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Not only ISCHEMIA — report from AHA Scientific Sessions, Philadelphia, 16–18 November 2019

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Należy cytować wersję pierwotną

Between 16 and 18 November 2019, Scientific Sessions, an event which the American Heart Association has organised for the last 94 years, was held in the city of Philadelphia. This international meeting attracted nearly 15,000 participants interested in progress concerning pathomechanisms, diagnosis and treatment of heart and blood vessel diseases. It was, as always, an opportunity to summarise the breakthrough results of clinical trials. In 2019, these included research programmes of particular significance which will undoubtedly influence clinical practice in the field of cardiology in the years to come.

The cardiologist (not only interventional) community was eagerly awaiting the announcement of results of the large-scale **ISCHEMIA** (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial, which was sponsored by the National Institute of Health and concerned the search for the most appropriate strategy with respect to patients with stable ischaemic heart disease and induced myocardial ischaemia proven in non-invasive tests. The trial included patients with moderate or severe ischaemia, defined via one of four methods: at least 10% stress-induced perfusion loss in scintigraphy; or at least 12% in MRI, magnetic resonance imaging, test; or new myocardial contractility disorders observed during stress in at least 3/16 myocardial segments assessed via echocardiography or MRI; or exercise electrocardiographic test. To meet the criteria for inclusion in the ISCHEMIA trial, it was required that ST segment depressions in exercise electrocardiographic test occur at fewer than seven metabolic equivalents (METs) or before peak heart rate was reached, below 75% of maximum heart rate, and be at least 1.5 mm deep in two adjacent leads or at least 2 mm deep in any lead, except for leads from above the prior myocardial infarction zone. It should be added that the presence of resting ST segment depressions of 1 mm or less, the presence of a left bundle branch block, the presence of left ventricular hypertrophy with repolarisation, or heart rhythm regulated by a pacemaker constituted the exclusion criteria. The aim of the trial was to identify the most appropriate choice between two management options for this patient group: i.e. either optimal pharmacological therapy or pharmacotherapy preceded by coronary angiography and possible surgical or percutaneous revascularisation [1]. It should be noted that, given the contradictory results of smaller trials devoted to this issue, the ISCHEMIA trial was designed to be large-scale and ultimately included 5,179 patients whose coronary artery anatomy was unknown prior to randomisation, although 73% of the included patients underwent a CT scan of coronary arteries in order to exclude significant stenosis of the left main coronary artery, which was found in 8.7% of examined patients; 13.5% of patients from this group exhibited no significant coronary stenosis. 75% of the patients were recruited for this trial on the basis of a positive result of imaging stress tests (scintigraphy, echocardiography, and magnetic resonance imaging [MRI]; according to central analysis, the severity of ischaemia was overestimated in 12% of patients), while the remaining 25% were included on the basis of a strongly positive exercise electrocardiography test. Five primary outcomes were defined: cardiovascular death, myocardial infarction, hospitalisation for unstable angina, hospitalisation for heart failure, and resuscitated cardiac arrest. Results were presented by Principal Investigator Judith Hochman from New York University; after five years of observation, the ISCHEMIA trial showed no significant differences in the number of events deemed primary outcomes: the percentage

