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Advances in the pharmacological prevention of the heart diseases — effective drugs, uneffective diet supplements Evidence from latest AHA and ACC congresses

Postępy farmakoterapii w prewencji chorób serca — skuteczne leki, nieskuteczne suplementy. Dane z ostatnich kongresów AHA i ACC

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Introduction

At the two largest American cardiological congresses held over the past year — the American Heart Association Scientific Session 2018 and the American College of Cardiology 2019 — there was, as usual, an abundance of important results of the latest clinical trials presented as part of the late-breaking clinical trials session. The following is a subjective selection of the most interesting of these, which confirmed the effectiveness of pharmacotherapy, as well as several reports that undermined the effectiveness of some supplements in the prevention of heart disease.

Prevention

With the current level of knowledge, it is debatable whether unsaturated omega 3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have the desired effect on overall mortality as well as the incidence of cardiovascular incidents. New information on their preventive effects was supposed to be provided by two studies presented at the congress: REDUCE-IT (primary and secondary prevention) and VITAL (VITamin D and OmegA-3 TriaL) (primary prevention).

REDUCE-IT — a new era of prevention of cardiovascular incidents with high doses of EPA ethyl ester?

REDUCE-IT was planned as a multicentre, randomised, double-blind, placebo-controlled clinical trial, which included both patients with documented cardiovascular disease (CVD) (secondary prevention group) and patients with diabetes and CVD (primary prevention group) as well as at least one risk factor.

The study included patients whose triglyceride fraction (TG, triglycerides) was 134–499 mg/dL, and whose low-density lipoprotein (LDL) cholesterol fraction was in the range 41–100 mg/dL. Patients were randomly divided into groups receiving placebo (mineral oil) or 4 g (in two doses of 2 g) of EPA ethyl ester per day — an organic chemical compound from the group of omega 3 acids, which is a highly purified and stable form [1]. The primary composite endpoint of the study was death, myocardial infarction, non-fatal stroke, coronary revascularisation, or unstable angina (UA). The secondary composite endpoint, however, included cardiovascular death, non-fatal myocardial infarction, and stroke. Eventually, 8,179 patients were enrolled in the study, of whom 70.7% were patients from the secondary prevention group of cardiovascular incidents.

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One year after enrollment in the study, the EPA ethyl ester group had a significantly greater reduction in the concentration of lipid profile TG fractions, the concentrations of which decreased by an average of 18.3% (median decrease of 39 mg/dL) from baseline, while in the placebo group they had increased by 2.2% (median 4.5 mg/dL). In addition, LDL cholesterol increased in both the intervention group (median increase 2 mg/dL) and the control group (median increase 7 mg/dL), but in the placebo group, this increase was 6.6% higher ($p < 0.001$).

During the average follow-up period of 4.9 years, the primary endpoint occurred significantly less frequently in patients receiving the EPA derivative than in those receiving placebo [17.2% vs. 22.0%; hazard ratio (HR) 0.75; 95 percentile confidence interval (CI): 0.68–0.83; $p < 0.001$]. The frequency of the secondary endpoint was 11.2% compared to 14.8% (HR = 0.74; 95% CI: 0.65–0.83; $p < 0.001$). Surprisingly, in the intervention group a statistically significant 20% reduction in the risk of death from cardiovascular causes was observed (4.3% vs. 5.2%; HR = 0.80; 95% CI: 0.66–0.98; $p = 0.03$). In terms of the safety of the treatment, it should be emphasised that a significantly higher incidence of hospitalisation due to atrial fibrillation/atrial flutter (3.1% vs. 2.1%; $p = 0.004$) and a trend towards more frequent major bleeding were observed among patients receiving the EPA derivative. 2.7% vs. 2.1%; $p = 0.06$), and that the exact origin of this type of side effect is not known.

