to the placebo group (RR = 0.74; 95% CI: 0.58–0.94, p = 0.013) but the treatment was not proven to affect the reduction of mortality rate (p = 0.81) [6].

EARLY-AF: Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation

Percutaneous ablation is a procedure with an undisputed and well-established position in treating arrhythmia. In the case of the first episode of AF, it is usually recommended that before ablation, treatment with at least one anti-arrhythmic medication should be attempted. Until present, no convincing data was available to confirm that this approach is more effective in maintaining sinus rhythm than ablation as the first-choice therapy.

The EARLY-AF trial involved a group of 303 patients with symptomatic, previously untreated paroxysmal AF. The patients were randomly assigned for treatment with balloon cryoablation (154 patients with a mean age of 57.7 years — 72.2% of whom were men) or for anti-arrhythmic pharmacological treatment (149 patients with a mean age of 59.5 years — 68.5% of whom were men). In an observation period of 12 months, all the patients were monitored with an implantable loop recorder.

The primary endpoint was defined as a recurrence of AF or AFL or atrial tachycardia in the period from day 91 until the end of the observation in the case of the ablation-treated group, or from the commencement of treatment until the end of observation. The event occurred in 42.9% of ablation-treated patients and 67.8% of patients receiving pharmacological treatment (p < 0.001). Symptomatic atrial tachyarrhythmia recurred in 11% and 26.2% of patients, respectively (HR 0.39; 95% CI: 0.22–0.68). Importantly, serious adverse events – including complications of the ablation procedure — occurred in 3.2% of patients treated procedurally, that is no more frequently than in patients treated conservatively (4%).

The study involved a relatively small group of patients and the effect of the intervention on overall cardiovascular risk was not determined. However, the results of the study provide a basis for considering ablation as a first-line treatment in patients with symptomatic AF. Novum EARLY-AF consists in the inclusion of patients with a new diagnosis rather than those after failed pharmacological treatment, as in most previous studies; the importance of evidence is also enhanced by the use of an electrocardiogram event recorder for detecting relapses [7].

SAMSON: Self-Assessment Method for Statin Side-effects Or Nocebo

The beneficial effect of statins in the prevention of cardiovascular diseases is undeniable. Although anti-scientific community groups frequently attempted to undermine that status, accurate scientific data unequivocally support the need for the use of statins in both primary and secondary prevention of numerous cardiovascular diseases. Muscular side effects are among the most common reasons for discontinuation of statin therapy among patients. However, many studies did not show any objective increase in the incidence of those symptoms during statin therapy compared to placebo therapy. Due to the non-specificity of the musculoskeletal symptoms and the intensification of the harmful activities of anti-statin lobbyists in the media, these drugs appear to particularly put patients at risk of a nocebo effect. This effect involves reporting the adverse effects of the drug regardless of its actual potential to cause such effects. The reason for the occurrence of such adverse effects is the patient's negative attitude towards therapy. That is why the nocebo effect can be called the inverse of the placebo effect.

The potential of statins to cause symptomatic side effects was the issue addressed in the precisely designed SAMSON study. The study involved 60 patients who discontinued statins within 2 weeks of starting treatment. Each patient received a total of 12 phials, 4 packagings (each for one month of therapy) containing 20 mg of atorvastatin, placebo, and 4 empty phials for the non-therapy time. The subject of randomisation was the order according to which the patient took an active drug or placebo. Patients used an electronic patient diary to report the onset of symptoms. They also had the option to discontinue the medication in the event they experienced particularly severe symptoms.

The primary endpoint was the intensification of nocebo-dependent side effects — the ratio of the severity of symptoms reported while taking placebo minus the severity of symptoms reported during the periods without intervention to the severity of symptoms reported by patients while taking statins, adjusted in the same manner.

During the follow-up, 11 patients stopped taking statins (4 by their own decision; in 3 cases it was the researchers' decision). The mean symptom severity (on a scale of 0–100) during non-treatment periods was 8 (95% CI: 4.7–11.3). While taking a placebo, patients rated the symptom severity at 15.4 points on average (a highly significant increase compared to non-treatment periods). During the actual statin treatment, the mean symptom severity was 16.3. Therefore, when comparing symptom severity during the statin treatment and placebo periods, the differences proved to be statistically insignificant (p = 0.39). The nocebo ratio was 2.2 (95% CI: 62.3–66.7); those calculations were distorted by individual cases of patients who reported high severity of side effects during periods without therapy, which was reflected in the undervaluation of values used for calculating the ratio. Individualised calculations ultimately determined the value of nocebo, which is 0.9.

