The European Society of Cardiology (ESC) Congress attracted more than 33,000 cardiologists and allied medical professionals to this year’s meeting in Rome, Italy, from August 27 to 31. We review key sessions from a wide range of therapeutic areas, including anticoagulation (in atrial fibrillation, acute myocardial infarction, and stenting), cardiac toxicity in cancer treatments, obesity, and hypercholesterolemia.

**ANNEXA-4: Andexanet Alfa for Reversal of Factor Xa Inhibitors in Patients With Acute Major Bleeding**

- Stuart J. Connolly, MD, McMaster University, Hamilton, Ontario, Canada

“Andexanet alfa is a recombinant protein that was specifically designed to reverse the anticoagulant activity of both direct and indirect factor Xa inhibitors and to assist physicians with the management of acute severe bleeding,” said Dr. Connolly, the ANNEXA-4 lead investigator, at an ESC press briefing.

In prior research, andexanet alfa (AndexXa, Portola Pharmaceuticals, Inc.) was shown to reduce anti-factor Xa activity in volunteers. For the first time, ANNEXA-4 tested andexanet alfa in patients with acute, potentially life-threatening anticoagulant-related bleeding. All of the patients had received their last dose of either a direct factor Xa inhibitor (apixaban [Eliquis, Bristol-Myers Squibb], rivaroxaban [Xarelto, Janssen Pharmaceuticals], or edoxaban [Savaysa, Daiichi Sankyo] or indirect factor Xa inhibitor (enoxaparin) within the last 18 hours. Patients included in the trial presented not just with acute major bleeding, but also with elevated anti-factor Xa activity. Most bleeding was gastrointestinal (approximately 50%) or intracranial (approximately 40%).

Because it would have been unethical to have a placebo control group, all patients received andexanet alfa, Dr. Connolly said. Patients were first treated with andexanet alfa as an immediate bolus over 15–30 minutes, followed by a two-hour infusion with all dosing based on the timing and specific agent of their exposure to factor Xa inhibition. Investigators assessed changes in anti-factor Xa activity and clinical hemostatic efficacy through 12 hours.

“It’s important to note that this was an elderly, compromised population with a mean age of 77 years, with most being treated for atrial fibrillation or venous thromboembolism, and having a high burden of prior myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, and heart failure,” Dr. Connolly said.

In interim findings, after 12 hours of treatment, 79% of patients did not change significantly. “The newer, more sensitive echocardiographic parameters of left ventricular systolic function did not change significantly. “The newer, more sensitive echocardiographic techniques, however, showed heart damage after chemotherapy in the control group,” she said. No significant changes in anti-factor Xa activity and clinical hemostatic efficacy were noted, said Dr. Connolly.

Thrombotic events occurred within three days of andexanet alfa discontinuation in four patients (6%) and by 30 days in 12 patients (18%). By 30 days, anticoagulation with andexanet alfa was restarted in 18 patients (27%). Among those in whom therapeutic anticoagulation was restarted, a thrombotic event occurred in only one patient. Six of the 10 deaths that occurred within 30 days were cardiovascular in nature, Dr. Connolly said.

“This preliminary report of the ongoing ANNEXA-4 study shows us that andexanet rapidly reverses anti-factor Xa activity in acutely bleeding patients, and this is associated with excellent or good hemostasis in most,” he concluded.

ANNEXA-4 results were simultaneously published in the *New England Journal of Medicine.*

**Protective Effect of Nebivolol on Anthracycline-Induced Cardiotoxicity, Assessed by Tissue Doppler Velocities And by Speckle-Tracking Echocardiography**

- Mirela Cleopatra Tomescu, MD, Professor, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

Anthracyclines are widely prescribed as a treatment for breast cancer. However, their cardiotoxicity, which can lead to heart failure, is a major limitation. Nebivolol is a beta blocker indicated in the United States for hypertension and in Europe for left ventricular heart failure as well. A study designed to test the ability of nebivolol to protect against heart failure and to confirm methods for detecting cardiotoxicity early and accurately enrolled 60 women with HER-2 negative breast cancer (mean age, 52 years). All were scheduled to start doxorubicin chemotherapy and were randomized into two groups of 30. One group received 5 mg of nebivolol once daily for the duration of chemotherapy, and the other served as the control group.

