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Pharmacotherapy after the ESC Congress 2018 in Munich — which questions have been answered?

Farmakoterapia po Kongresie ESC 2018 w Monachium — na które pytania znamy już odpowiedź?

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Należy cytować wersję pierwotną

Abstract

During 5 hot-line sessions at the ESC Congress 2018 in Munich several significant clinical trials' results were published. Authors selected top five trials answering the most important questions in pharmacotherapy of cardiovascular diseases.

Key words: pharmacotherapy, clinical trials, ESC Congress 2018, drugs, cardiovascular risk, mortality, safety, acetylsalicylic acid; infective endocarditis

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At the 5 hot-line session in the course of this year's Congress of the European Society of Cardiology, results of several interesting clinical trials were presented. The authors decided to present five works of the most important value in their subjective assessment. The works were presented from the perspective of current state of knowledge and the questions which practicing physicians have.

The first two hot-line sessions were dominated by research about one of the oldest drugs in use today — acetylsalicylic acid (ASA). This topic was presented by the presentation of (combined with a simultaneous publication in the "The Lancet") of the results of the **ARRIVE** (Aspirin to Reduce Risk of Initial Vascular Events) study [1].The main aim of the study was to analyze the effectiveness and safety of aspirin in primary prevention in patients with moderate risk of cardiovascular incident (10-year risk of coronary death 10–20%). So far, the effectiveness of acetylsalicylic acid has only been proven in secondary prevention. Despite the lack of clear evidence for the benefit of prophylactic effects of ASA administration, it is a quite common practice to include ASA in primary prevention in patients with indirect cardiovascular risk. It is worth stressing that this kind of practice is not clearly written in European guidelines and is quite controversial.

The ARRIVE study was a multi-center, prospective, double-blind, randomized study in which the studied group were individuals receiving 100 mg of ASA/day and the control group was a placebo. The study was conducted in 501 centers in 7 countries and included a total of 12,546 patients with indirect cardiovascular. After randomization, they were divided into 2 groups at a ratio of almost 1 to 1. The observation median was 60 months.

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Patients with diabetes or high risk of bleeding were not included in the study. The main efficacy measurement was the time to the first occurrence of a complex endpoint in the form of cardiovascular death, myocardial infarction, unstable angina, stroke or transient cerebral ischemia. Safety Endpoints were the occurrence of hemorrhagic incidents or other adverse events. The results of the study did not bring any expected breakthrough because of the lack of impact on the effectiveness of prevention. The main endpoint occurred in 269 patients from the studied group (4.29%) and in 281 patients from the control group (4.48%) — hazard ratio (HR) = 0.96; 95% confidence interval (CI) 0.81–1.13, p = 0.6038. Safety results are worth emphasizing, as the risk of bleeding with use of ASA increased more than two-fold: in the study group gastrointestinal bleeding occurred in 61 patients (0.97%) and in the control group in 29 patients (0.46%) — HR = 2.11; 95% CI 1.36–3.28, p = 0.0007. Other adverse events occurred with similar frequency in both groups. During the observation, 321 deaths were observed (160 in the ASA group — 2.55%, 161 in the placebo group — 2.57%) and therefore much less frequently than expected — it seems that the scales which are used, overestimate the risk in patients treated nowadays. Since the risk of bleeding when using ASA is constant, this explains the lack of "net"; benefits.

Therefore, both the researchers and the reviewers pointed out that the results of the study more accurately reflect the use of ASA in individuals with low cardiovascular risk and contrary to the assumptions do not refer to an indirect risk group. ASA therapy confirmed a significant reduction in the risk of myocardial infarction by 45–47% in a subgroup of patients with good therapeutic cooperation (> 60% of doses taken, 7702 individuals). The second study on acetylsalicylic acid, the results of which were presented and published in "The New England Journal of Medicine" on the same day, there was an **ASCEND** (A Study of Cardiovascular Events in Diabetes: Characteristics of a randomized trial of aspirin and of omega-3 fatty acid supplementation in 15,480 people with diabetes) trial [2, 3]. This study was designed to compare the effects of aspirin at a dose of 100 mg/day and omega-3 fatty acids at a dose of 1 g/day in people with diabetes mellitus as a part of primary prevention. The endpoints of the study were defined as follows: for efficacy, the first episode of a significant hemorrhagic cardiovascular incident (myocardial infarction, stroke or transient ischemic attack or death from any other vascular cause); for safety, the episode of significant bleeding (intracranial bleeding, bleeding into the eye which threatens loss of vision, gastrointestinal bleeding or other serious bleeding requiring intervention). What is worth emphasizing, the secondary endpoint for ASA was the occurrence of colorectal cancer.