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was 15% for the non-invasive group and 13.8% for the invasive group (p = 0.34). The trial revealed that for patients with symptomatic myocardial ischaemia confirmed in non-invasive tests, the strategy of utilising invasive coronary angiography to select management options (80% of patients underwent revascularisation of whom 3/4 underwent percutaneous revascularisation) does not affect prognosis over a period of observation lasting an average of 3.3 years. This result is surprising, especially given the low percentage of complications stemming from revascularisation. The ISCHEMIA trial also unexpectedly indicated that the commonly used non-invasive methods for stratifying risk and guiding invasive management do not meet expectations, and it is difficult to find their place in prognostic reasoning. Moreover, the described results do not apply to patients with class III/IV New York Heart Association (NYHA) heart failure, with a left ventricular ejection fraction of below 35% and an unacceptable level of angina, as well as with left main coronary artery stenosis or a recent (up to 60 days) history of acute coronary syndrome. Summarising the ISCHEMIA trial, Judith Hochman emphasised the relatively low mortality rate of patients treated in both trial groups and the ultimate conclusion stemming from the trial, *i.e.* the fact that, for the studied cohort, an invasive strategy did not lead to a lower risk of clinical events compared to a non-invasive strategy — the effect amounted to a stronger mitigation of angina in only three out of 100 treated patients. No criterion which would benefit either strategy was identified, including in a group of chronic kidney disease patients distinguished within the ISCHEMIA-CKD analysis.

The congress also provided interesting results concerning the use of non-cardiac drugs in order to reduce cardiovascular risk — termed the 'outside-the-box' approach — meaning an unconventional application in the field of cardiology of drugs utilised for non-cardiac indications.

DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) is a programme which has demonstrated that the drug dapagliflozin [a sodium-glucose cotransporter 2 (SGLT2) inhibitor] tested within the programme has similar benefits in terms of reduction of cardiovascular risk for both diabetic and non-diabetic heart failure patients [2]; this latter observation was presented in Philadelphia in detail. The trial, the results of which were published in September 2019, lasted 18 months and included 4,744 heart failure patients, of whom 45% were diabetic. Randomisation involved assignment to a group which received 10 mg dapagliflozin or to a group which received a placebo, irrespective of whether diabetes was diagnosed or not. Primary outcomes included death, hospitalisation for heart failure, or sudden events related to heart failure. Administration of dapagliflozin resulted in an approx. 26% reduction in primary outcomes not only for diabetic patients, but also — and this is the breakthrough — for non-diabetic heart failure patients. Comparison of effects of dapagliflozin and a placebo between diabetic and non-diabetic patients showed no significant differences in benefits stemming from administration of this drug: for instance, for the compared groups, the odds ratio for cardiovascular death was, respectively, 0.79 and 0.85 at p = 0.7, while the quotient of probability of worsening of heart failure was 0.77 and 0.67 at p = 0.23. Assessment of the quality of life change by at least 5 points, using the Kansas City Cardiomyopathy Questionnaire — Total Symptom Score (KCCQ-TSS) showed that for both diabetic and non-diabetic groups the percentage of patients whose quality of life had improved was greater than the percentage of patients whose quality of life had deteriorated (p = 0.74). The safety profile of the tested drug was favourable, and adverse effects in the form of hypoglycaemia or metabolic acidosis were observed in only one promile of patients. The UK's John McMurray, Principal Investigator for the DAPA-HF programme, stated during the congress that "this class of drugs, SGLT2 inhibitors, are more than just treatment for patients with diabetes. They're potentially a lifesaving treatment that reduce heart failure hospital admission and improves symptoms in people with heart failure, irrespective of whether they've got diabetes or their HbA_{1c} level". Interestingly, none of the presented diabetes severity parameters affected the benefits of treatment using the SGLT2 inhibitor, and the strength of protection for non-diabetic patients was at least equal to results achieved by diabetic patients.

In terms of the size of the studied group of patients, the **COLCOT** (Colchicine Cardiovascular Outcomes Trial) programme was similar to DAPA-HF; the trial examined the extent to which colchicine — an anti-inflammatory drug known for many years and used in the treatment of gout and pericarditis — could reduce the number of ischaemic cardiovascular events in myocardial infarction survivors [3]. The trial included patients who had suffered a myocardial infarction within the previous 30 days, randomly assigning them to a group which received 0.5 mg colchicine once daily or a placebo, in both cases as an addition to standard post-infarction treatment. Primary outcomes for the COLCOT trial were cardiovascular death, resuscitated sudden cardiac arrest, another myocardial infarction, stroke, or hospitalisation for unstable angina requiring revascularisation. After observation, which on average lasted 23 months, it was found that the group treated using colchicine exhibited a 23% reduction in the risk of a first vascular incident after a myocardial infarction and a 34% reduction in the risk of cumulative cardiovascular events in patients who recently suffered a myocardial infarction. The drug was well-tolerated by most patients, although a slight increase in the number of cases of pneumonia, and a statistically insignificant increase in gastrointestinal