Cytostatic chemotherapy consisted of six cycles of doxorubicin at intervals of 21 days. The cardiac imaging used to evaluate the patients included conventional two-dimensional tissue Doppler and speckle-tracking echocardiography.

The average cumulative doxorubicin dose, Dr. Tomescu said, was 520 ± 8 mg/m2. With treatment, the classical echocardiographic parameters of left ventricular systolic function did not change significantly. “The newer, more sensitive echocardiographic techniques, however, showed heart damage after chemotherapy in the control group,” she said. No significant

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changes in heart function were detected in the group receiving nebivolol. Tissue Doppler imaging showed that patients who did not receive nebivolol had significant changes in left ventricular diastolic function, with a decrease in myocardial velocities. Similarly, speckle-tracking imaging in the control group showed significant alterations in left ventricular function demonstrated by a decrease of longitudinal ($P = 0.04$) and radial ($P = 0.03$) strains, as well as strain rates ($P = 0.02$).

“Patients who received nebivolol were protected and had normal heart function.” She added, “Our study demonstrates the utility of new echocardiographic methods, such as tissue Doppler and speckle-tracking imaging, in the early detection of ventricular dysfunction induced by cytostatic treatment.”

While the study findings are encouraging, larger studies with a longer follow-up period are needed to confirm the results, according to Dr. Tomescu.

Healthy School, Happy School: A Randomized Clinical Trial Designed to Stop Obesity in Children

- Daniela Schneid Schuh, MHSc, Institute of Cardiology of Rio Grande do Sul, Porto Alegre, Brazil

A Brazilian school environment intervention that cost the equivalent of less than 20 U.S. cents per student led to increases in physical activity and fruit consumption while halting the rise in body mass index (BMI). “Obesity has reached a plateau in developed countries but continues to rise in many developing countries, such as Brazil,” said nutritionist and study author Daniela Schneid Schuh at an ESC press conference. While only 6% of Brazilian children were overweight in 1975, by 2009 the rate had increased to 34%, she said.

Feliz, the town where the study to test the intervention’s effectiveness was conducted, is heavily influenced by German immigration. It has one of the highest human development indexes (a measure combining longevity, education, and standard of living) in Brazil. It also is characterized by high rates of obesity, sedentarism, hypertension, chronic disease, urbanization, and less-healthy eating habits.

Schneid Schuh and fellow investigators at the Research Group on Cardiovascular Prevention in Childhood and Adolescence, along with town psychologists and nurses, recruited four public schools for the study, which included 73 students for the active program and 140 controls (54.4% female; age range, 5–16 years). Participants were randomized to the nine-month intervention, which focused on lifestyle changes at school and at home, or to the usual recommendations from the school curriculum.

While the intervention initially consisted of monthly at-school seminars and workshops about physical activity and nutritional habits, the topic of bullying was added after adverse reports by obese students about classmates’ behaviors. At the schools, the program made healthy snacks available, and displays about nutrition were created. At home, the program consisted of family interactions involving homework, commitment to goals, and occasional restrictions on television, Internet, and cell phone use.

Assessment after nine months revealed significant improvements in the endpoints of change in BMI and change in physical activity in the intervention group. Changes from baseline were observed in higher percentages of those who were “active” and decreasing percentages of those who were “irregular active” (overall, $P < 0.05$ versus baseline). Changes in the control group from baseline to nine months were not significant ($P = 0.134$). Differences in change in BMI for the intervention group ($-0.05\%$) versus the control group ($+0.84\%$) were significant ($P < 0.001$), as were the differences in consumption of fruit measured in portions per week (3.11 portions for the intervention group versus 0.71 for the control group [$P < 0.05$]).