ASCEND was a prospective, randomized study using placebo as a comparator for which 15,480 patients were recruited. The average observation time was 7.4 years. The results, although promising, also did not provide a definitive answer about the use of aspirin. The main endpoint occurred 12% less frequently when using ASA than in the control population: 658 (8.5%) vs. 743 (9.6%), p = 0.01. At the same time, patients undergoing ASA treatment were more likely to have serious bleeding by 29%: 314 (4.1%) vs. 245 (3.2%), p = 0.003, with a clear predominance of gastrointestinal bleeding and other non-cranial sites. In terms of oncological observation, there were no statistically significant differences. The results of this study confirm that in patients with diabetes mellitus without cardiovascular complications, ASA may reduce the risk of their occurrence, however, the benefits of this action are in the vast majority of cases balanced by a negative increase in the risk of serious bleeding.

Analysis of the use of omega-3 fatty acids in primary prevention in patients with diabetes mellitus did not show any benefit of such action compared to placebo. This calls into question the sense of their use in everyday practice as a dietary supplement. At the same time, the authors emphasize the sense of their use as a therapeutic additive in patients with severe hypertriglyceridemia.

Despite the differences in terms of subject matter Monday's hotline session was rich in interesting pharmacological research, with particular attention paid to the **ATTR-ACT** (The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial). Presentation of the results (as well as a publication in "The New England Journal of Medicine"; entitled "Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy") [4] were preceded by an introduction to the subject of a relatively rarely mentioned disease called cardiomyopathy in the course of amyloidosis with transtretin mutation (genetically conditioned storage disease which is described as an accumulation of deposits of abnormally shaped transtretin in the myocardium). The disease most often manifests itself in the 6th decade of life. The authors emphasize that the disease can occur quite often (in about 13% of patients with heart failure with preserved ejection fraction) and scintigraphy is one of the non-invasive diagnostic methods used. Prognosis is worth noting — the median time of survival from diagnosis varies between 2.5 and 3.6 years depending on the subtype of mutation.

ATTR-ACT was a multi-center, international, parallel designed, double-blinded, randomized, phase 3 clinical trial with placebo as control over the treatment strategy. The main aim of the authors was to investigate the influence of tafamidis on the natural course of the disease. Tafamidis was registered for the treatment of a pathomechanically similar disease so called transthyretin familial amyloid polyneuropathy. It has been proven that by binding itself, instead of thyroxine with transthyretin, it stabilizes it in the form of a harmless tetramer, which significantly inhibits

the development of the disease. In the presented study it was decided to verify the legitimacy of administration of this drug to patients with cardiomyopathic form of the disease. The study included 441 patients with the above diagnosis. 3 subpopulations were designed in the ratio of 2:1:2 respectively receiving: 80 mg of tafamidis daily, 20 mg of tafamidis daily and a placebo for 30 months. The main endpoints were: total mortality and frequency of hospitalizations related to cardiovascular diseases. Secondary endpoints were defined as a change in the results of the 6-minute walk test after 30 months in relation to the randomization and a change in the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS).

The results seem promising — in the study group (80 mg + 20 mg in total) the number of deaths from all causes turned out to be significantly lower than in the placebo group: 29.5% vs. 42.9%, HR = 0.70; 95% CI 0.56–0.96, p < 0.001. The frequency of hospitalizations reported in the study group was also lower by 32%, p < 0.001. The group treated with tafamidis achieved better results in the quality of life questionnaire and in the 6-minute march tests (for both analyses p < 0.001). Importantly, the authors point out that the number and type of adverse effects in both groups is at a similar level. During the next hot-line sessions, more excellent studies were presented. In the beginning, the results of the **FREED** study (Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy) were presented. [5] This trial was designed as a multi-center, prospective, randomized open-label study with a blinded endpoint and two parallel arms to investigate the potential of febuxostat (a selective xanthin oxidase inhibitor), which reduces uric acid concentration in the blood, in terms of prevention of brain, cardiovascular and renal incidents when compared to standard therapy.

