Folia Cardiologica 2019
vol. 14, no. 5, pages 537–541

ISSN 2353–7752

What's new at the American College of Cardiology Congress 2019? — New Orleans, March 16, 2019

Co nowego na Kongresie *American College of Cardiology* 2019? Nowy Orlean, 16 marca 2019 roku

Maria A. Sobczak-Kaleta, Jarosław D. Kasprzak

Department of Cardiology, Medical University of Lodz, Lodz, Poland

Artykuł jest tłumaczeniem pracy: Sobczak-Kaleta MA, Kasprzak JD. Co nowego na Kongresie *American College of Cardiology* 2019? Nowy Orlean, 16 marca 2019 roku. Folia Cardiol. 2019; 14 (5): 532–536. DOI: 10.5603/FC.2019.0105. Należy cytować wersję pierwotną

Introduction

The annual American College of Cardiology congress was held in New Orleans from 16 to 18 March 2019, during which the results of numerous clinical studies that could have a significant impact on the everyday practice of cardiologists were presented. Much attention was devoted to new technologies that are changing the philosophy behind medical research — used *e.g.* in the Apple Heart Study. Several promising new drugs have not lived up to expectations — *e.g.* neladenoson in heart failure with preserved ejection fraction, while some effective therapies [*e.g.* TYRX™ antibacterial pocket reducing the risk of infection with the cardiac stimulator bed in the WRAP-IT (World-wide Randomised Antibiotic Envelope Infection Prevention Trial) study] have no chance of routine use due to their low cost-effectiveness. However, in the authors' opinion, several of the presented studies were of great importance for cardiological practice, indeed sometimes even groundbreaking importance. Below we present our subjective selection.

Transcatheter aortic valve implantation in patients with severe aortic stenosis and low operational risk — PARTNER 3 and EVOLUT studies

Transcatheter aortic valve implantation (TAVI) is an alternative to surgery in patients with severe aortic stenosis. Until recently, this was reserved for patients at high risk of dying from conventional surgery. This year's congress brought groundbreaking data on the clinical results of TAVI used in low-risk patients. In the PARTNER 3 [1] and EVOLUT Low Risk [2] studies, TAVI results were compared to those of surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis and low risk of death during surgery in very similar patient populations [mean age approximately 74 years, calculated risk of death STS-PROM (Short Term Risk Calculator — Predicted Risk of Mortality) 1.9%]. 1,000 patients were enrolled in the PARTNER 3 trial and randomly assigned to TAVI (balloon-expanded SAPIEN 3 valve) or SAVR. The primary endpoint in the study was death from any cause, stroke or rehospitalisation within one year of surgery. The results of the study were surprising — contrary to current guidelines, significant clinical benefits were demonstrated in the group treated with transcatheter surgery. Within one year, the primary endpoint occurred in 8.5% of the TAVR group compared to 15.1% SAVR — a highly significant indicator of the advantage of a TAVI strategy (risk reduction by an impressive 46%, p = 0.001). Analysis of the annual occurrence of the primary endpoints showed a clear advantage of the transcatheter strategy: mortality 1.0% versus 2.5% (TAVI versus SAVR), stroke rate 1.2% versus 3.1% (a 62% decrease in risk), and 35% less frequent rehospitalisations — 7.3% vs. 11%. Two patients from the TAVI group and four from the surgical group died during hospitalisation. The hospital stay was significantly reduced, from seven to three days, thanks to TAVI. Patients treated with the transcatheter method required implantation of a cardiostimulator with a frequency similar to SAVR [6.5% vs. 4%, p = NS (not statistically significant)], while much less frequently (5% vs. 39.5%) developed atrial fibrillation in the month after the procedure. There were no clinical manifestations of valve thrombosis in any of the groups, and the percentage of moderate or large return waves on

Address for correspondence: Maria A. Sobczak-Kaleta MD, PhD, Katedra i Klinika Kardiologii, Uniwersytet Medyczny w Łodzi, ul. Kniaziewicza 1/5, 91–347 Lodz, Poland, e-mail: maria.sobczak@wp.pl

the new valve was similar (0.6% and 0.5% after a year). Mild reverse waves, as well as subclinical (asymptomatic) thrombosis were less common after SAVR.