Commenting on the increase in fruit consumption in the active treatment group, Schneid Schuh noted that fruit consumption in Brazil is lower than in Europe. Although fruit consumption does increase sugars, she acknowledged, fruit consumption also amply provides vitamins, antioxidants, and fiber and is better than consuming ultra-processed foods.

“This intervention in the school environment was able to stop an increase in BMI, while increasing physical activity and fruit consumption. The implementation cost of the intervention was very low. … This indicates that it could be reproduced in other low-resource settings,” she concluded.

ANTARCTIC: Platelet Function Monitoring In Elderly Patients Stented for an Acute Coronary Syndrome

- Gilles Montalescot, MD, PhD, Pitié-Salpêtrière Hospital, Paris, France

The ANTARCTIC trial confirmed the earlier results of the ARCTIC trial,2 showing that monitoring platelet function to adjust antiplatelet therapy in patients stented for acute coronary syndromes (ACS) does not improve prognosis. According to ANTARCTIC lead investigator Dr. Montalescot, the findings also showed that the failure was not attributable to the risk level of the population or to the type of P2Y$_{12}$ antagonist, as had been suggested when ARCTIC failed to show benefit.

ANTARCTIC was designed to answer such concerns, given that ARCTIC enrolled a low-risk, stable, elective percutaneous coronary intervention (PCI) population with a predominant use of clopidogrel and old P2Y$_{12}$ reaction unit (PRU) thresholds. ANTARCTIC addressed those concerns by including elderly, ACS, and urgent PCI patients with predominant prasugrel use and new PRU thresholds, he said.

“The whole question, of course, is to determine the optimal level of platelet inhibition that should prevent myocardial infarction and major bleeding for each individual patient,” Dr. Montalescot said at an ESC press briefing. Platelet reactivity has been shown to relate directly to outcomes,3 with PRU of 208 or greater associated with higher myocardial infarction risk (hazard ratio [HR], 1.47; 95% confidence interval [CI], 1.05–1.88; $P = 0.003$) and higher risk of major bleeding (HR, 0.83; 95% CI, 0.69–0.99; $P = 0.04$) at 12 months compared with PRU of less than 208.

The ANTARCTIC trial enrolled 877 ACS patients 75 years of age or older who underwent coronary stenting. All patients were started on the antiplatelet agent prasugrel (5 mg). The investigators randomized 442 patients to the conventional therapy with no adjustments made to treatment and 435 patients...
to the conventional therapy plus platelet reactivity monitoring and treatment adjustment if needed. Monitoring-臂 patients underwent a platelet function test at days 14 and 28, with subsequent adjustments for high or low platelet reactivity. Dr. Montalescot noted that monitoring led to a change of treatment in 44.8% of patients.

The primary composite endpoint of cardiovascular death, myocardial infarction, stroke, stent thrombosis, urgent revascularization, and bleeding complication at one year was reported at similar rates in both arms of the study: 27.6% in the monitoring group and 27.8% in the conventional group (HR, 1.003; 95% CI, 0.78–1.29; P = 0.98).

“This strategy did not improve ischemic or safety outcomes,” Dr. Montalescot said.

“This is a good message,” said ESC press conference moderator professor Stephan Gielen, MD, who commented further that the study confirms the safety of dual antiplatelet therapy at the reduced dose of 5 mg without a need for monitoring in this elderly population.

**Effect of Alirocumab on the Frequency of Lipoprotein Apheresis: A Randomized Phase 3 Trial**

- Patrick M. Moriarty, MD, University of Kansas Medical Center, Kansas City, Kansas

Heterozygous familial hypercholesterolemia (HeFH) is associated with severely elevated low-density lipoprotein-cholesterol (LDL-C) levels and a high risk for premature cardiovascular disease. HeFH patients taking alirocumab (Praluent, Sanofi-Aventis), however, may be able to end or reduce their reliance on lipoprotein apheresis, according to results from the phase 3 ESCAPE trial presented at an ESC press conference.