The study included 1070 patients aged 65 and above with diagnosed hyperuricemia (serum uric acid concentration between 7.0 and 9.0 mg/dl). The observation period lasted 36 months. In the study group there were 537 patients who took increasing doses of febuxostat (from 10 to 40 mg/day). In the control group allopurinol at a dose of 100 mg was administered only to those individuals in which significantly elevated serum uric acid levels were detected. In both groups decreasing of concentration of uric acid below 2.0 mg/dl was avoided. All patients had an increased cardiovascular risk in regard to the control of known risk factors. The main complex endpoint is defined as the occurrence of a cerebral, cardiovascular or renal incident or any new disease or even death of any cause. Febuxostat significantly reduced uric acid levels to an average of 4.5 mg/dl compared to a group without this drug: 6.76 mg/dl — the effect was observable after approx. 8–12 weeks of therapy.

In terms of drug efficacy in prevention of the occurrence of a complex endpoint, the results are promising — 23.3% of individuals in the group taking the drug and 28.7% in the group without the drug. Therefore, a 25% lower risk of the target endpoint in the group receiving the test substance was noted — HR = 0.75, 95% CI 0.592–0.950, p = 0.017, mainly due to reduced risk of kidney failure — study group (16.2%) vs, control group (20.5%) — HR = 0.745, 95% CI 0.562–0.987, p = 0.041. However, there were no statistically significant differences in the incidence of deaths from any cause, risk of a cerebrovascular incident or coronary disease. FREED was a small study and in the context of an earlier CARES trial (where an increased risk of death was observed in patients treated with febuxostat vs. allopurinol) febuxostat does not show protection against cardiovascular complications.

It certainly cannot be treated as an encouragement for broad treatment of asymptomatic hyperuricaemia with a purpose of prevention — the reduction of uric acid should be reserved for the treatment of symptomatic gout according to world guidelines. For the patient listeners, the last hotline session had one of the most interesting studies presented during this year's ESC Congress — **POET** (Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis), from the perspective of a practicing physician. At the same time, it was published in "The New England Journal of Medicine" [6], The studies aim was to explain, whether it is possible to accept a less strict therapeutic strategy of the treatment of left-sided infective endocarditis rather than the 6-week antibiotic intravenous therapy in hospital settings which is recommended by the guidelines. The trial was designed to assess the efficacy and safety of the transition from intravenous to oral therapy, after 2 weeks of standard treatment with the intention of stabilizing the clinical status of the patients.

POET was a Danish multicenter, randomized, prospective study of equivalence type, in which 400 hemodynamically stable patients with left-sided infective endocarditis were included. The patients selected had their diagnosis placed on the basis of blood cultures where methicillin-sensitive streptococci, enterococci or staphylococci were cultured.

All patients received intravenous antibiotic therapy for at least 10 days. Patients were randomized to 2 groups — still treated intravenously (199 people) and with continued oral treatment (201 people). If such a possibility existed, after the patients were set up on oral treatment, they were discharged and controlled in out-patient clinics. The main endpoint was total mortality, unplanned cardiac surgery, thromboembolic incidents or recurrence of bacteremia with the primary pathogen from the time of randomization to 6 months after the end of pharmacotherapy. It seems that the type of antibiotics used (selected based on pharmacokinetic properties) and a thorough echocardiographic exam (also transesophageal) are relevant to confirm if there is need of further intensive parenteral treatment

before the possibility of oral treatment is introduced. It is also far more important to check on patients more often if they are treated in outpatient conditions rather than in actual conditions.

However, despite the concerns raised by the reviewers, the results of the presented study were rewarded with thunderous applause, as they seem to be extremely optimistic. The median of primary intravenous treatment was 19 days in the group treated with standard therapy and 17 days in the target group treated orally (p = 0.48). The main complex endpoint occurred in 24 (12.1%) patients in the group treated intravenously and in 18 (9.0%) patients treated according to the study protocol — the difference between the groups was 3.1 percentage points, 95% CI –3.4–9.6, p = 0.40 — which corresponds to the fulfilment of the equivalence criterion — so the oral treatment strategy seems to be no worse than the standard long-term intravenous treatment recommended in the European and American guidelines. These data are encouraging and pave the way for further exploring the possibility of less restrictive treatment of patients with mild infective endocarditis.

Streszczenie

W trakcie 5 sesji *hot-line* Kongresu ESC 2018 w Monachium zaprezentowano wyniki kilku istotnych badań klinicznych. Autorzy wybrali subiektywnie 5 najważniejszych, odpowiadających na kluczowe pytania z zakresu farmakoterapii chorób układu sercowo-naczyniowego.

Słowa kluczowe: farmakoterapia, Kongres ESC 2018, badania kliniczne, leki, ryzyko sercowo-naczyniowe, śmiertelność, bezpieczeństwo, kwas acetylosalicylowy, infekcyjne zapalenie wsierdzia

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