The EVOLUT Low-Risk study included 1,468 patients with random assignment to TAVI (CoreValve, Evolut R, Evolut PRO, Medtronic self-expanding valves) or SAVR. The primary endpoint of the study was the incidence of the primary endpoint (death or stroke resulting in disability) in the 24-month follow-up. This was 5.3% in the TAVI group compared to 6.7% SAVR — therefore TAVI was non-inferior to cardiac surgery. TAVI proved to be a safer method — the secondary endpoint concerned peri-operative complications over a 30-month period, occurring in 5.3% of patients in the TAVI group, and in 10.7% after cardiac surgery. After 30 days, patients after TAVI had lower incidences of stroke causing disability (0.5% vs. 1.7% after SAVR), haemorrhagic complications (2.4% vs. 7.5% after SAVR), acute kidney damage (0.9 % vs. 2.8% after SAVR), and atrial fibrillation (7.7% vs. 35.4% after SAVR). At the same time, patients after TAVI reported a higher quality of life after 30 days. After a year, 2.4% of patients after TAVI and 3% after SAVR (p = NS) died. Due to the different design of the TAVI valves, unlike in the PARTNER study, patients treated with the transcatheter method required more frequent cardiac pacemaker implantation (19.4% vs. 6.7% after SAVR), but atrial fibrillation was also observed much less frequently (9.8% vs. 38.3%) and there were fewer hospitalisations for heart failure (3.2% vs. 6.5%, annual follow-up). Valve thrombosis in both groups was very rare (< 1%). The frequency of moderate or large return waves on the new valve was slightly higher after TAVI (3.5% vs. 0.5% after a year), but moderate or significant valve mismatch (too low effective outlet area) was less common after transcatheter treatment (1.78% vs. 8, 2% after SAVR). Therefore, the study showed at least the clinical equivalence of TAVI using a self-expanding valve compared to SAVR.

Both studies analysed for the first-time groups of patients with severe arterial stenosis and low operational risk, who comprise 80% of those currently undergoing surgery. Considering the data from the EVOLUT and PARTNER 3 studies, it seems justified to treat TAVI as an acceptable and perhaps more appropriate therapeutic alternative also for low-risk patients. However, planned future research still needs to assess the long-term effects of both strategies.

AUGUSTUS study supports the use of apixaban as part of DAPT for most patients with AF after ACS or PCI

The dilemma of risk and benefits dependent on anticoagulation in patients with atrial fibrillation (AF) and the indication for dual antiplatelet therapy may have become somewhat less challenging thanks to the results of the randomised AUGUSTUS study [3].

This study included 4,614 patients from centres in North America, Europe, Asia and South America, in whom AF was an indication for chronic oral anticoagulation, and in whom acute coronary syndrome (ACS) was diagnosed or percutaneous coronary intervention (PCI) was performed. Over 92% of patients were treated with clopidogrel (and the others with other $P2Y_{12}$ inhibitors). Two equally numerous patient groups were randomly assigned in a 2 × 2 schedule to two alternative therapies: apixaban (fixed-dose for AF) or vitamin K antagonist (VKA), plus in addition acetylsalicylic acid (ASA) at 81 mg/day or a placebo. The primary endpoint was major bleeding or other clinically significant bleeding during the six months of follow-up. Secondary endpoints included death or hospitalisation due to stroke, myocardial infarction, stent thrombosis or urgent revascularisation. The results of the study were in line with previous observations on new anticoagulants (RE-DUAL studies with dabigatran and PIONEER-AF with rivaroxaban), indicating the superiority of apixaban over VKA and the possibility of limiting indications to ASA. After six months of treatment, the risk of bleeding was reduced by 31% among patients taking apixaban compared to warfarin ($p < 0.001$) and by 47% among patients taking a placebo compared to aspirin. The highest bleeding rates were observed among patients treated with VKA with dual antiplatelet therapy (18.7%), and the lowest among those taking clopidogrel, apixaban and placebo (7.3%). The primary endpoint (major bleeding or clinically significant bleeding) occurred in 10.5% of patients receiving apixaban compared to 14.7% of patients receiving AWK ($p < 0.001$). The rate was 16.1% in the ASA randomisation analysis and 9% in the case of the placebo. The number of deaths and hospitalisations (the study's secondary endpoint) was highest in patients receiving AWK and ASA (27.5%), and lowest in patients receiving apixaban and placebo (22.0%). Apixaban reduced the risk of a secondary endpoint relative to AWK by 17%, while ASA did not change the risk relative to placebo. A 50% lower risk of stroke was observed in patients in the apixaban group compared to patients taking VKA. Patients enrolled to the study after acute coronary syndrome had a significantly reduced risk of bleeding during treatment with apixaban compared to VKA and when taking placebo versus ASA.