Unfortunately, in many HeFH patients, lipid-lowering therapies do not reduce LDL-C levels to target, Dr. Moriarty said. As a consequence, patients undergo apheresis, spending three to four hours every one to two weeks to clear their blood of excess LDL-C at apheresis centers at a cost of $50,000 to $75,000 per year.

ESCAPE tested the ability of alirocumab to reduce reliance on apheresis. Alirocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), was approved in the U.S. in 2015 as a second-line treatment for hypercholesterolemia in adults.

ESCAPE included 62 HeFH patients from 14 centers in the U.S. and Germany. All were undergoing apheresis either weekly or every two weeks, were on stable background treatment (e.g., statins, ezetimibe), and had undergone consistent lipoprotein apheresis weekly for four or more weeks or every other week for eight or more weeks. Investigators randomized them to subcutaneous injections of 150 mg of alirocumab (n = 41) or placebo (n = 21) every two weeks for 18 weeks. Patients’ regular lipid-lowering medications were continued.

The rate of apheresis treatments was fixed according to patients’ established schedules until week 6. Thereafter, until week 18, rates were adjusted based on individual needs. Apheresis was skipped if patients’ LDL-C dropped by 30% or more since the start of the study.

Apheresis was reduced by 75% more in alirocumab-treated patients than in controls by study completion. While no patients in the placebo group were able to discontinue apheresis altogether, 63.4% of the patients receiving alirocumab discontinued apheresis. In addition, 92.7% of patients receiving alirocumab were able to avoid at least half of their apheresis sessions compared with 14.3% in the placebo group.

Adverse events were generally not serious and occurred similarly in the alirocumab and placebo groups (75.6% and 76.2%, respectively).

“Alirocumab is a potentially easier, more efficient, and less expensive means of treating dyslipidemia in these patients,” Dr. Moriarty said. He estimated that alirocumab treatment costs $7,000 to $10,000 per year, a fivefold reduction compared to the cost of apheresis. He speculated that the response to alirocumab “is probably a class effect for PCSK9 inhibitors.”

“Alirocumab can now be considered part of standard care for patients intolerant to other lipid-lowering therapies,” he concluded.

**The Early Use of N-Acetylcysteine With Glyceryl Trinitrate in the STEMI NACIAM Trial: A Pilot Study**

- Sivabaskari Pasupathy, PhD Candidate, University of Adelaide, Adelaide, Australia

Early use of the addition of high-dose N-acetylcysteine (NAC) to low-dose intravenous glyceryl trinitrate (GTN) reduces infarct size and increases myocardial salvage in patients with ST-elevation myocardial infarction (STEMI), according to results from the NACIAM trial. The effect is greater in patients with a shorter duration of ischemia, Pasupathy said in an ESC press conference.

NACIAM tested whether the NAC/GTN combination would limit infarct size in a placebo-controlled, double-blind, multicenter trial including 112 STEMI patients (mean age, 64 years) undergoing percutaneous coronary intervention (PCI). NAC reduces oxidative stress and reperfusion injury, and GTN lowers platelet aggregation and inflammation while promoting vasodilation and tissue reperfusion.

All NACIAM patients received emergency PCI and low-dose GTN (2.5 mcg/min for 48 hours) but were randomized pre-PCI to either high-dose NAC (20 mg/min for one hour, followed by 10 mg/min for the next 47 hours) or placebo, both delivered intravenously. The primary endpoint was myocardial infarct size, and the secondary endpoint was myocardial salvage.

Magnetic resonance imaging performed on day 5 and at three months showed that myocardial salvage was approximately doubled in patients who received NAC (60% versus 27%; P < 0.001). There also was evidence of accelerated tissue reperfusion and hypochlorous acid “scavenging” in these patients. Infarct size was 16.5% in the placebo group and 11% in the NAC group (P < 0.05).