Among the main objections raised by the study protocol was the use of mineral oil (light, liquid paraffin oil) in the placebo group, the consistency, colour and even flavour of which were designed to imitate the EPA derivative used in the intervention group. The main doubts were raised by the fact that there was an increase in LDL cholesterol and high-sensitivity C-reactive protein (hs-CRP) relative to baseline in the placebo group. This could suggest an adverse effect of the substance used as the placebo, which by definition should have no effect on the patients. Nevertheless, the subanalysis presented by the researchers (excluding patients in whom these changes were observed) did not affect the observed effect of a significant reduction in the incidence of the complex endpoint.

The purpose of this study was not to explain biologically beneficial mechanisms of the EPA derivative. It can be assumed that this effect may be a derivative of an action leading to a decrease in TG value, anticoagulant, antiplatelet and membrane stabilising effects, stabilising atherosclerotic plaques, and reducing inflammation — this pleiotropism has been shown in numerous previous studies [2, 3].

REDUCE-IT Total Events

In their study, which is a continuation of the presented analyses on the effectiveness of EPA in the prevention of cardiovascular diseases, Bhatt et al. [4] also proved that its use according to the protocol presented earlier is not only associated with the reduction of first-time cardiovascular incidents, but it also significantly reduces the incidence of subsequent adverse events.

The primary endpoint of the study was to assess the overall incidence of cardiovascular incidents (first-time and subsequent) in the form of cardiovascular death, myocardial infarction, central nervous system (CNS) stroke, coronary revascularisation, or hospitalisation due to UA. The secondary evaluated endpoint was cardiovascular death, myocardial infarction, or stroke within the central nervous system. In the study group of 8,179 patients, which was observed for nearly five years (median 4.9 years), 1,606 (55.2%) had the first-time composite primary endpoint, and 1,303 (44.8%) an event within the composite primary endpoint. This endpoint was the next already reported cardiovascular episode in a given patient (in the case of 762 patients it was the second episode, in 541 it was the third or subsequent one. The use of EPA was found to reduce (relative risk [RR], 0.7; 95% CI: 0.62–0.78; $p < 0.001$) the risk of having a complex primary endpoint by 30%, as well as (RR = 0.72; 95% CI: 0.63–0.83; $p < 0.001$) the risk of the composite secondary endpoint by 28%. In-depth analyses showed that the use of EPA at a dose of 4 g/day in a group of 1,000 patients for five years would help avoid 12 deaths due to cardiovascular causes, 42 heart attacks, 14 strokes in the CNS, 76 cases of coronary revascularisation, and 16 hospitalisations because of UA [4].

EPA concentration in the serum phospholipid fraction and the risk of developing heart failure

The previously encouraging results of the cardioprotective effect of EPA supplementation on the occurrence of adverse cardiovascular events (mainly macroangiopathic), described above, have contributed to a search for its beneficial effects in other areas. In their study, Block et al. [5] attempted to assess the relationship between the percentage of EPA in the overall plasma phospholipid fraction and the risk of developing heart failure (HF). They included 6,562 patients aged 45–82 in their prospective cohort observational study and measured the baseline EPA fraction. During the clinical follow-up (median 13 years), 282 (4.3%) new episodes of HF were recorded: 128 cases with reduced ejection fraction (HFrEF), 110 cases of heart failure with preserved ejection fraction (HFpEF), and 54 HF with left ventricle (LV) systolic function. As demonstrated by the authors, the percentage of plasma phospholipid EPA fractions linearly correlated with a decrease in the risk of developing HF, regardless of its type (HR 0.73; 95% CI: 0.60–0.91; for logarithmised %EPA), and this relationship was maintained after making adjustments according to age, gender, individual lipid profile fractions, and co-morbidities such as diabetes or arterial hypertension (AH) [5].