AUGUSTUS confirms that the treatment of patients with AF requiring antiplatelet therapy with new anticoagulants is safe, and the combination of apixaban and clopidogrel, without ASA, can be a safe treatment regimen in this difficult patient population, without a significant increase in the risk of ischaemic events such as heart attack or stroke.

Home treatment for low-risk pulmonary embolism with rivaroxaban — the Home Treatment of Pulmonary Embolism (HoT-PE) trial

One of the most important studies for clinical practice discussed at the ACC's 2019 congress was one with the acronym HoT-PE (Home Treatment of Pulmonary Embolism Trial) aimed at assessing whether the early termination of hospitalisation (i.e. within 48 hours of admission) followed by community-based treatment with rivaroxaban of patients with a low-risk acute pulmonary embolism (APE) is effective and safe [4]. Patients were qualified to the low-risk group using the Hestia criteria, which have many overlapping features with the PESI scale but do not exclude patients older than 80 years or those with cancer. Rivaroxaban 2 × 15 mg/ /day was initiated in the hospital and continued for three weeks after discharge, followed by rivaroxaban 1 × 20 mg or 15 mg in selected patients for at least three months. The average hospitalisation time in the study was 34 hours, with 93.6% of patients discharged within 48 hours. Recurrence of symptomatic venous thromboembolism (VTE) or fatal APE (endpoint of efficacy) within three months occurred in 3/525 patients (0.6% — only PE recurrences, no deaths). The efficacy rate was one-third of the 1.7% threshold set by researchers based on 3-month VTE recurrence rates in previous home-based and EINSTEIN PE studies. In this study, there were two deaths due to advanced cancer. In the HoT-PE study, a single dose of heparin was administered to only 10% of patients (rivaroxaban was preferred from the beginning of treatment). Aspects of safety assessed separately were favourable — major bleeding (six out of 519 patients), any clinically significant bleeding (31 out of 519) or at least one serious adverse event (58 out of 519) rarely occurred. Only 2.3% of patients were re-hospitalised for suspected APE recurrence or bleeding.

Therefore, it appears that in patients with low-risk acute pulmonary embolism, without right ventricular dysfunction and intracardiac thrombi, early discharge and rivaroxaban treatment at home is effective and safe.

The results of the HoT-PE study strengthen the legitimacy of PE patients for outpatient treatment with oral anticoagulants, possibly reducing hospital complications and healthcare costs.

Alcohol abstinence and the occurrence of atrial fibrillation

One of the more important preventive studies was a randomised study on the effects of abstinence in people who drink moderate amounts of alcohol and have AF [5]. The study included 140 patients with paroxysmal (63%) or persistent AF (37%), currently in sinus rhythm, who consumed at least 10 alcohol equivalents weekly (12 g ethanol). Rhythm monitoring was carried out using an implantable loop recorder or pacemaker or an AliveCor home single--channel recorder. In the study group, all patients consented to total abstinence, which was checked by urine analysis for the alcohol metabolite. In the control group, drinking alcohol was allowed. Among patients with moderate alcohol consumption, alcohol abstinence was independently associated with a reduction in the duration of AF (5.6% ± 12.4% compared to 8.2% ± 14.5%), a reduction in the frequency of AF relapse, an improvement in arrhythmia symptoms, weight loss, and improved blood pressure control. The results of this study indicate that the recommendation of alcohol abstinence should be part of lifestyle interventions in people with AF who drink moderate amounts of alcohol.