The conclusions of the data analysis clearly state that the effect of statins on the severity of symptoms perceived as side effects is not significantly greater than the placebo effect. These results are of great importance as an argument against false but popular views concerning frequent statin intolerance [8].

OMENI: Omega-3 Fatty Acid Supplements in Elderly Patients after Myocardial Infarction

The n-3 polyunsaturated fatty acids (PUFAs) are considered to be an essential component of a balanced diet. However, there are many doubts concerning the advisability of their supplementation as a method of reducing cardiovascular risk. The authors of the OMENI study focused on a specific group of elderly patients after myocardial infarction (MI) to determine the effect of n-3 PUFA supplementation on the risk of cardiovascular events at a 2-year follow-up.

The effect of the intervention was evaluated in 1,027 patients, aged 70–82, who 2–8 weeks earlier had a clinical incident meeting criteria for MI. Patient cooperation was monitored by determining plasma fatty acid levels. The primary endpoints included nonfatal MI, unplanned revascularisation, stroke, death from any cause, and hospitalisation due to heart failure. A new diagnosis of AF was the secondary endpoint.

The incidence of the primary endpoint was not significantly different between the group receiving n-3 PUFAs — 108 (21.4%) and placebo-taking patients — 102 (20%) ($p = 0.06$). A similar relationship was observed for the secondary endpoint — 28 and 15 patients, respectively ($p = 0.06$). The study results clearly showed that supplementation with n-3 PUFAs had no clinical benefit, neither in the secondary prevention of MI nor in terms of reducing the broader concept of cardiovascular risk in elderly patients after MI. Those data are consistent with numerous already-completed prospective studies of this issue [9].

HARP-MINOCA: Coronary Optical Coherence Tomography and Cardiac Magnetic Resonance Imaging to Determine Underlying Causes of MINOCA in Women

Contemporary definitions of MI, for any subsequent modification, are based on the determination of cardiac troponin levels. Supporting and interchangeable criteria are other clinical determinants included in the definition. Despite a consistent definition, the aetiology of MI can vary and its accurate identification enables the choice of the most beneficial treatment for the patient. By far the most common cause of MI is coronary occlusion caused by a rupture of the atherosclerotic plaque. Therefore, coronary angiography and coronary angioplasty are the treatment of choice for most MI patients. According to the statistics of medical registers, coronary angiography fails to reveal significant coronary stenosis in 6–15% of patients, the vast majority of whom are women, despite meeting criteria for MI and the absence of a non-coronary cause for this diagnosis.

The authors of the HARP-MINOCA study further diagnosed 170 women with detected MI with non-obstructive coronary arteries (MINOCA, myocardial infarction with non-obstructive coronary arteries). In addition to coronary angiography, a coronary optical coherence tomography (OCT) imaging technique and cardiac magnetic resonance (CMR) were performed. A total of 145 and 116 cases were obtained respectively, which, for reasons of technical nature, could be fully analysed using a specific method. The OCT examination resulted in the detection of 67 (46.2%) cases of lesions that may affect the onset of MI (ruptures of the atherosclerotic plaque, atherosclerotic intraplaque haemorrhage). CMR confirmed an ischemic background of MI in 62 female patients (53.4%) while the non-ischemic background of MI (myocarditis, takotsubo syndrome) was found in 24 female patients (20.7%).

The use of two methods to identify the causes of MINOCA increased the effectiveness of each method in making a definitive diagnosis — 84.5% of diagnoses. An ischemic cause was confirmed in 63.8% of cases while a non-ischemic cause in 20.7% of cases. Assuming that the majority of patients would have received therapy typical of the ischemic form of MI in the case of the absence of a verified diagnosis, it can be concluded that the used diagnostic intervention enabled, in more than 20% of cases, an adequate treatment of which the patients might otherwise have been deprived of [10]. The results of this study confirm the growing interest in MINOCA and highlight the potential therapeutic implications of a precise diagnostic procedure regarding this uncommon disease entity.

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