VITAL — assessment of the effectiveness of omega 3 and vitamin D3 supplementation in the primary prevention of cardiovascular incidents and cancers

Nearly half of adults in Western countries take dietary supplements. Over the past decade, the number of people taking fish oil-based preparations has increased tenfold, and the number of people supplementing with vitamin D3 has increased fourfold. All this is happening at a time when we do not have research results presenting clear evidence of the health benefits of this type of long-term supplementation. New information in this regard was to be provided by the VITAL study, which was designed as a multicentre, randomised, double-blind, placebo-controlled observational study aimed to assess the impact of supplementation with omega 3 and vitamin D3 in the primary prevention concerning the incidence of cardiovascular events and cancers in the general population. The study included men aged 50-plus as well as women aged 55-plus. The primary composite endpoints were the occurrence of a major adverse cardiac event (MACE) in the form of a heart attack, stroke or cardiovascular death, and any invasive cancer. The secondary endpoints were all individual components of the primary endpoint separately, and the primary composite endpoint extended by coronary revascularisation (percutaneous coronary intervention [PCI]) or coronary artery bypass grafting [CABG], tumour specific to individual systems, and death caused by cancer. The safety of the treatment was also assessed.

VITAL — omega 3 and cardiovascular incidents and cancers

A total of 25,791 patients with an average age of 67.1 were included in the analysis of omega 3 supplementation. The intervention consisted of supplementation with a 1 g/day omega 3 preparation (1 g of fish oil containing 840 mg of fatty acids, including 460 mg of EPA and 380 mg of DHA). The median follow-up covered more than five years. There were no significant differences in the incidence of MACE incidents between the groups in the follow-up (MACE occurred in 386/12,933, *i.e.* 2.98% of the patients in the omega 3 group and 419/12,938, *i.e.* 3.23% of the patients in the group receiving placebo — HR 0.92; 95% CI: 0.80–10.6; p = 0.24). A newly diagnosed invasive tumour during the clinical follow-up was reported in a similar percentage of patients in both groups (820 patients in the omega 3 group and 797 in the placebo group; HR = 1.3; 95% CI: 0.93–1.13; p = 0.56). In the analysis of key secondary endpoints, no significant differences were observed in the incidence of the composite endpoint extended by the need for revascularisation (HR = 0.93; 95% CI: 0.82–1.04), stroke (HR = 1.04; 95% CI: 0.83–1.31), death because of cardiovascular causes (HR = 0.96; 95% CI: 0.76–1.21), or death caused by cancer (HR = 0.97; 95% CI: 0.79–1.20). However, there was a low risk of a heart attack in the group receiving omega 3 (HR = 0.72; 95% CI: 0.59–0.90), which partly seems to be consistent with the results of the REDUCE-IT study discussed earlier. There were also no significant differences between the omega 3 and the placebo groups in the risk of death from any cause (3.81% vs. 3.75%; HR = 1.02; 95% CI: 0.90–1.15; a total of 978 deaths during follow-up). Also, a subgroup analysis showed that potentially the greatest benefit of omega 3 supplementation in terms of MACE prevention could be for people with a low fish oil intake, defined as the average weekly consumption of less than 1.5 fish-based meals. In this group of patients, omega 3 supplementation was associated with a 19% reduction in the risk of adverse cardiovascular events (HR = 0.81; 95% CI: 0.67–0.98).

In terms of safety analysis, no effects of omega 3 supplementation on the incidence of significant bleeding, gastrointestinal symptoms, or other serious adverse effects were observed [6]. Further analysis regarding the effects of omega 3 on diabetes, atrial fibrillation, cognitive function, autoimmune disorders, and other conditions that may significantly impact the final benefit and risk assessment of omega 3 supplementation is ongoing [6].