Dapagliflozin in heart failure with reduced ejection fraction — DECLARE TIMI-58 study

The results of the large-scale DECLARE-TIMI 58 (Dapagliflozin and Effects on Cardiovascular Events) study subanalysis regarding the effects of treatment in patients with heart failure were eagerly awaited [6].

17,160 patients with type 2 diabetes mellitus and concomitant cardiovascular disease (41%) or its high risk (59% of the group) participated in the DECLARE-TIMI 58 study. Randomisation required adding 10 mg of dapagliflozin or placebo to regular diabetes medication (diabetes having lasted approximately 10 years on average). The median follow-up was four years. The current results use the fact that at the beginning of the study 30% of participants (5,202) had their left ventricular ejection fraction assessed, thus 13% of patients (671) were diagnosed with heart failure with reduced ejection fraction (HFrEF). It was observed that in this subgroup dapagliflozin reduced mortality due to cardiovascular diseases or the risk of hospitalisation due to heart failure to a greater extent (by 38%) than in other patients (by 12%, NS; p for interaction = 0.046). Most importantly, dapagliflozin reduced cardiovascular mortality by 45% and total mortality by 41% in patients with HFrEF, but not in people without HFrEF (HR 1.08, p = NS). The effect of the drug on mortality due to circulatory reasons and overall mortality showed a clear interaction with the decreasing left ventricular ejection fraction, disappearing above EF = 45%. Treatment also reduced the incidence of HF hospitalisation in both HFrEF (by 36%) and not-HFrEF (by 24%) patients.

Left ventricular ejection fraction (as well as a history of heart failure) is, therefore, an important parameter for identifying people with type 2 diabetes who may benefit particularly from SGLT2 inhibitors.

Antidote reversing the effect of ticagrelor — the molecule PB2452

Antiplatelet therapy is an important part of secondary prevention of cardiovascular events, but the possibility of reversing the effects of new oral anticoagulants is a major problem in everyday practice. The congress presented the first clinical evaluation of the PB2452 molecule as a method of reversing ticagrelor's effect [6].

Platelet function was tested in 64 healthy volunteers before treatment with ticagrelor and then after PB2452 (48 people) or placebo (16 people). Platelet aggregation was shown to be inhibited by approximately 80% after 48 hours of ticagrelor treatment. The new drug PB2452 was given as an initial intravenous bolus followed by a prolonged infusion (eight, 12 or 16 hours) and reversed the antiplatelet effect of ticagrelor within five minutes of treatment onset. This effect lasted for over 20 hours. No evidence of increased platelet activity (rebound effect) was observed after drug discontinuation, and drug-related adverse events were mainly related to infusion site problems. Study results indicate that intravenous administration of PB2452 can provide immediate and permanent reversal of ticagrelor's antiplatelet effect, which would be a unique opportunity for patients who need urgent surgery or experience life-threatening bleeding during ticagrelor therapy.

Does bempedia acid decrease LDL concentration — CLEAR Wisdom study

Another eagerly awaited study in the field of preventive cardiology was the CLEAR Wisdom study assessing the clinical possibilities of a new drug — bempedia acid [8]. This is a new drug that works in the same way as statins on the cholesterol synthesis pathway in the hepatocyte, but at an earlier stage — by inhibiting ATP-citrate lyase. Importantly, the safety profile of activated bempedia acid is not present in skeletal muscle. In the CLEAR Wisdom study, 779 patients were randomly assigned to treatment with 180 mg bempedic acid or placebo (for one year, in addition to the maximum tolerated statin doses) to assess the long-term efficacy and safety of patients at high risk for cardiovascular disease. A subgroup of 77 patients did not tolerate any statin dose. 740 patients (490 bempedia acid, 250 placebo) completed the study. Low-density lipoprotein (LDL) cholesterol in the bempedia acid group decreased from 119.4 mg/dL to 97.6 mg/dL at week 12 compared to no change from baseline in the placebo group (122.4 mg/dL vs. 122.8 mg/dL). The mean percentage change in plasma LDL cholesterol was 15.1% for bempedia acid compared to 2.4% for placebo ($p < 0.001$). In patients not using statins, the decrease in LDL cholesterol was about 25%. The addition of bempedia acid to the maximally tolerated statin dose in patients with hypercholesterolemia significantly and permanently reduced total cholesterol, LDL cholesterol, non-high-density lipoprotein (HDL) cholesterol, apolipoprotein B, and C-reactive protein compared to placebo. Side effects were similar to placebo, without any excessive muscle discomfort.