complications, were observed in the colchicine group. Jean-Claude Tardif from the Montreal Heart Institute Research Centre, who served as the Principal Investigator for this non-sponsored programme, stated that through colchicine cardiologists have gained a drug that is "orally administered, availably in every country of the world and inexpensive". Colchicine, with its recently identified mechanism of action through inflammasome inhibition, thus became an 'unsung hero' of the congress, one that will be hard to ignore in future editions of secondary prevention guidelines.

Presentation of results of therapies using innovative drugs was an important topic during the AHA session. One example of a completely new approach to hypolipidemic treatment is a drug called inclisiran — a short ribonucleic acid molecule interfering with messenger RNA, which blocks transcription of proprotein convertase subtilisin/ /kexin type 9 (PCSK-9) [4]; its unique feature is the fact that it need be administered only once every six months. The effects of inclisiran administration in patients with a stable course of atherosclerotic cardiovascular diseases and LDL (low-density lipoprotein) cholesterol concentration equal to or exceeding 70 mg/dL were tested in the **ORION-10** (Inclisiran for Participants with Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol) programme. The outcomes in this programme were firstly the degree of LDL-cholesterol reduction compared to placebo at day 510 of treatment, and secondly the percentage reduction in LDL cholesterol concentration between days 90 and 540 of treatment. Injections with the studied drug/placebo were administered on day 1, then after 90 days, and then every six months. The ORION-10 trial, which included 1,561 patients randomised 1:1 for active or placebo treatment, showed a 58% reduction in LDL-cholesterol concentration at day 510 of the trial, and a 56% reduction in this parameter between days 90 and 540 of the observation. The trial did not target clinical events, but their frequency was slightly lower in the group treated using inclisiran. Professor R. Scott Wright from the Mayo Clinic, who supervised this trial, stated that inclisiran is an "effective, long-lasting and strong" drug. Could it be that a serious competitor for recently introduced PCSK9 inhibitors has emerged?

Less spectacular, but no less noteworthy, were the results of the **BETonMACE** (Effect of RVX000222 on Time to Major Adverse Cardiovascular Events in High-Risk T2DM Subjects With CAD) trial, which studied whether apabetalone, a molecule created to block epigenetic transcription modulators (BET proteins) related to inflammatory processes, thrombogenesis and lipoprotein metabolism, would be able to reduce the number of vascular events in patients treated for acute coronary syndrome and diabetes [5]. 26 months of observation of 2,425 patients who underwent this innovative therapy failed to show a statistically significant advantage (achieved $p = 0.11$) of the new method of preventing new vascular events, although the frequency of these events in the apabetalone group was lower (9.5%) than expected (10.5%). Good tolerance of the new drug and few adverse effects during treatment encourage the continuation of studies concerning what Professor Kausik Ray from Imperial College London, Principal Investigator for this programme described as: "the first drug epigenetically modifying drug to be tested in cardsiovascular disease, with this very selective pathway; we remain optimistic".