VITAL — vitamin D3 and cardiovascular incidents/cancer

When analysing the VITAL study for vitamin D3 supplementation, 25,871 patients were randomised. They were divided into a placebo group (N = 12,944) and an intervention group with vitamin D3 (cholecalciferol) supplementation at a dose of 2,000 units of measure/day (N = 12,927). The average age of the studied population was 67.1 years, nearly half of the patients had AH (49.8%), and 13.7% had diabetes. The average baseline vitamin D3 concentration was 30.8 ± 10.0 ng/mL. In 12.7% of the patients this value was lower than 20 ng/mL (severe deficiency), and in the case of 32.2% of the patients vitamin D3 concentration was in the range of 20–30 ng/mL (deficiency). In the intervention group, the average vitamin D3 concentration increased by 40% after a year of observation (from an average of 29.9 ng/mL to one of 41.8 ng/mL), while in the control group it remained unchanged. During the follow-up period, whose median was more than five years, there were no statistically significant differences between the groups in the frequency of MACE (taking placebo — 3.16% vs. taking vitamin D3 — 3.06%; HR 0.97%, 95% CI: 0.85–1.12) or cancer (taking placebo — 6.36% vs. taking vitamin D3 — 6.13%; HR 0.96, 95% CI: 0.88–1.06). In terms of secondary endpoints, no significant differences were observed when it came to the risk of death from any cancer (HR 0.83; 95% CI: 0.67–1,02). There was no effect of vitamin D3 supplementation on the risk of any of the following cancers: breast (HR 1.02; 95% CI: 0.79–1.31), prostate (HR 0.88; 95% CI: 0.72–1.07), or

large intestine and rectum (HR 1.09; 95% CI: 0.73–1.62). In addition, an in-depth analysis did not show an effect of vitamin D3 supplementation on the incidence of MACE associated with coronary revascularisation (HR 0.96; 95% CI: 0.86–1.08), myocardial infarction (HR 0.96; 95% CI: 0.78–1.19), stroke in the CNS (HR 0.95; 95% CI: 0.76–1.20), death from cardiovascular causes (HR 1.11; 95% CI: 0.88–1.40), or death from any cause (HR 0.99; 95% CI: 0.87–1.12). Also, taking into consideration the baseline vitamin D3 levels, the subgroup analysis also showed no benefit in vitamin D3 supplementation in terms of reducing risk of occurrence cardiovascular incidents and cancers in patients with severe vitamin D3 deficiency. Nevertheless, the results of this analysis should be interpreted with caution, because due to the fact that more than 20% (5,106/25,304) of the patients included in the study were black, the study is more representative for the USA (where recruitment was carried out) than for example for the Caucasian population. Different skin pigmentation in the case of dark-skinned patients, and thus different production of endogenous vitamin D3, was not analysed in detail over time, so its effect on the results cannot be excluded.

Heart failure

DECLARE-TIMI 58

Patients with type 2 diabetes are at a high risk of developing cardiovascular disease and HF. Dapagliflozin is a compound belonging to a new group of drugs with a so-called hypoglycaemic effect. They act as selective inhibitors of the sodium glucose co-transporter 2 (SGLT2) responsible for the reuptake of almost 80% of glucose from primary urine. Their mechanism of action consisting in limiting renal glucose reabsorption, leading to glycosuria, is associated with a decrease in glycaemia, blood pressure and body weight, while at the same time, thanks to its diuretic effect, they reduce the frequency of rehospitalisations associated with HF exacerbation.

The goal of the DECLARE-TIMI 58 (Dapagliflozin Effect on CardiovascuLAR Events) study was to evaluate the effect of dapagliflozin on the incidence of major adverse cardiovascular events (MACE) defined as death, myocardial infarction, or ischaemic stroke, as well as cardiovascular mortality or rehospitalisation due to HF in patients with diabetes and concomitant atherosclerosis of the cardiovascular system [7]. The study was designed as to be randomised, multicentre, double-blind, and placebo-controlled. The study included patients with type 2 diabetes and preserved kidney function (glomerular filtration rate [GFR] > 60 mL/min) and previously diagnosed atherosclerotic cardiovascular disease (coronary heart disease, atherosclerotic cerebrovascular disease, peripheral vascular disease) or burdened with concomitant risk factors for cardiovascular disease (age ≥ 55 years old for men or ≥ 60 years old for women and a co-existence ≥ 1 of the following risk factors: AH, dyslipidemia, smoking). The study involved 882 centres from 33 countries recruiting a group of 17,160 patients (8,582 patients received dapagliflozin 10 mg/day and 8,578 patients placebo), with a mean age of around 64 years, mainly men (63%). At the time of enrollment, 10% of the patients had been previously diagnosed with HF. The mean glycosylated haemoglobin (HbA_{1c}) value was 8.3 ± 1.2%, and an average 11 (range 6–16) years had passed since the diagnosis of diabetes. Patients underwent clinical follow-up for an average of 4.2 (3.9–4.4) years.