The CLEAR Wisdom study indicates that bempedia acid may extend the range of treatment options for high-risk patients with atherosclerotic cardiovascular disease whose LDL cholesterol levels remain unsatisfactory due to statin intolerance — drug tolerance appears to be better.

Apple Watch helps detect AF — is this the future?

Today's patients have more options than ever before to monitor their own health data, and make decisions about what to do with such information, in the era of smartwatches and other devices, as well as new applications designed to monitor heart rate and other parameters.

The Apple Heart Study was designed to assess whether the Apple Watch can reliably detect AF and encourage subsequent clinical evaluation [9]. In the first study of this kind, which involved 419,927 (!) people, using an Apple Watch to identify an irregular rhythm was found to help identify AF. The results showed that 2,161 participants (0.5% registered) received an irregular rhythm notification. Of the 200,000 participants under the age of 40, the notification rate was 0.16% compared to 3.2% in the 25,000 people aged 65 or older. A positive predictive value of 84% confirms the ability to correctly identify AF among people who have been informed of an irregular rhythm by their Apple Watch. This study confirmed the soundness of the concept of using non-medical portable devices for medical applications, and will probably have a more clinically oriented continuation (HEARTLINE study).

References

1. Mack MJ, Leon MB, Thourani VH, et al. PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019; 380(18): 1695–1705, doi: 10.1056/NEJMoa1814052, indexed in Pubmed: 30883058.
2. Popma JJ, Deeb GM, Yakubov SJ, et al. Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 2019; 380(18): 1706–1715, doi: 10.1056/NEJMoa1816885, indexed in Pubmed: 30883053.
3. Lopes RD, Heizer G, Aronson R, et al. AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med. 2019; 380(16): 1509–1524, doi: 10.1056/NEJMoa1817083, indexed in Pubmed: 30883055.
4. Konstantinides SV. Outpatient management of patients with acute pulmonary embolism. The Home Treatment of Pulmonary Embolism (HoT-PE) trial. American College of Cardiology Annual Scientific Session (ACC 2019). New Orleans, LA, March 18, 2019.
5. Voskoboinik A, Kalman JM, Nicholls T, et al. Impact of alcohol abstinence in moderate drinkers with atrial fibrillation: results from the

alcohol-AF randomized controlled trial American College of Cardiology — 67th Scientific Sessions. New Orleans, LA, March 18, 2019.
6. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 2019; 139(22): 2528–2536, doi: 10.1161/CIRCULATIONAHA.119.040130, indexed in Pubmed: 30882238.
7. Bhatt DL, Pollack CV, Weitz JI, et al. Antibody-based ticagrelor reversal agent in healthy volunteers. N Engl J Med. 2019; 380(19): 1825–1833, doi: 10.1056/NEJMoa1901778, indexed in Pubmed: 30883047.
8. Goldberg AC. Efficacy and safety of bempedoic acid added to maximally tolerated statins in patients with hypercholesterolemia and high cardiovascular risk — CLEAR Wisdom. American College of Cardiology Annual Scientific Session (ACC 2019). New Orleans, LA, March 18, 2019.
9. Turakhia M, Perez M. Results of a large-scale, App-based study to identify atrial fibrillation using a smartwatch: the Apple Heart Study. American College of Cardiology Annual Scientific Session (ACC 2019). New Orleans, LA, March 18, 2019.