NAC-treated patients had fewer cardiac readmissions and deaths after two years of follow-up compared with those who did not receive NAC (two versus 16 patients; P < 0.01). “Intravenous NAC administration was also associated with more rapid chest pain resolution, improved myocardial salvage, and a favorable in-hospital safety profile,” Pasupathy said.
John F. Beltrame, MD, the NACIAM lead investigator, noted that NAC was used in combination with intravenous nitrates. "I think the potentiating effect of nitrates with NAC is also important," he said, adding that NAC is given in the emergency room when patients with STEMI arrive and does not add to procedure time.

"While the results of this study are encouraging, we would prefer to regard NACIAM as the precursor of a follow-up study, sized for clinical endpoints," Pasupathy said.

Optimal Dual Antiplatelet Treatment (DAPT) Duration Following Drug-Eluting Stent With Bioabsorbable Polymer and Abluminal Coating

- Masato Nakamura, MD, PhD, Toho University Ohashi Medical Center, Tokyo, Japan

In patients who have undergone placement of the Nobori (Terumo) drug-eluting stent for coronary artery disease or acute myocardial infarction, a shorter six-month course of dual antiplatelet therapy (DAPT) is noninferior to 18 months, according to a presentation of NIPPON study results at an ESC press briefing. The Nobori is a bioabsorbable (metabolized within six to nine months) abluminal-coated stent, said Dr. Nakamura, the lead investigator.

“A combination of short DAPT and a newer drug-eluting stent,” Dr. Nakamura said, “should be able to minimize the incidence of thrombotic events and bleeding complications simultaneously.” NIPPON investigators enrolled 3,775 patients who had undergone percutaneous coronary intervention and stent placement at 130 Japanese institutions. The trial, which had broad inclusion criteria to reflect real-world clinical practice, allocated 18 months of DAPT to 1,391 patients and six months of DAPT to 1,381 patients.

The noninferiority endpoint was met, and the rate for the primary endpoint of net adverse clinical and cerebral events (NACCE) was 1.45% for 18 months of DAPT versus 1.92% for six months of DAPT. NACC included all-cause death, Q wave or non-Q wave myocardial infarction, cerebrovascular events, and major bleeding. The difference of –0.46 (lower limit of 95% confidence interval, –1.48) fell within the prespecified noninferiority margin of –2, Dr. Nakamura said.

He noted that the trial had been terminated prematurely because of slow enrollment, and with the reduced population, low event rate, open-label design, frequent crossovers, and wide noninferiority margin, “the results need to be interpreted with caution.”

ESC press briefing moderator professor Stephan Gielen, MD, commented, “The key message is that a more individualized approach to dual antiplatelet therapy is more important than ever. We have new stents with abluminal coatings that reduce the thrombotic risk. On the other hand, you have the very high-risk patients with multivessel disease, multiple stents, or older stents for which the thrombotic risk may be very high. Those patients would qualify for prolonged antiplatelet therapy.”

Dr. Nakamura agreed with the moderator’s remarks.

**Meeting Highlights: European Society of Cardiology Congress**

**Optimal Dual Antiplatelet Treatment (DAPT) Duration Following Drug-Eluting Stent With Bioabsorbable Polymer and Abluminal Coating**

**Stroke and All-Cause Mortality With Non-Vitamin K Antagonist Oral Anticoagulation Versus Warfarin in Atrial Fibrillation: A Nationwide Study**

- Laila Staerk, MD, Gentofte Hospital–Copenhagen University Hospital, Hellerup, Denmark

Atrial fibrillation, the most common cardiac rhythm disorder, affects 10 million Europeans and 33 million people worldwide. It increases the risk of stroke fivefold. The oral anticoagulants that are known to reduce stroke risk, however, increase bleeding risk, especially for often-disabling intracranial bleeding.

An observational study comparing the new oral anticoagulants (NOACs) and warfarin in more than 43,000 new patients with atrial fibrillation found stroke prevention to be similar for all, but NOACs also reduced intracranial bleeding, according to an ESC press conference presentation. Dr. Staerk, the study author, noted the four oral agents available in Denmark: warfarin (the older vitamin K antagonist) and the NOACs dabigatran (Pradaxa, Boehringer Ingelheim), rivaroxaban (Xarelto, Janssen Pharmaceuticals), and apixaban (Eliquis, Bristol-Myers Squibb).