In the dapagliflozin group, a significantly lower incidence of death or rehospitalisation due to HF exacerbation was observed (4.9% vs. 5.8%; HR 0.83; 95% CI: 0.73–0.96; p = 0.005), and these differences were mainly caused by a lower frequency of rehospitalisation due to HF in the dapagliflozin group (HR 0.73; 95% CI: 0.61–0.88). There were no differences between the groups in terms of cardiovascular mortality (HR 0.98; 95% CI: 0.82–1.17), nor death due to any other causes (HR 0.93; 95% CI: 0.82–1.04). In addition, dapagliflozin was not associated with a lower incidence of MACE than in the placebo group (8.8% vs. 9.4%; HR 0.93; 95% CI: 0.84–1.03; p = 0.17), and these differences did not depend on whether the patients had previously been diagnosed with cardiovascular disease or only displayed the risk factors. In addition, in the dapagliflozin group, there was a significantly greater reduction in HbA_{1c} (on average 0.42%), SBP (on average 2.7 mm Hg) and body weight (on average 1.8 kg) compared to placebo. In terms of treatment safety, a higher risk of significant genital infections leading to discontinuation of treatment directly associated with glycosuria was observed among patients receiving dapagliflozin (0.9% vs. 0.1%; HR 8.36, 95% CI: 4.19–16.68; p < 0.001). In their summary, the authors emphasised that the use of SGLT2 inhibitors causes a much more pronounced effect on the prevention of episodes of chronic HF exacerbations and its new cases than in the case of the prevention of cardiovascular events themselves, which stem from atherosclerotic processes. Research is underway to clearly assess this effect of dapagliflozin in a specific patient population with documented HF.

EMPA-Heart Cardiolink-6

Another study evaluating the effects of a different SGLT2 inhibitor — empagliflozin in a patient population with type 2 diabetes and concomitant HF — was the EMPA-Heart Cardiolink-6 study. This study demonstrated the efficacy of empagliflozin in reducing cardiovascular mortality in patients with type 2 diabetes, but the exact mechanism of this effect remains unclear, and in particular, the question of whether its use can directly affect myocardial

remodelling remains unanswered. The EMPA-Heart study was a continuation of the clinical follow-up of another study — EMPA-REG OUTCOME, published in 2015, which included 7,020 patients with type 2 diabetes who were at high cardiovascular risk. This showed that the use of empagliflozin is associated with a significantly lower risk of death due to cardiovascular causes (38% reduction), lower incidence of HF hospitalisation (reduction by 35%), and death from any other cause (reduction by 32%).