Leaving what we might call the 'drugs of the future' and going back to everyday clinical practice, it is worth noting the results of the **TWILIGHT-ACS** (Ticagrelor With AspIrin or ALone In HiGH-Risk Patients After Coronary InTervention for Acute Coronary Syndrome) programme, in which patients who underwent a percutaneous coronary intervention for reasons other than STEMI and completed a three-month--long double antiplatelet therapy were randomly assigned for 12 months to either a group treated using ticagrelor and acetylsalicylic acid or to a group treated using ticagrelor and a placebo [6]. During the 12-month observation, the group of patients treated via ticagrelor monotherapy exhibited — with a comparable frequency of vascular events — a 53% reduction in types 2, 3 and 5 haemorrhagic complications as per the classification adopted by the Bleeding Academic Research Consortium (except for fatal hemorrhage, this means any bleeding which requires a medical intervention, except for bleeding occurring within 48 hours of surgical revascularisation of the myocardium, which is classified as type 4, and bleeding where the patient does not seek medical attention — type 1), with no sign of reduced anticoagulation efficacy compared to double therapy. Professor Usman Baber from the Mount Synai Hospital in New York, who reported on the results of this trial, stressed that some patients are currently being deprived of double antiplatelet therapy for fear of severe bleeding, and the results of the TWILIGHT-ACS trial suggest that the new strategy — ticagrelor monotherapy following an acute coronary syndrome — reduces the risk of bleeding and simultaneously preserves the antiplatelet effect.

The AHA as an organisation not only aims to influence the education of specialists in the field of cardiology, but also to recognise the importance of raising public awareness with respect to the ability to affect risk factors for cardiovascular diseases. Hence the large-scale information campaigns, which this year bore the slogan: "HEY BIG VAPE, #QUIT LYING". This campaign aims to disrupt thinking about e-cigarettes as a harmless form of stimulant because of numerous reports on the clearly pathogenic role of e-cigarettes. It aims to involve legislators and agencies which regulate access to such products in a fight to limit young people's access to e-cigarettes.

To conclude this selective overview of topics covered during the recent AHA sessions, a word about Polish accents

in Philadelphia 2019. Our country's centres presented 24 reports, either orally or via posters; the sessions were attended by selected Principal Investigators from the ISCHEMIA trial. Of note in the programme of Scientific Sessions is also a joint session of national cardiac societies, co-organised by the Polish Cardiac Society, entitled 'Global Roundtable: Arrythmia in Unique Circumstances'. During this session, Tomasz Rechciński, MD, PhD, presented the case of a patient with Brugada syndrome and perspectives for molecular diagnostics with respect to this nosological unit.

Conflict(s) of interest

The authors declare no conflict of interest.

References

1. Hochman JS, Reynolds HR, Bangalore S, et al. ISCHEMIA Research Group. Baseline characteristics and risk profiles of participants in the ISCHEMIA randomized clinical trial. JAMA Cardiol. 2019; 4(3): 273–286, doi: 10.1001/jamacardio.2019.0014, indexed in Pubmed: 30810700.
2. Kosiborod MN, Jhund PS, Docherty KF, et al. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. Circulation. 2020; 141(2): 90–99, doi: 10.1161/CIRCULATIONAHA.119.044138, indexed in Pubmed: 31736335.
3. Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019; 381(26): 2497–2505, doi: 10.1056/NEJMoa1912388, indexed in Pubmed: 31733140.
4. German CA, Shapiro MD. Small interfering RNA therapeutic inclisiran: a new approach to targeting PCSK9. BioDrugs. 2020; 34(1): 1–9, doi: 10.1007/s40259-019-00399-6, indexed in Pubmed: 31782112.
5. Ray KK, Nicholls SJ, Ginsberg HD, et al. Effect of selective BET protein inhibitor apabetalone on cardiovascular outcomes in patients with acute coronary syndrome and diabetes: Rationale, design, and baseline characteristics of the BETonMACE trial. Am Heart J. 2019; 217: 72–83, doi: 10.1016/j.ahj.2019.08.001, indexed in Pubmed: 31520897.
6. Mehran R, Cao D, Baber U, et al. Ticagrelor reduces thrombus formation more than clopidogrel, even when co-administered with bivalirudin. Thromb Haemost. 2014; 112(5): 1069–1070, doi: 10.1160//TH14-03-0269, indexed in Pubmed: 25104302.