“There has been a need to investigate safety and effectiveness of NOACs versus warfarin in a ‘real world’ population,” Dr. Staerk said. “Our Danish registries provide this opportunity.”

In the 43,299-patient cohort from the Danish nationwide administrative registries, 42% of patients were taking warfarin, while 29%, 16%, and 13% were taking dabigatran, apixaban, and rivaroxaban, respectively.

The endpoint of absolute stroke risk within one year of initiation of treatment was similar for each of the four groups: 2.01% for warfarin, 2.12% for dabigatran, 2.06% for rivaroxaban, and 2.46% for apixaban (P versus warfarin = NS for each). The risk translates to approximately 20 to 25 patients per 1,000 with atrial fibrillation treated with NOACs or warfarin, Dr. Staerk said.

For the patients who took NOACs, however, the standardized absolute risk of intracranial bleeding at one year was reduced. Absolute risk was 0.60% for warfarin, 0.26% for dabigatran, 0.47% for rivaroxaban, and 0.40% for apixaban. For warfarin, the intracranial bleeding risk was approximately six patients per 1,000 compared with approximately four patients per 1,000 for apixaban and approximately three patients per 1,000 for dabigatran.

“Among patients with atrial fibrillation who were new users of oral anticoagulation, while treatment with NOACs was not associated with a significantly lower risk of stroke, treatment with dabigatran and apixaban was associated with a significantly lower risk of intracranial bleeding compared with warfarin,” Dr. Staerk concluded.

ESC commentator Ian Graham, MD, cautioned against over-interpretation of the differences between NOACs, given that the study was observational and subject to bias. “It showed that in the ‘real world’ it is safe to use warfarin and NOACs, with NOACs being a bit safer than warfarin. That is reassuring.”
NorStent trial investigators, in the largest coronary stent trial ever conducted, sought to determine the long-term effects of DES versus bare metal stents on mortality, myocardial infarction, revascularization, stent thrombosis, and quality of life. The investigator-initiated trial included patients with stable angina pectoris (n = 2,636) or acute coronary syndromes (n = 6,377) who needed percutaneous coronary interventions. They were randomized at multiple Norwegian centers to either bare metal stents or DES, with 83% of DES recipients receiving everolimus-eluting stents, 12% receiving zotarolimus-eluting stents, and 5% receiving older-generation DES. The inclusion period was from 2008 through 2011. The primary endpoint was combined death and nonfatal spontaneous myocardial infarction.

Dr. Bonaa reported that primary endpoint events occurred similarly in the two groups after six years: 16.9% in the DES group and 17.4% in the bare metal stent group (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.88–1.09; P = 0.66). All-cause mortality was also similar (HR, 1.10; 95% CI, 0.94–1.29; P = 0.22). Need for revascularizations, however, was lower in the DES patients, with a six-year rate of 16.5%, compared with 19.8% for bare metal stents (HR, 0.76; P < 0.001). The number needed to treat with DES to avoid one revascularization was 30. In addition, definite stent thrombosis was 0.4% lower with DES (P = 0.0498).

The two groups had remarkably similar scores on quality-of-life measures assessing physical limitations, angina frequency, and overall quality of life.

“The long-term benefit of contemporary drug-eluting stents over bare metal stents was less than expected. … Both contemporary drug-eluting and contemporary bare metal stents may be recommended for coronary revascularization,” Dr. Bonaa said.

ESC discussant Stefan James, MD, professor of cardiology at Uppsala University in Sweden, commented: “New-generation drug-eluting stents should remain recommended over bare metal stents due to better performance with a 5% (53% relative) reduction of target lesion revascularization, a 3.3% (24% relative) reduction of any revascularization, and a 0.4% (36% relative) reduction of stent thrombosis. Bare metal stents should not be specifically recommended for patients with high risk of stent thrombosis or patients who do not tolerate dual antiplatelet therapy.”

REFERENCES