Researchers involved in the EMPA-HEART study randomised 97 patients with type 2 diabetes and a history of confirmed ischaemic heart disease (previous revascularisation or previous myocardial infarction) for treatment with empagliflozin 10 mg/day (N = 49) or placebo (N = 48). The patients' hearts were evaluated functionally and structurally by means of magnetic resonance imaging after six months of this treatment. The study excluded patients with severe left ventricular (LV) systolic dysfunction (ejection fraction [EF] < 30%), decompensated HF (New York Heart Association Class IV), and poorly controlled diabetes (HbA_{1c} > 10%). The primary endpoint was LV muscle mass assessment in month 6, and secondary LV parameters such as end-systolic volume, end-diastolic volume, EF value, and biomarker change over time (N-terminal fragment of the N-terminal pro-B-type natriuretic peptide [NT-proBNP], troponin I, sST2 proteins [soluble suppression of tumourigenicity]). The average age of patients enrolled in the study was about 63 years, and most were men (93%) with concomitant AH (91%), and the average time since the diagnosis of diabetes was about 11 years. In the empagliflozin group, a significant reduction in systolic blood pressure (SBP) (an average decrease of 6.7; 95% CI: 2.3–11.2 mm Hg; p = 0.003) and no significant change in diastolic blood pressure (SBP) were noted (p = 0.22), while no difference was seen in the placebo group. In addition, a greater increase in haematocrit (2.4% vs. 0.4%; p = 0.006) was also seen in the empagliflozin group. Most interestingly, in the intervention group there was a significant decrease in left ventricular mass indexed (LVMI) [on average by 3.35 (95% CI: 0.81–3.35) g/m^2; p = 0.01], regardless of the type of indexation adopted (*i.e.* to body surface or to height). An in-depth analysis showed much more limited LV remodelling (LVMI reduction) in patients with a higher LVMI at the beginning of the study (> 60g/m^2). There were no significant changes over time in terms of NT-proBNP, troponin, or sST2 protein levels, which was probably the result of their low initial values. Importantly, the incidence of adverse events during six months of follow-up was comparable in both groups. The study provided significant "translational" results indicating a direct cardiac effect of empagliflozin on LV weight reduction — a parameter for which a close relationship with prognosis had previously been demonstrated. The authors also suggested that the effect on cardiac remodelling may be the result of a class of flosins showing a very similar effect on prognosis in reducing the frequency of cardiovascular incidents observed in previous studies. Based on this, it can be assumed that SGLT2 inhibitors may have a positive effect on the prevention of adverse heart remodelling [8].

PIONEER-HF

In a short follow-up, the exacerbation of chronic HF is associated with a high risk of unplanned rehospitalisation and mortality associated with hospitalisation. The basis of the modern treatment of acute HF is stasis reduction [diuretics intravenous (i.v.)] and haemodynamic support (vasodilating and inotropic positive drugs), which has remained virtually unchanged for several decades.

Positive effects of the use of a new group of drugs — angiotensin II receptor antagonists and neprilysin inhibitors (ARNI) — sacubitril/valsartan, improving survival and reducing the risk of rehospitalisation due to HF exacerbation, were confirmed in a patient population with chronic HFrEF in the PARADIGM-H study. On the other hand, the role of ARNI in the acute decompensated HF phase remains unknown, and information about the potential benefits of early initiation of treatment with sacubitril/valsartan in this group of patients was supposed to be provided by the PIONEER-HF study [9].

This study was designed as a multicentre, double-blind, control group to which patients with acute decompensation of chronic HFrEF were recruited in 129 centres in the USA. After initial haemodynamic stabilisation, the patients were randomised to the intervention group (target dose of 97 mg sacubitril and 103 mg valsartan 2 ×/day) or to the control group receiving enalapril (target dose of 10 mg 2 ×/day). The primary endpoint of treatment efficacy was to evaluate the change in NT-proBNP concentration in weeks 4 and 8 from baseline. In terms of safety, the incidence of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema was assessed.

Eventually, 881 patients were enrolled in the study (440 patients were enrolled in the sacubitril/valsartan group and 441 patients in the enalapril group) with an average age of 61 ± 14 years, mainly male (72.1%). Of the patients previously diagnosed with HF (65.4%), the majority (59.5%) were hospitalised because of HF exacerbation in the last year. At the time of admission, 52.1% of the patients were not receiving angiotensin-converting enzyme (ACE) inhibitor or sartan. Median NT-proBNP concentration upon admission was 4,812 (3,050–8,745) pg/mL. The overwhelming majority of the patients received furosemide i.v. during hospitalisation (93%), and 7.7% of the patients were administered inotropic drugs. The median time of hospitalisation associated with HF exacerbation was 5.2 (4.09–7.24) days.

During clinical follow-up, a significantly higher reduction in NT-proBNP concentration was obtained over time — the

mean reduction at weeks 4 and 8 in the sacubitril/valsartan group was 46.7% compared to 25.3% in the enalapril group ($p < 0.001$), and significant differences in the reduction of NT-proBNP concentration in favour of the intervention group were already recorded a week from the time of inclusion in the study. Interestingly, the change in NT-proBNP concentration was also accompanied by a significantly greater reduction of average troponin T levels determined by the high-sensitivity method (hs-TnT) (reduction in the group receiving sacubitril/valsartan vs. the group receiving enalapril: 36.6% vs. 25.2%; $p < 0.05$). In addition, in additional subanalyses, early inclusion of sacubitril/valsartan in the intervention group was associated with a 44% lower risk of rehospitalisation within eight weeks of study enrollment (HR 0.56; 95% CI: 0.37–0.84). In terms of safety, there were no significant differences in the incidence of renal impairment, hyperkalaemia, symptomatic hypotension, or angioedema between the two groups.

The PIONEER-HF study was the first to confirm the safety and efficacy of early initiation of ARNI treatment in a patient population with decompensated HF, newly diagnosed acute HF, as well as patients who had not yet taken ACE inhibitors/sartans, or their doses were not optimal. Importantly, the beneficial effect of sacubitril/valsartan on the reduction of NT-proBNP, which is a biomarker of neurohormonal activation and haemodynamic stress, and also a prognostic marker of poor prognosis, was accompanied by a significant decrease in hs-TnT concentration — another biomarker reflecting myocardial damage, and one directly associated with a worse long-term prognosis in patients with HF. However, in order to be able to clearly assess the impact of the strategy of early initiation of ARNI treatment on the occurrence of hard endpoints (*i.e.* death, adverse cardiovascular events) in this patient population, we need to wait for the results of further clinical follow-ups.

INFINITY — difficulties in choosing optimal therapeutic goals in the case of hypertension

In the INFINITY study, researchers set out to assess the impact of intensive (compared to standard) ambulatory hypotension on improving physical fitness and cognitive function in elderly patients (≥ 75 years of age) with poorly controlled AH. The study included patients with SBP with measurements in the 150–170 mm Hg range treated with at least one antihypertensive drug, and patients with SBP over 170 mm Hg not treated or receiving a maximum of one antihypertensive drug, as well as patients with mean daily SBP greater than or equal to 140 mm Hg. Each patient was evaluated initially and after the follow-up in terms of areas with pathological enhancement of brain white matter and walking speed. During the follow-up, the primary endpoints were changes in both the parameters mentioned above. Eventually, 199 patients with an average age of 80 years were enrolled in the study and subjected to three years of follow-up. 99 patients were included in the intensive treatment group (target ≤ 130 mm Hg, achieved average daily SBP 131 mm Hg), and 100 patients were recruited to the standard treatment group (SBP target ≤ 145 mm Hg, reached 146 mm Hg). During the follow-up period, it was shown that the intensive reduction of SBP significantly reduced the progression of subcortical lesions (indirect exponent of vascular brain damage — percentile change in the intervention group in the area of white matter enhancement: 0.29% vs. 0.48%, $p = 0.03$). In contrast, intensive AH pharmacotherapy did not translate in any way to a change in physical fitness — there were no significant differences in walking speed over time between the groups ($p = 0.91$), nor did it change cognitive functions (no significant changes were observed in time, as indicated by the Symbol Digit Modality, between the groups ($p = 0.29$).

These results reflect the difficulties in setting a uniform goal of AH treatment in the older population while excluding the impact on the rate of brain tissue damage [10].

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